THE PREVALENCE OF DEEP VEIN THROMBOSIS AND ASSOCIATED FACTORS IN ADULT MEDICAL PATIENTS ADMITTED TO THE UNIVERSITY TEACHING HOSPITAL, LUSAKA, ZAMBIA

BY

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DISSERTATION

THE PREVALENCE OF DEEP VEIN THROMBOSIS AND ASSOCIATED FACTORS IN ADULT MEDICAL PATIENTS ADMITTED TO THE UNIVERSITY TEACHING HOSPITAL, LUSAKA, ZAMBIA

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DECLARATION

I hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or at any other University.

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DEDICATION

This work is dedicated to my late mum, Mrs Sylvia Kaulu Mwandama for the great inspiration and unconditional support. I also dedicate this work to my wife Maggie Tangu Mwandama, my children, Kaulu Mwandama and Wizaso Mwandama. Thank you a million times for allowing me to be away from home repeatedly during the time I was conducting this study. I promise to make up.

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ABBREVIATIONS

ACA	anticardiolipin antibodies
APC	Activated protein C
aPLs	antiphospholipid antibodies
APS	Antiphospholipid syndrome
ARTEMIS	Arixtra for ThromboEmbolism Prevention in a Medical Indications Study
AT III	Antithrombin III
BMI	Body mass index
CHF	Chronic heart failure
DVT	Deep venous thrombosis
FDPS	Fibrinogen degradation products
FN	False Negative
FP	False Positive
HMWK	High molecular weight kininogen
LA	lupus anticoagulant
MEDENOX	Medical patients on Enoxaparin
MP	Microparticles
NET	Neutrophil Extracellular Trap
NPV	Negative predictive value
NS	Nephrotic syndrome
OCs	Oral contraceptives
PAI-1	Plasminogen activator inhibitor 1
PAI-2	Plasminogen activator inhibitor 2

PE	Pulmonary embolism
PK	Pre Kallikrein
PPV	Positive predictive value
PREVENT	Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial
t-PA	Tissue plasminogen activator
TAT	Thrombin antithrombin complex
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TM	Thrombomodulin
TN	True negative
TNF	Tumour necrosis factor
TP	True positive
u-PA	Urokinase-like plasminogen activator
USS	Ultrasound scan
UTH	University Teaching Hospital
VTE	Venous thromboembolism
vWF	von Willebrand factor

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ABSTRACT

Deep vein thrombosis (DVT) and pulmonary embolism (PE) collectively referred to as venous thromboembolism (VTE) are a global concern with substantial morbidity and mortality. Symptomatic DVT commonly occur in hospitalized patients with acute medical illnesses. Thromboprophylaxis for DVT is not routinely given to hospitalized medical patients in most hospitals in Zambia.

The purpose of this study was to determine the prevalence of DVT and associated factors in medical patients admitted to the University Teaching Hospital (UTH).The main objectives were: to determine the prevalence of DVT in medical patients admitted to the UTH for at least 7 days; document the anatomical distribution of DVT in medical patients admitted to the UTH; establish demographic and clinical characteristics of medical patients with DVT and finally determine the accuracy of the Well's score for DVT in patients who develop DVT at UTH.

We carried out a descriptive, cross sectional analytical study. The sample size comprised 296 medical patients admitted for at least 7 days. A questionnaire was used to obtain demographic characteristics and relevant clinical history. A focused detailed physical examination was done to screen for DVT of the lower limbs and Well's score for DVT computed. Laboratory tests including HIV test and full blood count were done. Compression ultrasound scans (USS) were done on lower limbs of recruited patients to determine the presence of DVT. Variables of interest were compared by chi-square, Kruskal-Wallis and t-tests. Multivariate and univariate logistic regression analysis were used to assess for associations between DVT and independent variables of interest

Prevalence of DVT was found to be 11.1 % (33/296). The prevalence of proximal lower limb DVT was 9.1 %(27/296). Eighty two (27/33) percent of all patients with DVT had proximal lower limb DVT.

The Mean age of patients with DVT was 42.12 years (SD 12.71) while mean hospital admission was 11.91 days (SD 7.77) days. Patients with primary diagnosis of infectious origin accounted for 67 % of all cases of DVT. Primary diagnosis of tuberculosis was the most common infection among patients with DVT accounting for 60.6 % of all infections. Of all patients with DVT, 69.7 % were HIV positive.

The Wells score specificity for DVT was 73.4% while the sensitivity was 100%. The accuracy was 76.3%.The positive and negative predictive values were 32% and 100% respectively.The pre-test Wells score correlated well with the USS findings and could be used as a rule out test for those with suspected DVT.

Proximal Lower limb DVT is common among HIV positive medical patients admitted for at least 7 days at the UTH. In our study, lower extremity proximal DVT was more common in patients with tuberculosis and a low BMI. Up to 85% of lower limb DVT was asymptomatic. Without a high index of suspicion, lower limb DVT is likely to be missed. The pretest Wells score correlated well with the USS findings .A follow up study to evaluate for genetic and biochemical factors that predispose to DVT need to be undertaken in the near future. There is need to advocate for thromboprophylaxis in medical patients with acute illness and prolonged hospital stay.

CHAPTER 1

1.0 INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) collectively referred to as venous thromboembolism (VTE) are a major cause of morbidity and mortality in hospitalized medical patients with acute illness worldwide.[1,3,6,7]

Approximately 10 million cases of VTE occur every year across low, middle and high income countries worldwide.[225] In the United States of America (USA), it is estimated that over 300 000 patients die from complications of VTE every year.[1] Over 500 000 deaths occur as a complication of VTE annually in Europe.[2] Very few published studies have been done in Africa on prevalence of VTE.

A retrospective autopsy study done by Sotunmbi et *al* in Nigeria found a prevalence of VTE of 2.9%, with increased risk in male patients older than 40 and in those with cancer.[220]

Both DVT and PE share very similar pathophysiological mechanisms, laboratory findings, treatment modalities and prevention options. This makes discussion of DVT and PE as separate clinical entities difficulty. While this study was on prevalence DVT, the term VTE was used in the literature review to refer to DVT and PE collectively.

The Medical patients on Enoxaparin (MEDENOX) study, a multi-centre randomized, double-blind controlled study conducted in nine countries found overall prevalence of VTE in the placebo group of 14.9%.[3] It is estimated that up to 70% of symptomatic VTE occur in hospitalized patients with acute medical illness such as congestive cardiac failure, myocardial infarction, stroke, infection and renal failure.[4] In over 70% of patients, VTE is asymptomatic making it difficult to diagnose, treat and prevent.[4]

Anecdotally, DVT is common in most hospitals in Zambia and especially in the era of HIV. Currently the prevalence of DVT in medical patients admitted to the University Teaching Hospital (UTH) and associated morbidity and mortality are not known.

The purpose of this study was to determine the prevalence of DVT and associated risk factors in medical patients admitted to the UTH with aim of understanding the magnitude of the problem and help guide appropriate future interventions.

CHAPTER 2

2.0 LITERATURE REVIEW

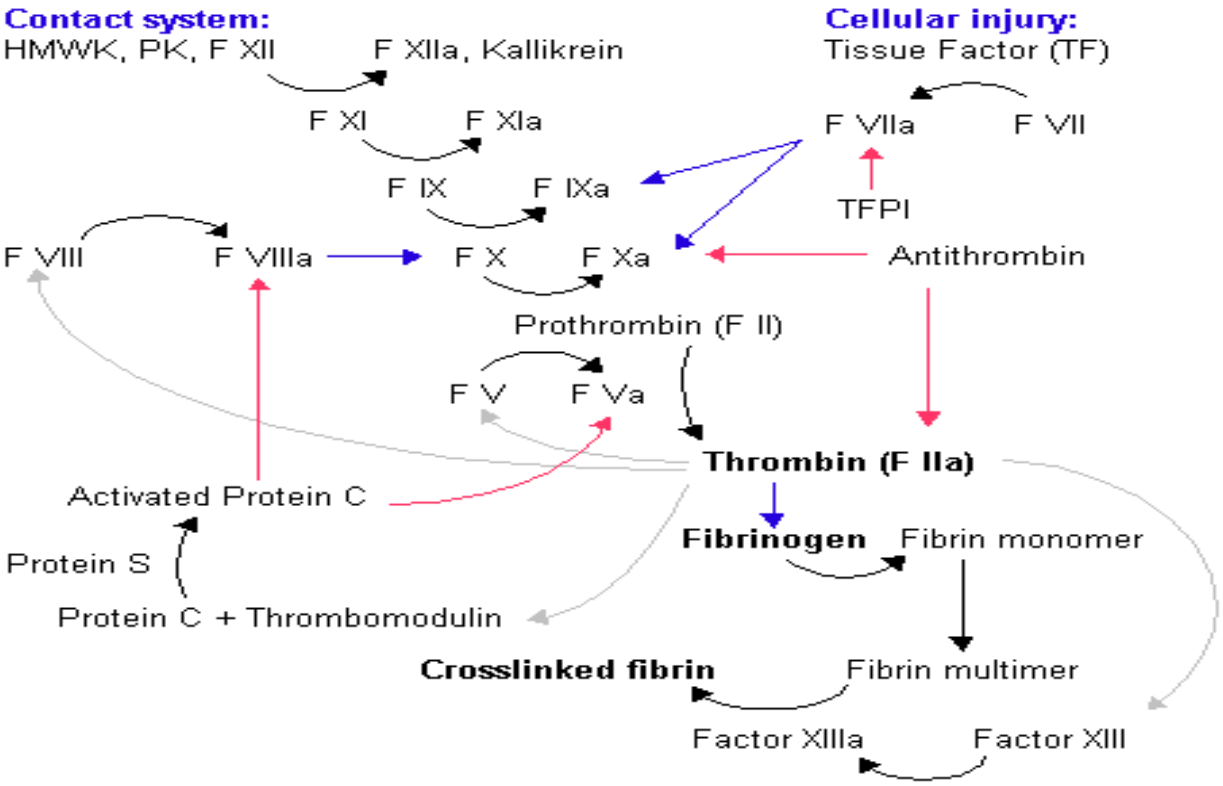
Globally, the prevalence of asymptomatic and symptomatic DVT in hospitalized medical patients not receiving thromboprophylaxis is estimated to be between 10 and 20 %.[5] DVT affects both hospitalized and non-hospitalized patients. Other than the MEDENOX study, two other multi-centre randomized, double-blind, controlled trials, namely the ARTEMIS (Arixtra for ThromboEmbolism Prevention in a Medical Indications Study) and the PREVENT (Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial) studies have given an insight to the global prevalence of VTE. In the ARTEMIS study, the prevalence rate of VTE was 10.5% in the placebo arm compared to 5.6% in the fondaparinux arm.[6] The PREVENT study revealed a prevalence rate of 4.96% in the placebo arm compared to 2.77% in the Dalteparin arm.[7]

In the United States of America up to 2 million people develop DVT annually.[8] In addition, in the USA alone, DVT and PE account for up to 600 000 hospital admissions.[8] Studies have also revealed that death occurs in about 6% of individuals with DVT within a month of diagnosis and in 10% of those with PE within the same period.[9]

Causes of DVT are multifactorial and can be classified as modifiable and non-modifiable.[10] Modifiable risk factors include, sepsis, HIV infection, Diabetes Mellitus, smoking, hypertension, obesity, heart failure, high cholesterol, immobility, cancer and kidney failure.[10] Non modifiable risk factors include age, gender and hereditary risk factors such protein C and S deficiency, antithrombin deficiency, factor V Leiden and Prothrombin gene mutation G20210A.[10] Clinical manifestation of VTE is influenced by the additive effects of modifiable and non-modifiable risks when they occur simultaneously.[11]

The lower extremities are the most common site of DVT. Other sites were DVT occurs include pelvic, mesenteric, cerebral veins and upper extremities. Typical symptoms and signs of DVT include pain, swelling, increased warmth, tenderness and erythema.[2]

2.1 Pathophysiology



www.thrombosisadviser.com/the-coagulation-cascade *2015*[226]

Figure 1.The coagulation cascade

Thrombus formation is a complex process that depends on interaction between the blood vessel wall, platelets, the coagulation and fibrinolytic systems. Vessel wall injury exposes collagen and together with tissue injury brings in motion a series of events leading to platelet aggregation and formation of a platelet plug. The platelet plug is strengthened and stabilized by fibrin strands formed from soluble fibrinogen through the coagulation cascade.[12]

The coagulation cascade involves a series of enzymatic reactions as shown in Figure 1.The coagulation factors XII, XI, X, IX and thrombin are serine protease enzyme precursors while V and VIII are cofactors.[12]

The coagulation cascade is schematically outlined as Y-shaped with distinct intrinsic and extrinsic pathways.[13] The intrinsic pathway is initiated by factor XII (FXII) while the extrinsic pathway is initiated by FVIIa/tissue factor (TF) and the two pathways then converge at the level of the FXa/FVa (prothrombinase) Complex.[13] Activated factor X in the presence of activated factor V converts Prothrombin to thrombin. Thrombin catalyzes hydrolysis of peptide bonds of fibrinogen releasing fibrinopeptides A and B which polymerize to form fibrin. Activated factor XIII then stabilizes fibrin clot by cross-linking adjacent fibrin molecules.[13]

2.1.1 The Antithrombotic systems

The human body possesses natural antithrombotic mechanisms that counteract thrombosis. A very tight balance exists between thrombosis and fibrinolysis. As soon as the fibrin clot starts forming, the antithrombotic systems are initiated to disrupt it. This balance limits thrombosis to the site of vascular injury and prevents dangerous generalized thrombosis .The body's natural antithrombotic systems are now discussed below:

2.1.1.1 Antithrombin III

Antithrombin III (AT) is a broad spectrum serine protease inhibitor.[12] It has both anti-coagulant and anti-inflammatory effects. It inhibits the action of thrombin, VIIa, IXa, Xa, XIa and XIIa.[14] Antithrombin III binds to thrombin to form the thrombin-antithrombin (TAT) complex which is a potent regulator of excessive clot formation. Antithrombin III also contributes to inhibition of platelet aggregation. The anti-coagulant effects of antithrombin III are potentiated 1000x by heparin.[14]

2.1.1.2 The Thrombomodulin(TM)/ Protein C/Protein S system

Protein C and its cofactor protein S are vitamin K dependent serine antiproteases.[12] Protein C has potent anticoagulant, profibrinolytic and anti-inflammatory actions. Initial step in the activation of protein C is the binding of thrombomodulin (TM) to thrombin.[15] The TM-thrombin complex then rapidly binds and activates protein C. Activated protein C (aPC) in association with its cofactor protein S inactivates factors Va and VIIIa.[14]

2.1.1.3 The Tissue Factor pathway inhibitor

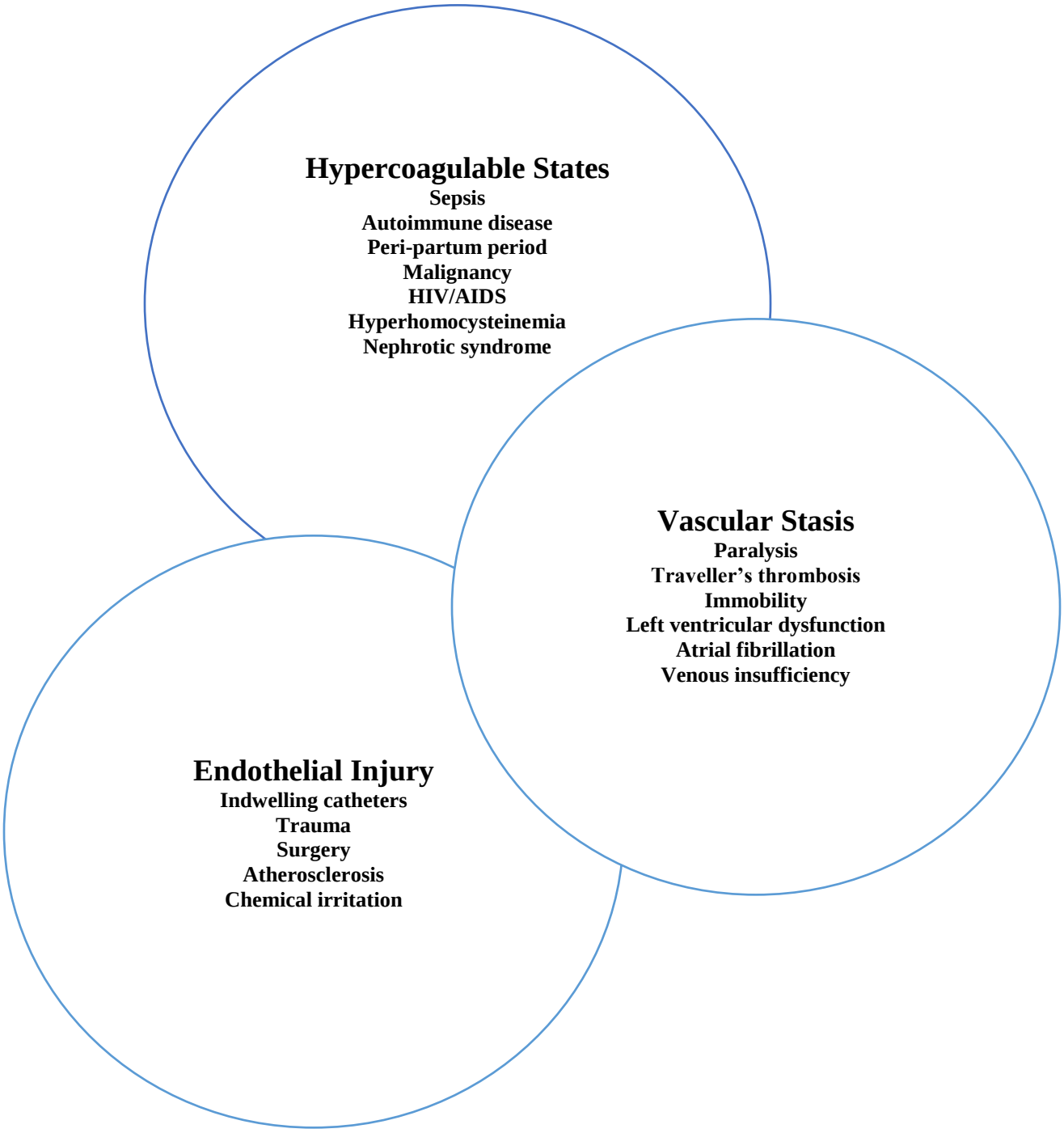
Tissue factor pathway inhibitor (TFPI) is a serine protease inhibitor.[12] TFPI directly inhibits factor Xa and the FVIIa – TF complex. It is the only endogenous inhibitor of TF-VIIa.[14]

2.1.1.4 The Fibrinolytic Pathway

The fibrinolytic system is initiated by the formation of the enzyme plasmin from its inactive precursor plasminogen.[14] Plasmin breaks down fibrinogen and fibrin into fragments known as fibrin degradation products (FDPs).[14] Conversion of plasminogen to plasmin is facilitated by tissue-type plasminogen activator (t-PA) and urokinase-like plasminogen activator (u-PA).[13] The activity t-PA and u-PA are regulated by Plasminogen activator inhibitor-1(PAI-1) and 2(PAI-2) which inhibits the ability of t-PA and u-PA to activate plasminogen respectively.[16]

2.2 The Virchow's triad

The components of the Virchow's triad are shown in figure 2 below. Pathophysiology of DVT was first described by German pathologist Rudolph Virchow in 1846.Virchow postulated that interplay of a triad, vascular stasis, hypercoagulability and blood vessel wall injury culminated into venous thromboembolism.[17] The components of the Virchow's triad and associated risk factors are now discussed below.



(Amalgamation of anti-clot.com 2015 & thrombosisadvisor.com 2012)

Figure 2.Virchow's Triad

2.2.1 Hypercoagulable states

Hypercoagulable states refer to disorders of blood coagulation with great tendency towards thrombosis.

Hypercoagulable states are classified as below:

- **Inherited or primary hypercoagulable states**: Antithrombin III deficiency, Protein C deficiency, Protein S deficiency, activated protein C resistance due to factor V mutation, Prothrombin gene mutation and rarely dysfibrinogenemias.
- **Acquired or secondary hypercoagulable states**: Malignancy, antiphospholipid syndrome, nephrotic syndrome ,pregnancy, postpartum period, estrogen therapy, advancing age ,sepsis, HIV, inflammatory bowel disease, trauma, recent surgery, obesity and congestive cardiac failure.
- **Mixed hypercoagulable states**: Hyperhomocysteinemia

2.2.1.1 Sepsis

Sepsis is characterized by a shift in the balance between procoagulant and anticoagulant factors towards an overall prothrombotic state.[18]

Endotoxins produced by bacteria trigger release of proinflammatory cytokines, tumor necrosis factor (TNF), interleukin -1 and interleukin-6 from macrophages that initiate and propagate the prothrombotic state associated with sepsis.[18,19] The cytokines activate monocytes and endothelial cells to release Tissue Factor (TF). TF combines with factor VII and activate the extrinsic pathway of the coagulation cascade.[20] TF is also thought to be generated by direct injury of endothelial cells by microorganisms.

Sepsis is characterized by an overall reduction in the activity of the natural anticoagulants of the coagulation cascade.[21,22,23] There is an overall depletion and decreased activity of antithrombin III and protein C. Antithrombin III consumption is increased as a result of ongoing thrombin generation significantly shortening its half-life.[21] In addition there is enhanced

Antithrombin III degradation by elastases produced by activated neutrophils.[21,22] Hepatic synthesis of Antithrombin III is also decreased in sepsis.[23]

Protein C levels are markedly decreased primarily as a result of sepsis-induced increased consumption.[23] Studies have reported high levels of C4bBP, an acute-phase protein in infection which bind free protein S, thus limiting protein C anticoagulant activity.[25] Activity of protein C is further reduced due to cytokine mediated decreased endothelial expression of thrombomodulin.[25]

Sepsis also results in overall inhibition of the fibrinolytic pathway through the TNF mediated increased activity of plasminogen activator inhibitor, type 1 (PAI-1).[26]

2.2.1.2 HIV infection/AIDS

HIV infected individuals are prone to multiple and persistent acquired thrombophilic abnormalities compared to the healthy general population.[27]
Epidemiological studies have shown that HIV infected patients have a 2-10 fold risk of developing VTE compared to the general population.[28]

Studies have further shown that patients with full blown AIDS have a higher risk of thrombosis compared to HIV-infected patients with a more robust immune system.[29] HIV-infected patients tend to have a median age of 40 at time of first venous thromboembolic event, 20 years younger than the median age of non-infected patients.[30] Autopsy studies have revealed high rates of previously undiagnosed thromboembolism among patients with AIDS.[31]

Several mechanisms have been proposed to explain the hypercoagulable associated with HIV infections. HIV infection culminate into vascular endothelial cell dysfunction , activation of the coagulation cascade and down-regulation of the fibrinolytic pathway.[32] Endothelial cell activation has been associated to cytokines ,tumor necrosis factor, interleukin-1 and interleukin-6 that are up-regulated during the course of HIV infection.[33]

HIV infection, directly and indirectly through cytokine production, induces monocyte TF expression with resultant activation of the extrinsic pathway of the coagulation cascade.[33] It is also thought that HIV may have a direct role in endothelial cell activation and dysfunction.[34] Endothelial cell activation has been linked to high levels of von Willebrand factor and plasminogen activator inhibitor I (PAI-I) that have been reported in patients infected with HIV.[35, 36]

Recently microparticles (MPs) have been linked to the activation of the coagulation cascade in HIV patients.[37] Microparticles refers to small cellular membrane vesicles, circulating in plasma released from activated or apoptotic cells.[38] Patients infected with HIV have been reported to have high levels of microparticles thought to be generated by HIV induced apoptosis of CD4+ lymphocyte.[39] Microparticles promote coagulation through activated phospholipids on their surfaces that cluster clotting factor complexes.[37]

Decreased activities of Protein C, Protein S and antithrombin III have been reported in HIV patients with thrombotic events.[40] The prevalence of protein C deficiency has been estimated to range between 0-14 % while that of protein S ranges between 27-76%.[28,41]

A number of studies have associated prothrombotic state in HIV infected patients to high levels of anticardiolipin antibodies (ACA) and lupus anticoagulant (LA) that have been reported.[42,43] Estimated prevalence of ACA ranges between 7-94% while that of LA between 0-72%.[42]

Some studies have linked antiretroviral drugs such as protease inhibitors (PIs) to thrombotic events seen in some HIV patients. It has been suggested that PIs may have procoagulant activity by increasing plasminogen activator inhibitor.[44]

Malignancy has been reported to be an independent risk factor for thrombosis in patients with HIV infection.[45] Mechanisms of venous thrombosis in malignancy is discussed below.

2.2.1.3 Antiphospholipid syndrome

Antiphospholipid syndrome (APS) refers to a systemic autoimmune condition characterized by thrombosis (venous or arterial), recurrent pregnancy loss (3 or more at >10 weeks gestation) and persistent antiphospholipid antibodies (aPLs).[46] The aPLs include anticardiolipin antibodies (ACA), lupus anticoagulant (LA) and anti-β2 glycoprotein I (anti- β2 GPI) antibodies and should be measured on at least two occasions 12 weeks apart.[47]

Antiphospholipid antibodies have been reported to be risk factors for venous thrombosis.[48] DVT of the lower limbs is the most common manifestation of the antiphospholipid syndrome occurring in 29% to 55% of patients.[49]A study done in England reported that hospitalized patients with SLE have 3.7 times higher risk of developing VTE compared to a reference group of inpatients.[50]

APLS is further classified into primary and secondary sub groups.
Primary APLS is not associated with any other disease conditions. Patients with primary APLS can be further sub classified into three groups.[52] The subclasses are as below.

- Patients having idiopathic deep vein thromboses (DVT), pulmonary embolism and pulmonary hypertension in the absence of any autoimmune disease.
- Patients with stroke, transient ischemic attacks and other large vessel occlusions, including myocardial infarction or peripheral vessel thrombosis, particularly under the age of 45.
- Patients with recurrent miscarriages

Secondary APLs occurs in association with other disease entities such autoimmune conditions, drug-induced diseases, infectious diseases and neoplasms.[52] Systemic Lupus Erythematosus (SLE) is the most common autoimmune disease associated with APLS.[52]

Multiple mechanisms have been linked to venous thrombosis in APLS. Firstly it has been suggested that aPLs may combine with the endothelial cell membrane phospholipids along with beta 2 GPI and induce endothelial cell damage resulting in increased platelet adhesion and aggregation.[53] Furthermore it is thought that aPLs may combine with platelet membrane phospholipids, resulting in increased platelet adhesion and aggregation.[53]

Acquired protein S deficiency and inflammation have been linked to thrombotic events in SLE.[54, 55] It has also been suggested that microparticles may also contribute to the thrombotic risk among patients with APLS.[56]

Lastly it has been postulated that endothelial cell damage may also result in decreased production of endothelium derived relaxing factor and thus, increased vasospasm, ischemia and endothelial cell activation resulting into venous thrombosis.[53]

High levels of Rheumatoid factor are associated with systemic inflammation and increased risk of venous thromboembolism.[58] The Copenhagen City Heart Study and the Copenhagen General Population Study conducted in Denmark revealed that increased levels of rheumatoid factor in the general population was associated with up to 3-fold increased long-term risk and up to 9-fold increased 1-year risk of deep venous thrombosis.[57]

2.2.1.4 Erythrocytosis, Thrombocytosis and Leukocytosis

2.2.1.4.1. Erythrocytosis

Primary and secondary erythrocytosis are hypercoagulable states with increased tendency for venous and arterial thrombosis.[59,60] The Tromsø study conducted in Norway found that hemoglobin and RBC count were significantly associated with increased risk of VTE.[59]

An age adjusted haematocrit of 42% or more in women was associated with 50% higher risk of total VTE and 62% higher risk of unprovoked VTE compared to women with a hematocrit less than 39%. In men a hematocrit of 46% or more was linked with a 54% higher risk of total VTE and a 2-fold higher risk of unprovoked VTE compared to those with a hematocrit less than 43% respectively.[59]

The Tromsø study also found that Women with a hemoglobin concentration of 14.1g/dL or more had a 1.45-fold higher risk of total VTE compared to women with a hemoglobin level less than 13.2 g/dl.[59] The study also revealed that men with a hemoglobin a 15.6 g/dL or more had a 1.6-fold higher risk of total VTE and 2.2-fold higher risk of unprovoked VTE compared to men with hemoglobin concentration was less than 14.7 g/dl.[59]

Haematocrit plays a significant role in determining the viscosity of blood. A high haematocrit is associated with increased blood viscosity, increased adhesiveness of platelets leading to an overall hypercoagulable state.[61]

2.2.1.4.2 Thrombocytosis

Primary thrombocytosis associated with myeloproliferative disorders (MPD) and secondary or reactive thrombocytosis have been linked to thrombotic complications.[62,63] In both primary and secondary thrombocytosis the incidence of thrombotic complications has been reported to range from 11% to 80.[64]

An absolute reticulated platelet count of greater than 60×10^9/L is associated with a positive predictive values for developing symptomatic thrombosis of 88% while a reticulated platelet count of greater than 6% has a positive predictive value of 38%.[64]

The Cancer and thrombosis (CATS) study by Simanek *et al* found that a platelet count higher than 350×10^9/L increased the risk for VTE more than 2-fold in univariate analysis.[65]
High platelet count is associated with increased platelet adhesion to endothelium and leukocytes resulting in an overall hypercoagulable state.[64]

2.2.1.4.3 Leukocytosis

A number of studies have shown that leukocytosis when present in medical conditions such as primary polycythemia and cancer increases risk of VTE.[66,67] A study by Blix *et'al* showed that Cancer patients with WBC count ≥ 8.6 x 109 cells/L measured on average 7 years before the cancer diagnosis, had a 2.4-fold increased risk of VTE compared to those with WBC count below 6.4 x 10^9 cells/L) in multivariable analysis.[67] A VTE registry study found that leukocytosis in cancer patients with VTE had a 1.6-fold increased risk of recurrent VTE compared to subjects with WBC count less than 4 x 10^9 cells/L who have a decreased risk of recurrence.[68]

A study on patients with primary polycythemia and VTE found that the risk of thrombosis was increased in patients with a white blood cell count above 10×10^9/L.It was further noted that a WBC above 15×10^9/ was statistically significant for developing VTE.[66]

Various mechanisms have been proposed to explain the role white blood cells play in VTE. Firstly, a leukocyte adhesion molecule, P-selectin is increased and expressed on activated endothelial cells and platelets.[69] This has been shown to be associated with increased risk of thrombosis in cancer patients.[70]

Recently, it has been demonstrated that Neutrophil extracellular traps (NETs) adhere to platelets and red blood cells resulting in an overall hypercoagulable state.[71] NETs are webs of DNA released during stressful conditions such as sepsis and serve as anti-bacterial traps.[72] Furthermore it has been suggested that activated or apoptotic leukocytes, especially monocytes, may play an important role in the pathogenesis of cancer-related venous thrombosis by shedding microparticles expressing tissue factor.[73,74]

2.2.1.5 Malignancy

Thromboembolic events are a major cause of morbidity and mortality in cancer patients.[75] Malignant processes have been for a long time associated with venous thrombosis. The clinical association between venous thromboembolism and occult malignancy was first described by Armand Trousseau in 1865.[76] In 1878, Billroth, a pathologist noted in his postmortem studies that blood vessels draining malignant tumors contained fibrin clots.[77]

Activation of the coagulation cascade in malignancy and resultant thrombi formation is due to multiple mechanisms.[78] Firstly tumor cells are able to express tissue factor (TF) and secrete a cysteine protease called cancer procoagulant (CP) that trigger the coagulation cascade.[79] Secondly tumor cells are able to produce cytokines such as TNF, IL-1, IL-8 and vascular endothelial growth factor (VEGF) that activate vascular endothelial cell, macrophages and monocytes to expression TF.[79,80] These cytokines further promote thrombogenesis by down regulating thrombomodulin (TM) production and increasing the synthesis of plasminogen activator inhibitor-1 (PAI-1).[79]

Thirdly, tumor cells are able to induce direct conversion of fibrinogen to fibrin in a mechanism that does not involve the coagulation cascade.[80] Fourthly, the activity of Antithrombin III, Protein C and protein S are all depressed. AT III expression is down regulated in malignancy.
This is supported by the high levels of thrombin-antithrombin complexes (TAT) and low levels of AT III noted in most patients with disseminated malignancy.[81] Activated protein C resistance C (APC) has been noted in malignancy although levels of protein C are significantly increased.[82] Protein S has also been noted to be significantly elevated in patients with metastases compared with patients without metastases and healthy control subjects.[81]

Elevated levels of plasma coagulation factors V, VIII, IX, and X, increased levels of fibrinogen, fibrin degradation products (FDPs), Von Willebrand factor (VWF) and thrombocytosis have also been reported in patients with malignancy.[83]

2.2.1.6. Inherited Thrombophilias

Inherited thrombophilias are a group genetically determined prothrombotic states with increased and recurrent tendency to venous thrombosis occurring in young patients less than 45 years old.[84] Inherited thrombophilias include deficiencies of the three natural anticoagulants, namely, antithrombin, protein C and protein S and specific mutations in the genes for factor V (factor V Leiden) and Prothrombin (Prothrombin 20210 G -A).[84]

It is estimated that approximately one third of individuals with VTE have an identifiable inherited risk.[85] Studies have revealed that at least 15 % of patients before age of 45 years who present with VTE have an inherited deficiency of either antithrombin III ,Protein C or Protein S.[86]

Acquired predisposing risk factors such as immobility, surgery, trauma, cancer, hormonal therapy, pregnancy and non-modifiable risk factors such as advancing age provoke venous thrombosis in at least 50% of individuals with heritable thrombophilias.[87]

Factor V Leiden, named after the city of Leiden in Netherland where it was first characterized by Bertina *et al* at the University of Leiden, is the most common inherited thrombophilia.[88] Factor

V Leiden is a consequence of the replacement of guanine by adenine at nucleotide 1691 (G1691) resulting in the substitution of arginine by glutamine(Arg506Gln).
This mutation renders factor V Leiden not susceptible to cleavage at position 506 by activated protein C resulting in a hypercoagulable state with increased generation of thrombin.[89]
In the United States of America, prevalence of factor V Leiden in Caucasians is estimated to be 5% and 1.2% in African Americans.[90] .Individuals with factor V Leiden have a 3 to 8 times increased risk to thrombosis.[91]

The Prothrombin gene G20210A is a consequence of a single nucleotide substitution of guanine by Adenine at 20210 in the 3' untranslated region of the Prothrombin gene.[92] This mutation is relatively more common in the white population than in the black and Asian population.[93]
The prevalence of Prothrombin G20210A gene mutation in the United Kingdom is estimated to be about 2% with associated 3 fold risk of deep vein thrombosis.[92]

Inherited Antithrombin III (AT) deficiency is acquired in an autosomal dominant manner and thus affects both sexes equally. Its prevalence in the UK is estimated to be 0.02%.[91]
Individuals with inherited Antithrombin III deficiency have a 25-50 fold risk of developing venous thromboembolism.[91]

Inherited protein C deficiency is acquired in an autosomal dominant manner and associated with familial venous thrombosis.[89] Its estimated prevalence in the UK is about 0.3%.[91] Individuals with inherited protein C deficiency have 10-15 times risk to venous thromboembolism .[91]
Individuals with inherited protein S deficiency have a 10 time risk of venous thrombosis.[91]In the UK, Inherited protein S deficiency is estimated to a prevalence of 2%.[91]

Other inheritable thrombophilias like Dysfibrinogenemia characterized by production of abnormal fibrinogen that exhibits an abnormal thrombin-mediated conversion to fibrin, are very rare and thus not discussed in this literature review.

2.2.1.7 Heart failure

Thromboembolism is the most frequent complication of chronic heart failure (CHF).[94] Compared with other medical conditions, heart failure (HF) is associated with a 2- to 3-fold increased risk of DVT and PE.[95] This increases further by 38.3 fold in patients with Ejection Fractions [EF] less than 20%.[96] In the MEDENOX trial, 15% of HF patients not on enoxaparin developed VTE during a follow-up of 14 days after discharge from hospital.[3] Incidence of VTE in patients with myocardial infarction approaches 20%.[97]

Causes of hypercoagulable state in heart failure are multiple. CHF is characterized by impaired myocardial contractility and tissue hypoperfusion.[98] These in turn leads to ischemic metabolic changes and oxidative stress with resultant activation of endothelial cells, platelets, leukocytes and production of proinflammatory cytokines.[98] Significantly high levels of cytokines TNF-α and IL-6 have been found in patients with CHF and left ventricle systolic dysfunction.[99] These cytokines as discussed above have been shown to be important in the progression and maintenance of prothrombotic state in heart failure. More recently, CD40L, a protein of TNF-α super family with pro-coagulant properties, has been found elevated in HF.[100] Apart from having inflammatory properties,CD40L promotes over expression of tissue factor and activation of the extrinsic pathway of the coagulation cascade.[101]

Markers of coagulation and fibrinolysis such as von Willebrand factor (vWF),fibrinogen, intercellular adhesion molecules (ICAM), platelet and endothelial adhesion molecules (PECAM), vascular cell adhesion molecules (VCAM),platelet factor 4 (PF4), P-selectin ,D-dimer, fibrinopeptide A, thrombomodulin, thrombin-antithrombin III complex (TAT-III) and endothelial growth factor have been reported to be elevated in CHF.[102]

2.2.1.7 Nephrotic syndrome

Venous thromboembolism manifesting as DVT and PE ranks as one of the most serious complications of Nephrotic syndrome (NS).[103] Regardless of the type of glomerular histological pattern, NS is associated with an increased incidence of thromboembolic complications with substantial morbidity and mortality.[104]

Patients with nephrotic syndrome are estimated to have a 39% increased risk of DVT and a 72% increased risk of pulmonary embolism compared to patients without nephrotic syndrome.[105]

In adults membranous nephropathy is thought to have the greatest risk for development of thromboembolism with incidence of renal vein thrombosis(RVT) estimated to be as high as 37%,while the combined incidence of other histological types estimated to be about 24%.[106]

Various mechanisms have been proposed to account for the prothrombotic state in nephrotic syndrome.NS is characterized by multiple hemostatic derangements such as decreased endogenous anticoagulants, decreased fibrinolysis, the activation of procoagulants, enhanced platelet activation and aggregation.[107]

Multiple studies have consistently reported lower levels of antithrombin in patients with nephrotic syndrome.[108] The low levels of antithrombin are presumed to be as a result of increased urinary loss of antithrombin out of proportion to its synthesis. The primary glomerular defect in NS does not only result in leakage of antithrombin but also other low molecular weight protein such as albumin and protein S that are then pathologically excreted in urine.[109] While some studies have shown a direct association between low antithrombin level and high risk of VTE, others have shown no association.[110]

Protein C plasma levels have been reported to be preserved or up regulated.[111] Serum levels of free protein S have not been shown to be consistently low with some studies reporting increased concentrations during the nephrotic state.[111]

Activity of the fibrinolytic system in NS is low. Serum levels of plasminogen and tissue-type plasminogen activator are mildly decreased in concentration. Levels of inhibitors of fibrinolysis such α-2-macroglobulin and lipoprotein-A are increased in concentration resulting in diminished fibrinolytic activity.[104]

Markedly elevated levels of procoagulant proteins have been noted in NS. These include fibrinogen and factors V, VII, VIII and von Willebrand factor.[112] The elevated levels are due to increased synthesis out of proportion to urinary losses. Serum levels of factors IX, XI, and XII have been reported to be low believed to be due to increased urinary loss.[107]

Studies have shown evidence that platelets may be constitutively activated in NS.[113] P-selectin which is a marker of platelet activation, has been shown to be elevated in nephrotic syndrome patients.[104]

2.2.1.8 Hyperhomocysteinemia

Case control studies have shown that mild and moderate hyperhomocysteinemia is an independent risk factors for venous thrombosis.[115] A study by Mudd *et al* involving 629 patients with homocystinuria, reported a prevalence of 50% for DVT.[116]
Another study involving 60 patients with unexplained thrombotic events by Marchant *et al* reported hyperhomocysteinemia as the only coagulation abnormality.[117]

Hyperhomocysteinemia can result from inherited and acquired disorders. The most common inherited genetic defect involve methylenetetrahydrofolate reductase (MTHFR) an important enzyme in remethylation of homocysteine in which cytosine is replaced by thymidine (C→T) at base position 677 of the gene.[118] This variant of the enzyme has reduced activity and result in elevated levels of serum homocysteine of about 20%.[119] Genetic defects involving the enzyme Cystathionine ß-synthase results in impaired trans-sulfuration of homocysteine to cysteine with resultant high levels of homocysteine and hypercoagulable state.[120]

Acquired causes of hyperhomocysteinemia are due to multiple causes. Nutritional deficiencies of vitamin B6, vitamin B12 and folate are associated with high serum levels of homocysteine. Folate antagonists such as carbamazepine and phenytoin and vitamin B6 antagonists, theophylline and estrogen are linked with hyperhomocysteinemia.[121]

Elevated levels of homocysteine have been reported in malignancies such as acute lymphoblastic leukemia and cancers of the pancreas, breast and ovaries.[122] Renal failure and Psoriasis have also been linked to hyperhomocysteinemia.[123]

Various mechanisms have been attributed to hypercoagulable state associated with hyperhomocysteinemia. Homocysteine has been shown to up regulate expression of IL 8 which

then activates coagulation cascade by inducing tissue factor production and down regulation of Protein C, thrombomodulin and t-PA production.[124] Hyperhomocysteinemia is associated with generation of hydrogen peroxide that cause vascular endothelial damage.[123]

2.2.1.9 Obesity

The world health organization (WHO) recognizes obesity as a global pandemic with an estimated population of 700 million worldwide by 2015.[125] It is estimated that as the world population of obesity increases, there will be a parallel increase in the incidence of venous thromboembolism.[125] Obesity is a recognized proinflammatory and hypercoagulable state with haemostatic alterations that predispose to venous thromboembolism.[126]

Body mass index (BMI) is the most frequently used indicator of obesity.[127] Normal range of BMI is 18.5 - 24.9 kg/m^2 in adults aged 20 years and above. Individuals with a BMI of 25 - 29.9 kg/m^2 are considered to be overweight while those with a BMI $\geq$ 30 kg/m2 are classified as obese. The World Health Organization further sub classifies obesity into three categories as follows:

- Class I obesity is a BMI of 30 - 34.9 kg/m^2
- Class II obesity is a BMI of 35 - 39.9 kg/m^2
- Class III obesity, or morbid obesity, is a BMI $\geq$ 40 kg/m^2

High BMI is a known risk factor for VTE. Individuals with a BMI of 30kg/m^2 have twice the risk of developing VTE compared to normal population.[125] Individuals in class III obesity have the highest risk of developing VTE.[8] Obesity has been associated with recurrent DVT episodes.[128]

The hormone Leptin has been linked to the pathogenetic mechanism of hypercoagulable state in obesity. Consistently high plasma leptin levels have been observed in obese individuals.[129] Leptin induces prothrombotic state through elaboration of TNFα and IL-6 from monocytes which then induce TF expression and eventual activation of the extrinsic pathway of the coagulation cascade.[130] Leptin has also been shown to induce the expression of TF in human peripheral neutrophils and thus triggering the extrinsic coagulation cascade.[131]

Abdominal obesity has been linked with hypofibrinolysis and elevated levels of PAI-1 attributed to ectopic production from adipose tissue.[132]
Abdominal obesity has also been associated with leptin induced platelet hyperactivity leading to a prothrombotic state.[133]

2.2.1.10 Oral contraceptives

Thromboembolism is the most frequently occurring serious side effect of combined oral contraceptives (OCs).[134] More than 100 million women use hormonal contraception worldwide.[135]

Most OCs contains an estrogen and a progestagen.Ethinylestradiol,a synthetic estradiol is the most common estrogen used in OCs .Earlier forms of OCs have been reported to have a high rate of VTE attributed to the high estrogen content of up to 150 μg.[136] Newer OCs have reduced ethinylestradiol content of 20-30 μg.[136]

Progestagens are classified into generations depending on the time they were first introduced. The first-generation progesterone produced in the 1960s include norethisterone and lynestrenol.[135] Second generation progestagens were first introduced in the 1970s and include levonorgestrel, norgestrel, and norgestrione.[135] Third-generation progestagens with less androgenic effect were introduced in the 1980s. Examples of these include desogestrel, and gestodene.[135]

Recent studies indicate that the risk of VTE does not differ between the older formulations of OCs and the newer ones.[137] Studies have also shown that the introduction of new progestagens and lowering of the estrogen dose has not resulted in a substantial risk reduction for venous thrombosis.[138]

Earlier studies involving OCs with high-dose estrogen content of 50 μg or more of ethinylestradiol reported an estimated a fourfold risk of venous thrombosis in users.[139]

Recent studies involving low-dose oral contraceptives with 30 to 40 μg of ethinylestradiol estimate risk of venous thrombosis to be three to six times in users.[136]
OCs containing third generation progestagens (desogestrel and gestodene) are associated with a twofold increased risk of venous thrombosis compared with OCs with previous generations of progestagens .[140]The greatest risk has been reported to occur during the first year of use.[141]

The mechanism by which OCs cause a hypercoagulable state in users in not fully understood. It has now been established that OCs users develop acquired resistance to activated protein C with resultant impaired effect of anticoagulant effect of activated protein C.[142]
OCs use is associated with overall increase in procoagulants fibrinogen, prothrombin, factor VII, factor VIII, factor X and reduction in anticoagulants factor Antithrombin III, protein C and protein S.[143]

There is now evidence suggesting that levels of thrombin- activatable fibrinolysis inhibitor (TAFI) are higher in women taking OCs containing desogestrel compared to those containing levonorgestrel.TAFI when activated, inhibits fibrinolysis and when elevated is a known risk factor for venous thrombosis.[144]

2.2.1.11 Pregnancy

Pregnancy has been described as a prothrombotic and a hypercoagulable state. The risk of venous thrombosis has been estimated to be 4 to 5-fold increased during pregnancy and 60 to 84 fold increased three months after delivery.[145]

A meta-analysis by Ray et *al* found that two thirds of cases of deep-vein thrombosis occurred in the ante partum period.[146] More than 60% cases of pulmonary embolism related to pregnancy appear to occur in the puerperium.[147]

In up to 90% of cases, the left leg is more commonly affected by VTE than the right. This has been attributed to compression of the left iliac vein by the right iliac artery at their crossing.[146]
Physiologic changes that occur to the hemostatic system during pregnancy meant to protect the mother from excessive bleeding during delivery result in an overall hypercoagulable state.

In normal pregnancy, plasma levels of coagulation factors VII, VIII, IX, X, XII, fibrinogen,Von Willebrand factor become elevated .[148] In addition markers of thrombin generation, thrombin-antithrombin complexes and the prothrombin fragment F1+2 are also elevated.[148]

Acquired resistance to activated protein C and decreased free protein S levels have been reported in pregnancy and puerperium.[149]Hemostatic changes in pregnancy have been noted to result in a reduction in venous flow velocity of up to 50% occurs in the legs by 25 to 29 weeks of gestation and continues until at least 6 weeks after delivery predisposing to VTE.[150]

Women with inherited thrombophilias tend to have even a higher a risk for VTE during pregnancy and the postpartum.[151]

2.2.2 Endothelial Injury

Endothelial dysfunction is now regarded as the most important component of Virchow's triad due to its ability to interact and influence the other constituents of hemostasis.[152] The endothelium that is intact plays an important role in maintenance of a patent vasculature and blood fluidity by protecting against vascular injury. Under normal physiological function the intact endothelium is antithrombotic and inhibits platelets activation and adhesion.[152] It also promotes vasodilatation and fibrinolysis. The endothelium produces prostacyclin, nitric oxide and an ectonucleotidase CD39 which prevent thrombus formation.[153,154,155]

Endothelial wall disruption or injury results into exposure of collagen and activation of the coagulation cascade resulting in to thrombus formation.

2.2.2.1 Trauma

Major trauma is considered to be a hypercoagulable state and in most instances complicated by venous thromboembolism.[156] Trauma patients at the highest risk of developing VTE include those with brain injury, spinal cord injury, pelvic fracture and lower extremity fractures. In the absence of thromboprophylaxis deep-vein thrombosis and pulmonary embolism are common complications of major trauma.[157]

DVT rates in major trauma exceed 50% without thromboprophylaxis.[158] In major trauma patients who survive beyond the first day of admission, PE is estimated to be the third leading cause of mortality.[156]Autopsy studies on fatally injured patients have reported high DVT prevalence rates of up to 65 % and PE prevalence of up to 20%.[159]

Trauma results in the exposure of collagen and tissue factor to blood components triggering platelets activation, generation of thrombin and formation of fibrin from fibrinogen. High levels of tissue factor and markers of thrombin generation have been reported in trauma patients.[160] Levels of antithrombin III, Protein C and protein S have also been found to be consistently low in trauma patients.[160]

2.2.2.2 Surgery

Deep vein thrombosis and pulmonary embolism are often common complications in patients undergoing major surgery.[161] Without thromboprophylaxis patients undergoing major surgery are estimated to have up to 20-fold risk of developing venous thromboembolism.[1] Pulmonary embolism remains the most common preventable cause of mortality in patients undergoing major surgery.[162]

In the absence of thromboprophylaxis rate of VTE is estimated to be 20–25% in patients undergoing general surgery and 45–60% for orthopedic surgery involving the hip or knee.[161] In patients undergoing major surgical procedures prevalence of DVT is estimated to be approximately 20% while that of PE is 1% to 2 %.[163] In orthopedic patients prevalence of DVT is even higher at 50% and PE at 30% without thromboprophylaxis.[164]

Mechanism of VTE in major surgery is similar to that described above in major trauma patients. Endothelial damage exposes blood to collagen and tissue factor which then activate the coagulation cascade leading to VTE.In addition General anesthesia has been documented to induce hypoxic endothelial activation and a prothrombotic state through reduction of blood flow to the lower limbs.[165]

2.2.2.3 Central venous catheterization

Central venous catheters (CVCs) play an important role in the management of critically ill patients. The most frequently used sites for central venous cannulation are the internal jugular, subclavian and femoral veins. Central venous catheterization has been associated with a high risk of developing deep venous thrombosis.[166]

Improved sterile techniques and use of less thrombogenic modern polyurethane catheters compared to the old polyvinyl and polyethylene catheters has resulted in a reduction in rate of catheter related venous thrombosis.[167]

Patients with femoral catheters are estimated to have on average, a six fold increased risk of iliofemoral DVT.[168] In patients where femoral triple-lumen and dialysis catheters are used, prevalence rate of a proximal lower limb DVT is estimated to be 25% by duplex ultrasound.[169]

In view of the high prevalence of DVT in patients with femoral vein catheters, ultrasound screening of the lower limb should be considered after removal of catheter.[169]

2.2.3 Vascular stasis

Blood stasis plays an important role in the initiation and propagation of venous thromboembolism. Various autopsy studies have shown that in hemiplegic stroke patients venous thrombosis is more common in the immobilized limb.[170] Autopsy studies have also revealed a high prevalence of venous thrombosis in individuals bed-ridden for more than 1 week before their death.[171]

The high rate of VTE associated with, hospitalization, paralysis, immobility, obesity, pregnancy, cancer, surgery, age and long-haul travel is attributable partly due to stasis and reduced blood flow.[172]

Several mechanisms have been proposed to explain how stasis promotes a prothrombotic state. The endothelial cells are primarily oxygenated by blood in the vessel lumen. Evidence suggests that stasis causes hypoxic injury to the endothelium as result of hemoglobin desaturation.[173]

Endothelial cells express P-selectin that allow binding of tissue factor-bearing microparticles from monocyte/macrophage cells and eventual activation of the coagulation cascade and thrombosis.[173]

2.2.3.1 Immobility

Immobility is an important risk factor in the development of venous thromboembolism. A number of conditions can predispose to immobility. Hospitalization for paralysis following acute stroke, decompensated heart failure, limb fracture, advanced cancer, comatose states and following surgery are all conditions associated with immobility. Long travel is also associated with long periods of immobility.

In the MEDENOX study immobile patients in the placebo group had a 20.3% incidence of VTE.[3] An autopsy study conducted by Gibbs found 15% incidence of VTE in patients on bed rest for less than 1 week and up to 80% in patients in bed for longer periods.[171]

Calf muscles in the legs act as pumps and return blood from the venous system of the lower limbs to the heart. The valve sinuses in large veins are prone to thrombosis because of low oxygen tension, especially during immobilization.[174]

2.2.3.2 Stroke and Paralysis

VTE is one of the most frequent complications occurring in patients with acute ischaemic stroke. In a study conducted by Warlow *et a*l involving stroke patients with paralyzed limbs, prevalence of asymptomatic DVT was found to be 60% in paralyzed limbs compared with 7% in the non-paralyzed limbs.[170] Incidence of symptomatic DVT in these patients is about 5% while confirmed PE can be detected in approximately 2% of patients in absence of thromboprophylaxis.[175]

It is estimated that about 5% of all deaths occurring early after acute ischaemic stroke are attributable to PE.[176] In a prospective cohort study by Goldstein *et al* involving 988 patients with intracerebral hemorrhage, incidence of symptomatic VTE at 90 days was 2.9%.[177]

2.2.3.3 Heart Failure

Hospitalized heart failure [HF] patients are at increased risk of developing VTE. Thrombo-embolic risk is due to a variety of mechanisms including stasis of blood due to dilatation of cardiac chambers, reduced myocardial contractility, decreased mobility and increased intracardiac and central venous pressures.[178,179] Studies have shown a correlation between degree of left ventricular dysfunction and risk of VTE.

As discussed above, a study by Howell *et al* reported a 38.3 fold risk of VTE in chronic heart failure patients with ejection fractions lower than 20%.[96]

2.2.3.4 Traveler's Thrombosis

Prolonged travel of any form has been linked to venous thromboembolism.[180] VTE associated with any form of prolonged travel is now termed 'traveler's thrombosis'.[181] The first report on the association between long travel and DVT was presented in 1954 and termed "economy-class syndrome".[182] It was thought that passengers in economy class on long distance flights with restricted space to moves their legs were prone to develop DVT as a result of blood stasis.

In recent years, the World Health Organization (WHO) through panel of experts acknowledged in 2001 an association between air travel and VTE.[183] The syndrome has since been described in first- or business-class passengers and prolonged overland journeys.[180]
Up to 75% of air travel related VTE has been linked to immobility during long-distance flights.[184]

A randomized controlled trial by Scurr *et a*l involving 231 subjects reported an incidence of 10% of asymptomatic calf vein thrombosis in air travelers above 50 years of age traveling for more than 8 hours.[185] The study revealed that individuals wearing compression stockings had no evidence of DVT on subsequent duplex ultrasonography while 10% of untreated individuals developed asymptomatic DVT.[185]

Despite the findings above, it is generally agreed that clinically significant VTE after long travel is rare.[186]Traveler's thrombosis appear to affected individuals with known risk factors described above like previous history of DVT,elderly,oral contraceptive use ,pregnant, cancer and known thrombophilia.

2.2.3.5 Age

Old age is a known risk factor for VTE. Risk factors for VTE in old age are multiple. Generally old age is associated with Sedentarism and restricted movement. Patients over 40 years of age are at increased risk of developing VTE than younger patients with risk approximately doubling with each decade thereafter.[187]

2.3 Complications of VTE

2.3.1 Pulmonary embolism (PE)

Pulmonary embolism is the most acute, serious, potentially life-threatening complication of DVT.[188] PE associated with DVT is the most common cause of preventable hospital death.[188] In the United States of America it is estimated that up to 300,000 people die each year from PE complicating DVT.[189] In a study by Kakkar *et al* , 4 out of 9 patients who had proximal DVT detected by ultra sound scan subsequently developed PE diagnosed clinically.[190] Another study by Cogo *et a*l revealed that up to 99% of patients with proximal DVT also had calf vein thrombosis suggesting that most thrombi originated in the calf.[191]

In the absence of thromboprophylaxis it is estimated that up to a third of patients with symptomatic, distal DVT develop proximal limb DVT.[192] Recent studies have shown that patients with PE demonstrate a 3 month all-cause mortality ranging between 15% and 30%.[193]

2.3.2 Chronic thromboembolic pulmonary hypertension (CTEPH)

As many as 4% of patients with PE tend to develop chronic thromboembolic pulmonary hypertension (CTEPH).[194] CTEPH is a complication of acute and recurrent pulmonary emboli causing obstruction to the large pulmonary arteries followed by lysis and organization of the blood clots.[195]

Patients with CTEPH present with exertional dyspnea as the main symptom. Late features of the disease include syncope attacks related to low cardiac output as a consequence of high pulmonary artery pressure.[196]

2.3.3. Post thrombotic syndrome (PTS)

Post-thrombotic syndrome (PTS) formerly called post-phlebitic syndrome is a significant complication of DVT that is often overlooked. PTS usually manifests as chronic leg pain, swelling, skin induration, edema and hyperpigmentation.[197] In severe form it is characterized by painful intractable venous leg ulcers and decreased mobility.[198]

A number of studies have revealed that most cases of PTS become clinically apparent within 1 to 2 years after initial acute episode of DVT.[199] Its estimated prevalence is between 17 to 50 %.[199] PTS is usually characterized by venous hypertension as a result of venous valve damage and reflux.[200]

2.3.4 Recurrent thromboembolism

The incidence of long-term recurrent thromboembolism is high in patients with malignancy and in those with either hereditary or acquired thrombophilia.[201] Studies has shown that individuals with factor V Leiden have a fourfold increase in risk of recurrent events. In a study by Simioni and colleagues, cumulative incidence of recurrent thromboembolism in carriers of factor V Leiden mutation after 8 years was 39.7% compared to 18.3% in patients without this mutation.[202]

Recurrent VTE tend to be extremely uncommon in patients with temporal risk factors for DVT such as acute infection, surgery and trauma.[203]

2.4 Diagnosis of DVT

Diagnosis of DVT relies upon eliciting symptoms, signs, risk factors from a good medical history and physical examination complimented by investigative procedures. However up to 50% of patients who have VTE do not present with any symptoms.[204] Patients with symptomatic DVT can present with pain, swelling, tenderness along the distribution of the deep leg veins, erythema, or cyanosis. Important risk factors for venous thrombosis as described above include, recent hospitalization, prolonged, immobilization, pregnancy and the puerperium, use of hormonal agents, Obesity, long distance flights, malignancy, recent major surgery or trauma, and known thrombophilia.

In patients suspected to have DVT, pretest probability scoring system such as the Wells score for DVT can be used for screening.[206]The Wells score for DVT and various imaging techniques are discussed in details below.

2.4.1 Well's score for DVT

In 1995, Wells and colleagues developed a clinical pretest predictive scoring system for DVT called the Wells score for DVT.[205] This pretest probability score is based on clinical signs, symptoms and risk factors.[206] Components of the Wells score are shown in table 1 below.

Using the Wells score patients with a score of ≥ 3 are classified as high risk, those with a score of 1 or 2 as moderate risk and those with a score of ≤ 0 as low risk. Well's score is further used to stratified patients into categories of DVT likely if the clinical score is more than 1 and DVT un likely if the score is 1 or less.[206]

Cohort studies have showed that patients classified as low risk by Wells score and having a negative D-dimer test can be excluded from having DVT.[207]
Follow up studies have further shown that less than 2% of patients with a low pretest probability and a negative D-dimer develop symptomatic DVT in 3 months.[208]
Table 1 below shows the components of the Wells score for DVT.

Table 1.Wells Score for DVT[206]

Clinical Findings	Points
Paralysis, paresis or recent orthopedic casting of lower extremity	1
Recently bedridden (> 3 days) or major surgery within past 4 weeks	1
Localized tenderness in the deep veins	1
Swelling of entire leg	1
Calf swelling 3 cm greater than other leg (measured 10 cm below the Tibial tuberosity	1
Pitting edema greater in the symptomatic leg	1
Collateral non-varicose superficial veins	1
Active cancer or cancer treated within 6 months	1
Alternative diagnosis more likely than DVT (Inguinal lymphadenopathy, Cellulitis, external venous compression, muscle damage, post-phlebitic Syndrome, superficial venous thrombosis, Baker's cyst)	-2

2.4.2 Doppler compression venous ultrasound scan

Doppler compression ultrasound with real-time, B-mode imaging is now the preferred choice of imaging DVT in patients with high or moderate pretest probabilities.[209] Amongst its advantages includes its noninvasive nature, reliability, availability and safety.[210] The major diagnostic criterion for venous thrombosis by compression ultrasound scan is demonstration of venous non compressibility.[210]

A study conducted by Kearon *et a*l showed that compression B-mode ultrasonography with or without color duplex imaging has a sensitivity of 95% and a specificity of 96% for diagnosing

symptomatic, proximal DVT.[211] The sensitivity and specificity for calf vein DVT were much lower ranging between 60% and 70%.[211]

One short coming of compression ultrasound is that it is not specific or sensitive for the detection of DVT in patients with asymptomatic proximal DVT as well as symptomatic or asymptomatic calf DVT.[210] In addition its accuracy in obese and edematous patients is limited.[212]

2.4.3 Contrast venography or phlebography

Contrast venography or phlebography is the reference gold standard for the diagnosis of both proximal and calf DVT.[213] Venography is nearly 100% specific and sensitive.[210] Venography is now not widely used due to its invasive nature of injecting contrast medium.[210] This makes it contraindicated in patients with renal insufficiency.

The other drawback of contrast venography is its inaccuracy in visualizing an intraluminal defect in previously thrombosed veins.[213] In situations where noninvasive testing is inconclusive venography is still indicated. A normal venogram has a negative predictive value of 98.1 %.[214]

2.4.4 Magnetic Resonance Venography (MRV)

Magnetic Resonance Venography (MRV) is a noninvasive procedure that does not require contrast media.[215] A notable advantage of MRV over US is that it can be used to evaluate pelvic veins were up to 20% of DVTs are isolated.[216] In addition MRV can be used to visualize extravascular structures compressing on the venous system .A meta-analysis study by Sampson *et al* found that MRV had high sensitivity of 92% and specificity of 95%.[217]

Disadvantages of MRV include that it is relatively expensive not widely availability and not portable. In addition it is contraindicated in patients implanted metal devices that pace makers and metal plates.

2.4.5 D-dimer testing

D-dimers are a degradation product of cross-linked fibrin. D-dimer testing is the preferred test in patients with low pretest probability.[210] D-dimer levels are usually high in confirmed cases of DVT. D-dimers assay testing is recommended as first diagnostic approach for the excluding DVT.[218] As discussed above patients with a negative D-dimer test and having a low risk Wells score can be excluded from having DVT.[207]

D-dimer testing lack specificity in that levels are elevated not only in acute thrombosis, but in other conditions such as Infection, malignancy and pregnancy.[210]

CHAPTER 3

3.0 STATEMENT OF THE PROBLEM

The prevalence of DVT and associated risk factors in medical patients in Zambia are not well documented. In addition thromboprophylaxis for DVT is not routinely given to hospitalized medical patients despite its documented high prevalence, associated morbidity and mortality worldwide.

4.0 STUDY JUSTIFICATION

Medical patients have a high risk of developing both deep vein thrombosis and pulmonary embolism. Studies done in Europe and the USA have shown that up to 70% of symptomatic DVT and PE occur in hospitalized medical patients. In the absence of thromboprophylaxis DVT is linked to an estimated 50% risk of PE.In Europe and the USA, PE is the third most common cause of hospital-related death and the most common preventable hospital-related death.

Disease patterns and life styles in Western countries are very unlikely to be identical to those of African countries and Zambia in particular. Anecdotally, sudden deaths of acutely ill stable medical patients from suspected PE have been reported but only occasionally confirmed by postmortems. True extent of the problem has never been investigated in Zambia.

Knowing the prevalence of DVT and its associated risk factors in medical patients admitted to the University teaching hospital will not only highlight the magnitude of the problem but will be a basis to estimate the potential impact of thromboprophylaxis in patients at high risk.

5.0 RESEARCH QUESTION

What is the prevalence of DVT and associated factors are in medical patients admitted to the UTH?

6.0 STUDY OBJECTIVES

The main study objectives were;

I. To determine prevalence of DVT in medical patients admitted to the UTH medical wards for at least 7 days.

II. To document the anatomical distribution of DVT events in medical patients admitted to the UTH

III. To establish demographic and clinical characteristics of medical patients with DVT

IV. To determine the accuracy of the Wells score for DVT in patients diagnosed with DVT at UTH.

CHAPTER 4

7.0 METHODOLOGY

7.1 Study design and setting

We carried out a cross sectional analytical study. The study was conducted at the UTH, a tertiary hospital in Lusaka, Zambia.

7.2 Sample size

We estimated the prevalence of DVT was 26 % on assumption that it would be about twice that found in the MEDENOX study (based on personal observations). Using the prevalence formula[219], sample size was calculated as follows;

$n = Z^2 X (P) X (1-P)/C^2$,
Where, Z=1.96, P= 0.26, C =0.05
N = 296

7.3 Study duration

The study was conducted from 1st July to the 30th of November 2015.

7.4 Case Definition of DVT

DVT was defined as symptomatic or asymptomatic DVT diagnosed by compression US scan.

The inclusion and exclusion criteria were as below;

7.5 Inclusion criteria

I. Patients admitted to medical wards for at least 7 days
II. Age of at least 16 years

7.6 Exclusion criteria

Patient on thromboprophylaxis or anticoagulation therapy prior to enrollment.

7.7 Study population

Medical patients admitted for at least 7 days and meeting the study inclusion criteria were consented and recruited to the study. The criterion of 7 days was selected to allow sufficiently long admission time for the development of DVT in previously ambulatory patients. Purposive sampling was utilized.

7.8 Study Procedure

Patients were enrolled from medical wards at the UTH. A provider initiated counseling and testing for HIV was introduced to recruited patients not yet tested for HIV.

A questionnaire was used to obtain details of the demographic characteristics such age and sex were obtained. In addition, a focused medical history to identify possible risk factors for DVT including recent history of being bed ridden for at least 3 days, previous documented DVT, paralysis, active cancer, swollen leg, contraceptive use, pregnancy, puerperium and major surgery in the last 12 weeks was obtained.

Physical examination to identify features suggestive of DVT or alternative diagnosis such as swelling of the legs, pitting edema, localized tenderness of swollen limb and collateral superficial veins was conducted.

In addition BMI and details of admission diagnosis were obtained.

Blood samples were collected to test for hemoglobin, white cell count, platelet count and CD4 count. The Wells score was calculated from parameters obtained from medical history and physical examination to determine pretest predictive score for DVT.

A compression ultrasound scan was done on both lower limbs of recruited patients.

7.9 Ethical approval

Ethical approval was granted by the University of Zambia (UNZA) Biomedical Research Ethic Committee (UNZABREC).Permission was also sort from the UTH Management and the department of Medicine. The study was undertaken following into the Helsinki declaration[223] Figure 3 below shows a schematic presentation of our study.

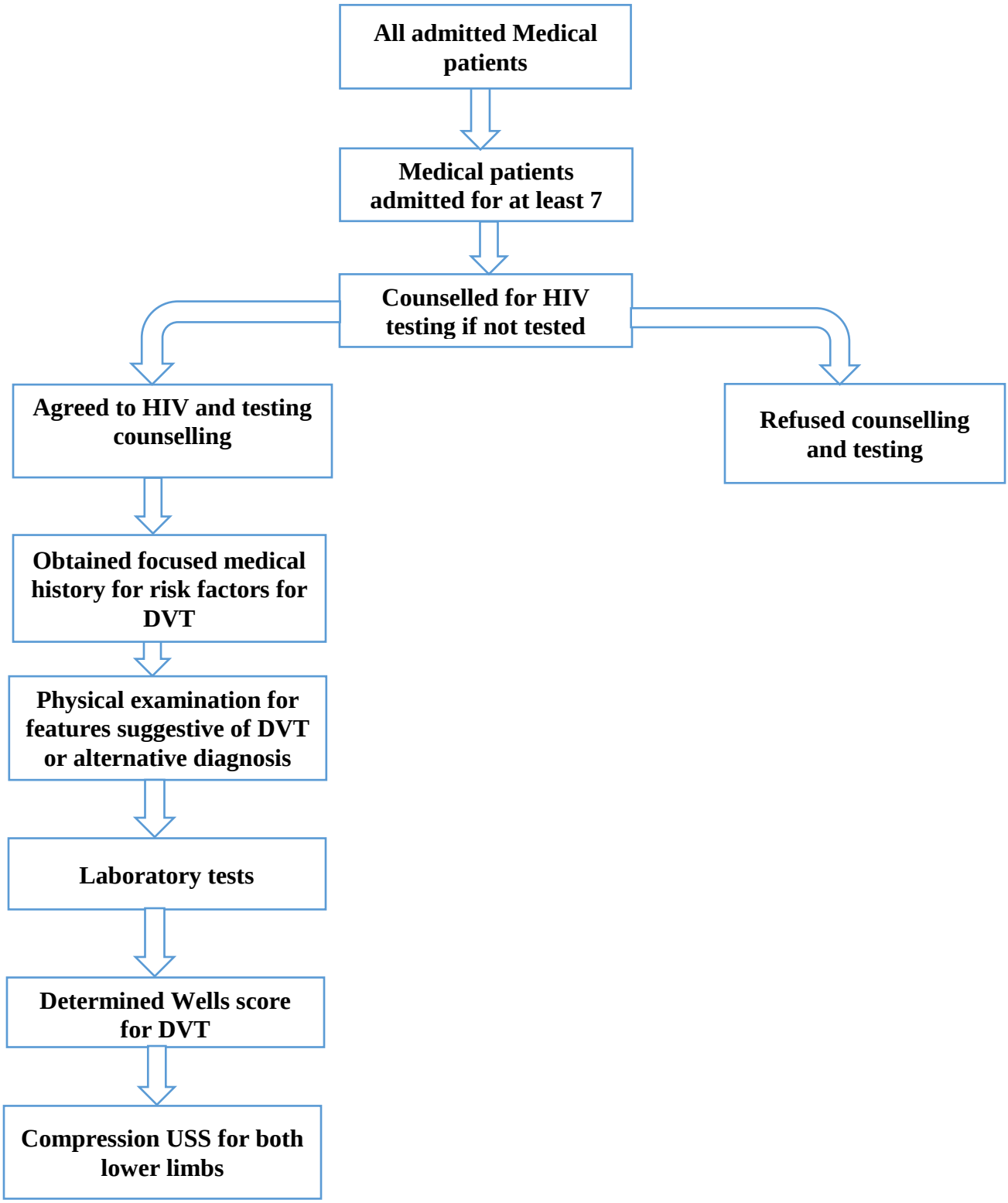


Fig 3.Study flow chart

7.9 Dependent variables

The following were the dependent variables;

1. Presence of DVT confirmed by compression ultrasound scan
2. Anatomical location of DVT

7.10 Independent variables

Independent variables included Age, Sex, HIV status, recent immobilization and duration, recent surgery in last 12 weeks. Others included previous history of DVT, family history of DVT, known malignancy, drug history, Glasgow coma scale, body mass index, hemoglobin, platelet count and Wells score for DVT.Primary diagnosis and comorbid diagnoses were also recorded as independent variables. Biochemical and genetic markers of hypercoagulable state such as homocysteine, protein C, protein S,antithrombin III, anticardiolipin antibodies, lupus anticoagulant and anti-β2 glycoprotein I antibodies, mutations for factor V Leiden (Arg506Gln) and prothrombin gene (G20210A) where not done in this study due to financial constraints

7.11 Data entry and analysis

Demographic and clinical details were entered in Microsoft excel spread sheets 2013 version. Data analysis was done using SPSS 16.0.

Normally distributed continuous variables were described as means and standard deviation and compared by t-test.
Continuous variables not normally distributed were described as medians, Interquartile ranges and compared by Kruskal-Wallis test.
Categorical variables were described as frequencies and percentages. Comparisons were made by Chi- square and fisher's exact test where applicable.

A step-down multivariate logistic regression was used to determine variables of significant association from the Virchow's triad and the primary outcome of interest.

Sensitivity, Specificity and Accuracy, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of the Wells score for DVT were then computed using formulae outlined below.[221'222]

$$\text{Sensitivity}(\%) = \frac{TP}{TP + FN} \times 100$$

$$\text{Specificity}(\%) = \frac{TN}{TN + FP} \times 100$$

$$\text{PPV}(\%) = \frac{TP}{TP + FP} \times 100$$

$$\text{NPV}(\%) = \frac{TN}{TN + FN} \times 100$$

$$\text{Accuracy}(\%) = \frac{TP + TN}{TP + TN + FP + FN} \times 100$$

where,

- **TP** = True Positive
- **FP**= False Positive
- **TN** =True Negative
- **FP** =False Negative
- **PPV=** Positive Predictive Value
- **NPV=** Negative Predictive Value

CHAPTER 5

8.0 RESULTS

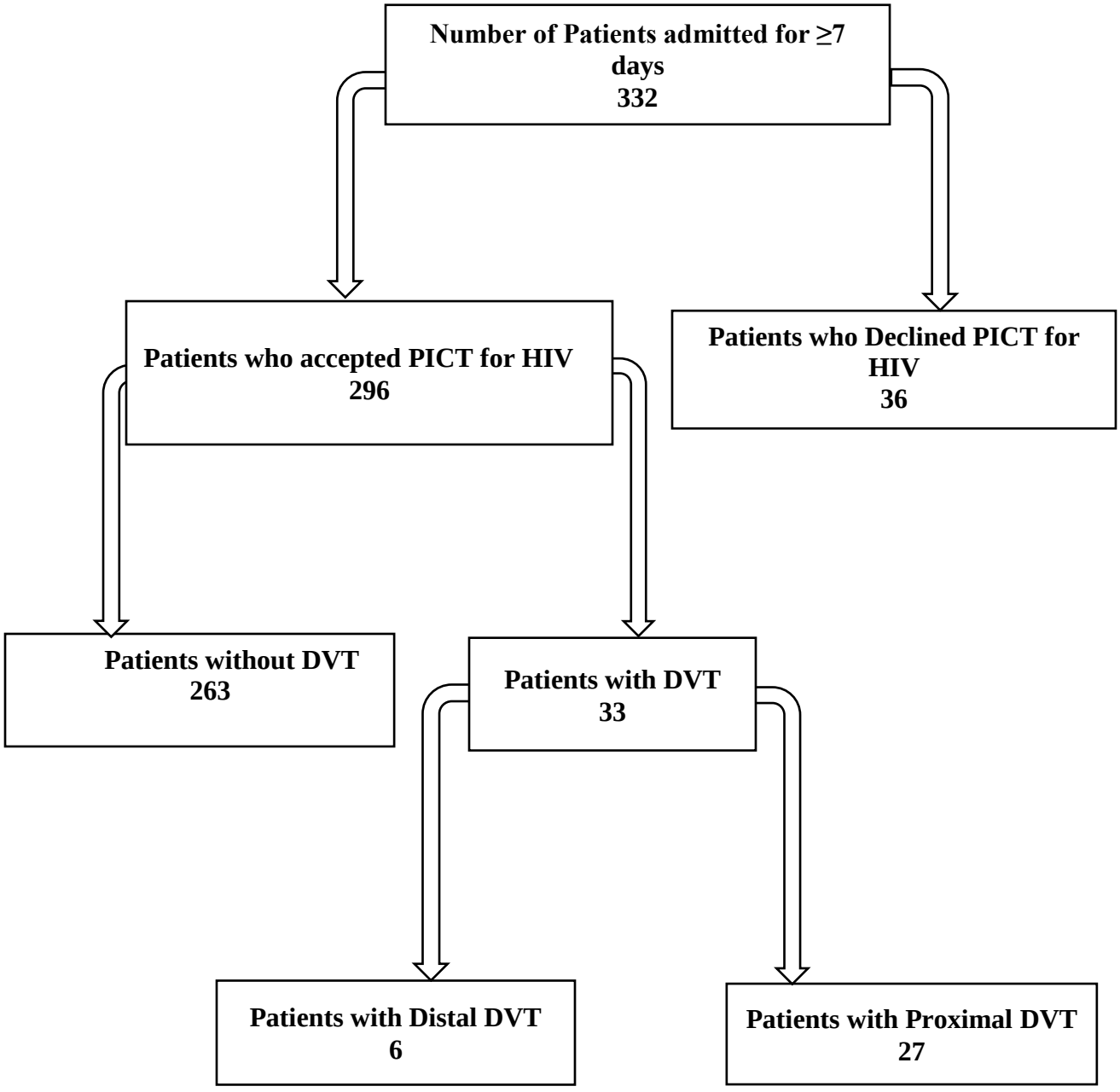


Figure 4.Schematic presentation of results

8.1 Demographic and clinical characteristics

Table 2. Baseline clinical characteristics of recruited patients

Variable	n=296	Percentage (%)
Male	140	47.3
HIV Positive	173	58.4
Patients on ART	128	43.2

Table 3. Primary Diagnosis of recruited patients

Primary Diagnosis	n =296	Percentage (%)
Infectious Disease	156	52.7
Heart Failure	51	17.2
Renal Failure	23	7.8
Active Malignancy	20	6.8
Stroke	11	3.7
Microcytic Anaemia	8	2.7
Diabetes Mellitus	8	2.7
Others	19	6.4

A total number of 332 patients were identified for possible recruitment to the study. Thirty six patients declined to give consent to undergo provider initiated counselling and testing (PICT) for HIV. Female patients accounted for 52.7 % (156/296) of all patients recruited to the study. Fifty two percent (154/296) of all recruited patients were aged 40 years or more.

Although majority of recruited patients were HIV positive, only 43.2 % (128/296) were on antiretroviral therapy (ART). Two patients had defaulted ART. The majority of HIV positive patients had at least a World health organization (WHO) clinical stage 3 condition (140/173).

Twenty five percent (44/173) of all HIV positive patients did not have records of their CD4 counts. Of all the HIV positive patients recruited to the study, 49 % (85/173) had a CD4 count of less than 200 cell/ml.

Infectious diseases were the most common primary diagnosis in the patients recruited to this study. The diagnoses were made by the attending physicians. Tuberculosis was the most common infectious disease accounting for 66 % (103/156) of all infections. Other common infectious diseases were acute bacterial meningitis and cryptococcal meningitis accounting for accounting for 12.2 % (19/156) and 7.7% (12/156) respectively.

Of all patients with heart failure, 43.1% (22/51) had dilated cardiomyopathy (DCM).The second most common diagnosis amongst patients with heart failure was hypertensive heart disease (HHD).

Active malignancy accounted for 6.8 % (20/296) of all primary diagnoses. Hematologic malignancies and Kaposi's sarcoma were the commonest malignancies accounting for 3 % (6/20) and 2.5 % (5/20) respectively.

Only 3.7 % (11/296) of all recruited patients were obese.

None of the patients recruited to our study had a previous history of DVT. No family history of DVT was noted in any of the patients.

None of the women recruited to our study had a history of using oral contraceptives or any form of hormonal replacement therapy.

There was no history of recent surgery noted in any of the patients in this study

Forty one (13.9%) patients recruited to our study had a history of smoking.

Anaemia was present in over seventy percent (210/296) of all the patients in our study. Of all male patients, 110 (79.7%) had a haemoglobin below 15g/ml. A total of 100 (64.5%) of all female patients had a haemoglobin of less than 13g/ml.

Thrombocytosis was noted in 11.8 % (35/296) of all patients in this study. Leukocytosis was present in 23.6 % (70/296) of all patients recruited to this study.

8.2 Prevalence of DVT

The prevalence of DVT in our study population was 11.1 % (33/296) as illustrated in Pie chart in figure 5 below. Compressible, hyperechoic, very sluggish venous blood flow was noted in 25 patients (9%) recruited to our study.

Bilateral lower limb DVT was observed in 9(27%) of all patients with DVT. Only 5 patients (16%) out of 33 had symptomatic DVT. Figure 4 below shows prevalence of DVT.

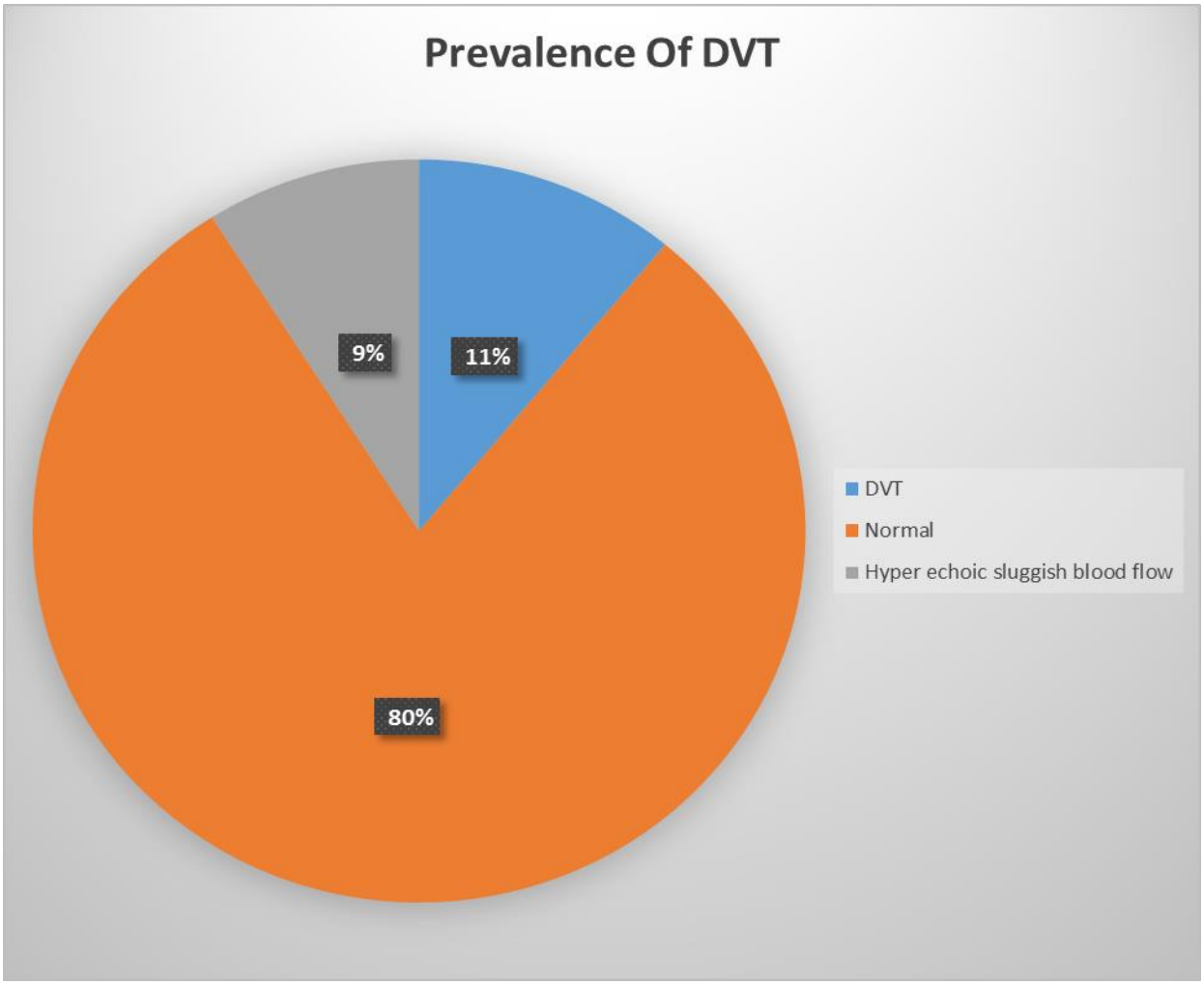


Figure 5. Prevalence of DVT

8.3 Demographic and clinical characteristics of patients with DVT

DVT was more common in the age group, 40 years and more accounting for 60.6% (20/33) of all patients with DVT. None of the obese patients recruited to our study had DVT.

Eighty one percent (n=27) of all patients with DVT had been admitted in hospital for 7 to 14 days. Patients with DVT admitted for more than 14 day accounted for 18.2 %(6/33).The majority of patients with DVT, accounting for up to 87.8 %(29/33) gave a history of having

being immobile for more than 3 days prior to hospital admission. Only 5((15.1%) patients with DVT had a history of smoking. Of all patients with DVT, 51.5% did not have a record of CD4 count. Thirty nine percent (13/33) had a CD4 count of 200 cells/ml and below.

Eighty two percent (27/33) of all patients with DVT had anaemia as classified by age and sex. The mean haemoglobin was 8.64 (SD 3.10).Eighty percent (12/15) of all male patients were anaemic with a haemoglobin of less than 13g/dL. Of all female patients with DVT, 83 % (15/18) had anaemia with haemoglobin of less than 11g/dL.

Most of the patients with DVT had a normal platelet count accounting for 63.6 % (21/33).Only 2 patients with DVT had thrombocytosis while 10(30.3%) had thrombocytopenia. Leukocytosis was present in 27.3 % (9/33) of all patients with DVT.There remainder (24/33) had a white cell count of 11 cells/ ml and below. Table 3 below shows details of the clinical characteristics of the patients with DVT.

Table 4.Baseline clinical characteristics of patients with DVT

Variable	n=33	Percentage
Male	15	45.5
HIV Positive	23	69.7
Patients on ART	19	57.6

Table 5.Primary Diagnoses in patients with DVT

Primary Diagnosis	n =33	Percentage (%)
Infectious Disease	22	66.7
Heart Failure	6	18.2
Diabetes Mellitus	2	6.1
Active Malignancy	1	3.0
Stroke	1	3.0
Microcytic Anaemia	1	3.0

8.4 Anatomical location of DVT

The prevalence of proximal lower limb DVT was 9.1% (27/296) in our study. Eighty two percent (27/33) of all patients with DVT had proximal lower limb DVT. Majority of proximal lower limb DVT was located in the common and superficial femoral veins. Only 4 patients had iliac vein DVT. Figure 6 below shows anatomical distribution of lower limb DVT by bar graph.

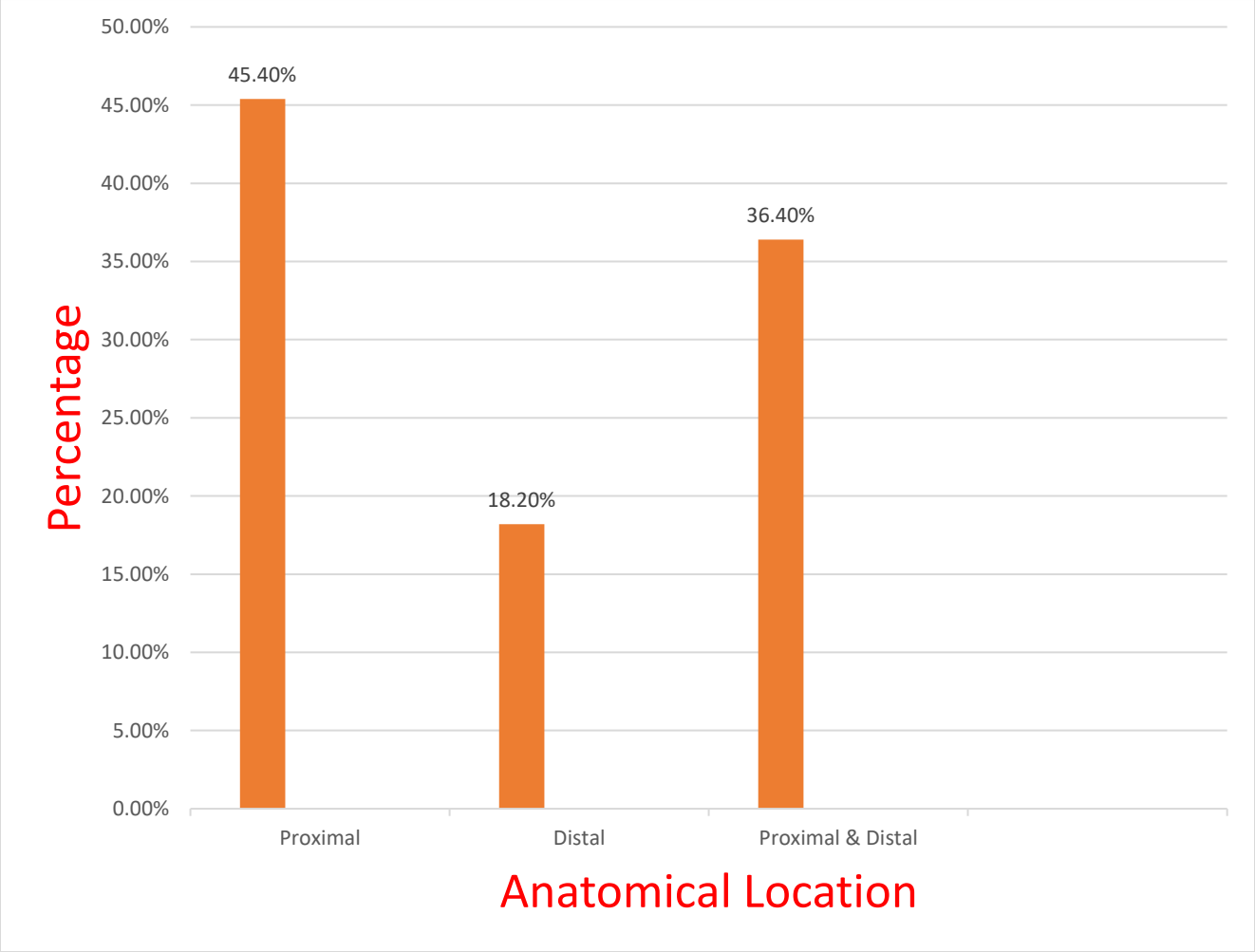


Figure 6.Anatomical location of DVT

8.5 Comparison of Demographic and clinical characteristics

Table 6.Comparative descriptive characteristics of patients with and without DVT

Variable	DVT(n = 33)	No DVT(n=263)	p
Age, years, mean (SD)	42.1 (12.7)	42.0 (16.8)	0.98
Male, n (%)	15 (45.5)	125 (47.5)	0.82
BMI, mean (SD)	18.73 (4.0)	20.6 (4.7)	0.03
Total days of immobility, mean (SD)	24.0 (12.8)	21.8 (11.9)	0.33
HIV+, n (%)	23 (69.7)	150 (57.0)	0.16
Haemoglobin, g/dL, mean (SD)	8.6 (8.1)	9.4 (3.5)	0.44
Platelet count, mean (SD)	197 (17)	231 (137)	0.17
Primary Diagnosis			
Tuberculosis	20 (60.6)	83 (31.6)	0.002
Heart failure	6 (18.1)	45 (17.1)	0.88
Renal failure	2 (6.0)	21 (8.0)	0.70

The difference in the mean BMI between patients with and without DVT was significant (p = 0.03). The patients with DVT had a lower BMI compared to those without DVT. Primary diagnosis of tuberculosis was statistically significant between the two groups (p=0.002).In terms of percentage proportions ,tuberculosis was more common among patients with DVT compared to those without DVT.There rest of the variables representing demographic and clinical characteristics of patients with DVT and without DVT did not differ significantly as shown in table 6. Platelet count was further sub-classified into three classes namely:

- Low platelet count(Less than 150 x 10^9/L)
- Normal platelet count(150-400 X 10^9/L)
- High platelet count (More than 400 x 10^9/L)

Sub-analysis of the platelet classes did not show any association with DVT.

8.6 Association between DVT and independent variables

Table 7.Multivariate and univariate logistic regression for variables of interest

Variable	Unadjusted Odds Ratio (OR)	95% CI Lower and Upper limits	Adjusted Odds Ratio (OR)	95% CI Lower and upper limits
Sex	0.920	0.445 - 1.903	1.298	0.369 - 4.573
Age group >40 years old	0.562	0.268 - 1.177	0.517	0.156 -1.719
HIV Status	0.577	0.264 - 1.261	0.682	0.568 - 1.368
CD4 count ≤200 cells/ml	2.287	0.614 - 8.523	2.568	0.644 - 10.239
HAART	0.758	0.544 - 1.055	0.276	0.035 - 2.178
Hospital admission of >15 days	1.729	0.686 - 4.360	1.296	0.300 - 5.607
Immobility >3 days prior to admission	0.429	0.145 - 1.266	1.023	0.181 - 5.771
Haemoglobin >13g/dl	1.110	0.406 - 3.035	1.962	0.209 - 18.436
Platelets count >400 cell/ml	1.299	0.712 - 2.369	2.068	0.775 - 5.522
White cell count >11000 cells/ml	0.804	0.355 - 1.823	0.553	0.142 - 2.152
Infectious Disease	2.078	0.969 - 4.456	0.710	0.181 - 2.781
Smoking	0.888	0.322 - 2.449	0.530	0.095 - 2.944

The multivariate and univariate logistic regression of variables of interest in the two groups did not show any associated with DVT.

8.9 Wells score risk stratification for DVT

Table 8. Pretest probability for risk of DVT by Wells score

Wells score	Frequency	Percentage
≥3 (High risk)	22	66.7
1-2 (Moderate risk)	11	33.3
≤0 (Low risk)	0	0

By Wells score risk stratification, 66.7 %(22/33) were classified as high risk for DVT, while 33.3 %(11/33) were classified as moderate risk. The pretest risk stratification correlated well with the eventual USS diagnosis of DVT

8.10 Wells score specificity, sensitivity, accuracy, positive and negative predictive values

Table 9. Compression USS scan findings and Wells score for DVT

Compression Ultrasound scan findings	**Wells Score for DVT classification**		**Total Number of Patients**
	DVT Likely	**DVT Unlikely**	
DVT Present	**33**	**0**	**33**
No DVT Present	**70**	**193**	**263**

From our study, the Wells score specificity for DVT was 73.4% while the sensitivity was 100%. The calculated accuracy of the scoring system for our population was 76.3%. The positive and negative predictive values were 32% and 100% respectively.

CHAPTER 6

9.0 DISCUSSION

The prevalence rate of DVT in our study of 11.1% falls within the range found in the three major randomized controlled studies, namely MEDENOX, PREVENT and ARTEMIS.[3,6,7]The prevalence rate for VTE in the three studies ranged between 4.96 to 14.9 % in the placebo groups. Patients with DVT had a lower mean BMI and were more likely to be admitted with a diagnosis of tuberculosis. A low likelihood Wells score (0 or 1) had 100% negative predictive value for excluding DVT

The definition of VTE in our study differed from that in the three studies. In the three studies VTE was defined as asymptomatic DVT, symptomatic DVT, symptomatic PE and fatal PE. [3,6,7] In our study VTE was defined as asymptomatic or symptomatic proximal and distal lower limb DVT diagnosed by compression USS .Our study did not screen for pulmonary embolism. I Hyperechoic, sluggish blood flow was noted in 25 individuals. This may suggest either developing or resolving DVT. If the 25 patients with hyper-echoic sluggish compressible venous blood were to be diagnosed as developing DVT, the prevalence for DVT will rise up to 18.9%.This prevalence rate will slightly be higher than that found in the MEDENOX,PREVENT and ARTEMIS studies.

The MEDENOX study using venography to diagnose DVT found prevalence of 14.9% in the placebo group.[3] Compression USS was used in the PREVENT study and prevalence of VTE was 4.96% in the placebo group.[7] In the PREVENT study, only proximal lower limb DVT was considered significant. The ARTEMIS study employing venography to diagnose DVT found the prevalence of VTE of 10.5% in the placebo group.[6]

The prevalence of proximal lower limb DVT of 9.1% in our study was higher than that found in the ARTEMIS, MEDENOX and PREVENT studies. In the ARTEMIS study prevalence of proximal lower DVT was 3.4%.[6] The MEDENOX and PREVENT studies found prevalence rate of proximal DVT of 6.6% and 5.0% respectively.[3,7]

All the patients diagnosed with DVT were treated and followed up using American College of Chest Physicians (ACCP) guidelines for management of DVT and PE[224] that have been adopted at the UTH.

The clinical and demographic characteristics of patients in our study differed in a number of aspects from those recruited in the ARTEMIS, MEDENOX and ARTEMIS studies. The patients with DVT in our study were relatively younger compared to those in the three major studies. In the MEDENOX and PREVENT studies minimum recruitment age was 40 years. .[3,7] In the ARTEMIS study , 60 years was the minimum age of recruitment. .[6] Forty eight percent (141/296) of the patients in our study had age of 40 years or more. Among the patients with DVT, 60.4 %(20/33) were 40 years or older.

The patients recruited to our study had lower Body Mass Indices (BMI) compared to those recruited in the 3 major VTE studies. The mean BMI in our study was 20.4 (SD 4.7).The BMIs in the ARTEMIS, MEDENOX and PREVENT studies were 25.8 (S.D 5.6), 25.0 (SD 6.2) and 27.4(SD 5.9) respectively. .[3,6,7] In our study, 3.7 %(11/296) of the recruited patients were obese. The low average BMI in our patients could be attributed to chronic ill health and adult malnutrition. In the MEDENOX and PREVENT studies, prevalence of obesity was 20.1 % (222/1102) and 30.2 % (1118/3706) respectively. .[3,7] The p-value of 0.03 for the means of BMI between patients with and without DVT was statistically significant. Patients with DVT had a lower mean BMI of 18.73 compared to those without DVT with mean BMI of 20.64. It is possible that low BMI was a marker of chronic debilitating illness that predisposed to DVT formation. DVT in our patients could be attributed to other markers of hypercoagulable state other than obesity. None of the obese patients (11/296) in our study had DVT. Tuberculosis was statistically associated with a high likelihood of developing DVT (P=002).
Acute infectious disease was the most common reason for hospital admission in patients recruited to our study accounting for 52.7% (156/296) of all primary diagnoses. It was followed by heart failure and renal failure accounting for 17.2 %(51/296) and 7.8 %(23/296) respectively.

In the ARTEMIS study, acute infectious or inflammatory disease was the commonest condition making up 25.2 %(214/849).[6] Congestive heart failure and acute respiratory disease accounted for 24.9 % (212/849) and 19.7 % (167/849) respectively.[6]

Acute respiratory failure was the most common primary diagnosis making up 53.4 % (589/1102) of all primary diagnoses in the MEDENOX study.[3] Acute infectious disease and congestive heart failure made up 53 % (584/1102) and 34.1(376/1102) of primary diagnoses respectively.[3]

Acute congestive heart failure made up 51.4% (1905/3706) of the primary diagnoses in the PREVENT study.[7] Infectious disease and respiratory failure followed, accounting for 36. 7(1360/3706) and 30.2 % (1121/3706) respectively.[7]

In our study, 66.7 % (22/33) of all patients with DVT had acute infectious disease as the primary diagnosis. This was followed by heart failure accounting for 18.2 % (6/33) and renal failure 6 % (2/33).Tuberculosis accounted for 80% of all infectious diseases in patients with DVT.

Up to 58% (173/296) of all patients in our study were HIV positive with 43.2% (128/296) on anti-retro viral therapy (ART).Seventy percent (23/33) of all patients with DVT were HIV positive and of these 57.6 % (19/33) were on ART. HIV was however not significantly associated with DVT. In the MEDENOX study patients who were HIV positive were excluded from the study. It was not clearly stated whether or not HIV status was part of the inclusion or exclusion criteria in the ARTEMIS and PREVENT studies.

Anaemia was a common finding in patients recruited to our study. By haemoglobin alone majority of patients in our study had a lower threshold for venous thromboembolism as revealed in the literature review. It can be argued be that the low haemoglobin in the majority of our patients might account for a relatively lower prevalence of DVT than predicted. The anaemia in majority of patients in this study could be attributed to chronic ill health and malnutrition.

Up to 82% of DVT in our patients was proximal. This finding implies that without thromboprophylaxis, majority of our patients with DVT are prone to pulmonary embolism. Unlike the above- referenced clinical trials, we did not routinely perform any imaging tests to rule out pulmonary embolism. Thus, the real prevalence of combined lower extremity DVT plus pulmonary embolism may have been much higher.

The univariate and multivariate regression analysis for independent variables in our study did reveal any associations with DVT. Our study did not investigate all independent variables associated with hypercoagulable states due to financial constraints.

These include,homocysteine,protein C, protein S,antithrombin III, anticardiolipin antibodies, lupus anticoagulant ,anti-β2 glycoprotein I antibodies and genetic studies for factor V Leiden and prothrombin gene mutations.

The sensitivity and specificity for Wells score for likelihood of DVT in our study were 100% and 73.4%.These findings correlated well with the eventual USS diagnosis for DVT. The Wells pretest score for DVT does not require sophisticated equipment and can be done in any setting.

Thromboprophylaxis in the ARTEMIS, MEDENOX and PREVENT studies showed a reduction in prevalence of VTE of between 45% to 63%.[3,6,7]In the ARTEMIS study, thromboprophylaxis with 2.5mg once daily dose of Fondaparinux for 14days reduced risk of VTE by 47%.[6]
The MEDENOX study revealed a decreased risk for VTE by 63% in the group that took enoxaparin at a dose 40mg once daily for 14days.[3]In the PREVENT study, the group taking a once daily dose of 5000 U of Dalteparin for 14 days had a decreased risk for VTE and sudden death by 45%.[7]The three studies have provided overwhelming evidence that thromboprophylaxis can reduce prevalence of VTE in medical patients with acute illness.

Our data provide valuable information in the Zambian setting regarding risk stratification for thromboprophylaxis decision making at the start of hospital admission. Among patients with expected duration of stay greater that 7 days ,those with low BMI and primary diagnosis of tuberculosis appear to be at the highest risk of DVT.There patients would be the most likely to benefit from subcutaneous heparin or enoxaparin prophylaxis. We do note, however that it is not always easy to predict hospital length of stay.

For patients who have been admitted for over 7 days and in whom the diagnosis of DVT is being considered, negative Wells score appears to perform very well for ruling out DVT, with 100% negative predictive value. However, a positive Wells score of 2 or more points does not perform as well as a rule-in test and would need to be followed up with an ultrasound.

Study limitations

This study had a number of limitations. Due to financial constraints biochemical markers of inflammations such as homocysteine, protein C, protein S,antithrombin III, anticardiolipin antibodies, lupus anticoagulant and anti-β2 glycoprotein I antibodies. In addition genetic studies to screen for specific mutations for factor V Leiden (Arg506Gln) and Prothrombin gene (G20210A) could not be not be done.

Furthermore, patients with very low Glasgow coma scores and those requiring ventillatory support were not enrolled to this our due to logistical problems in transporting them to the radiology department for compression ultra sound scans of the lower limbs.

CHAPTER 7

10. CONCLUSION AND RECOMMENDATIONS

Lower limb DVT is common among HIV positive medical patients admitted for at least 7 days at the UTH. Tuberculosis and a low BMI were statistically associated with a high likelihood of developing DVT in our patients. Our study reveals that up to 9.1 % of lower limb DVT occurs in the proximal veins. This implies that without thromboprophylaxis majority of patients with lower limbs DVT at UTH are likely to develop pulmonary embolism.

Our study has also revealed that up to 85% of lower limb DVT is asymptomatic. Without a high index of suspicion, lower limb DVT is likely to be missed in our setting.

Our study did not investigate the prevalence of pulmonary embolism due to diagnostic challenges. The overall prevalence of venous thromboembolism (DVT and PE) remains unknown at the UTH. In addition markers of hypercoagulable states linked to DVT were not investigated due to financial constraints.

From the findings of our study, we came up with the following recommendations:

- There is need to advocate for thromboprophylaxis in medically ill patients admitted for at least 7 days.
- A follow up study for all patients diagnosed with proximal limb DVT would be useful to assess the evolution of the thrombi and prevalence of pulmonary embolism.
- A study should be done to evaluate for markers of hypercoagulable state in patients diagnosed with DVT.There include homocysteine, protein C, protein S,antithrombin III, anticardiolipin antibodies, lupus anticoagulant , anti-β2 glycoprotein I antibodies and genetic studies for factor V Leiden and prothrombin gene mutations. .
- Physicians should be encouraged to carry out a Wells score pretest for DVT in all medical patients admitted for at least 7 days.

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12.0 Appendix

Appendix 1: Demographic and clinical characteristics of study patients

Identification No…….Enrolment date……

Date of admission……Age……File No…….

	Question	Answer	Code
01	Sex	M…… F……..	1 2
02	Glasgow coma score	E (1-4) …… V (1-5) …… M (1-6] ……. Total score……	
03	Body Mass Index	Weight (Kg) ……. Height (M) …….. BMI……..	
04	HIV Status	Reactive…….. Non-Reactive…… Unknown……..	1 0 99
05	Latest CD4 count if Reactive	Absolute…… Unknown……..	
06	HAART	Yes…… No…….. Unknown……	1 0 99
07	Primary Diagnosis	Infection……. …….. Heart Failure…… Stroke…….. Diabetes Mellitus…… Renal Failure…….. Active Malignancy…… ……..	1 2 3 4 5 6

		Other……..	7
08	Secondary Diagnosis	……..	
09	Recently bedridden	Yes…….. No…….. If Yes number of days……..	1 0
10	Previous history of DVT	Yes…….. No……..	1 0
11	Family history of DVT	Yes…….. No……..	1 0
12	History of smoking	Yes…… No……..	1 0
14	Oral Contraceptive use	Yes…….. No…… If Yes ,state type……..	1 0
15	Hormone replacement therapy	Yes…….. No…….. If Yes, Type……..	1 0
16	Major surgery within previous 12 weeks requiring general or regional anesthesia	Yes…… No……..	1 0
17	RPR	Yes…….. No…….. Unknown……	1 0 99
18	Urine Protein	Positive…… Negative…….. Unknown……	1 0 99
19	Hemoglobin(g/dl)	……	
10	Platelet count	……	
21	White cell count	……	

Physical examination of lower limbs

	Question	Answer	Code
22	Paralysis/Paresis	Yes…… No……	1 0
23	Entire leg swelling	Yes…….. No……	1 0
24	Calf swelling >3cm compared to asymptomatic leg(10 cm below tibial tuberosity	Yes…….. No……	1 0
25	Pitting edema confined to symptomatic leg	Yes…… No…….	1 0
26	Localized tenderness along distribution of deep venous system	Yes …….. No……..	1 0
27	Non-varicose collateral superficial veins	Yes…….. N……	1 0
28	Warmness to touch confined to symptomatic leg	Yes…….. No…….	1 0

Duplex ultra sound scan report of lower limb

	Limb	Question	Code
29	Left lower limb	Is DVT present? Yes…….. No…… If DVT present, anatomical location & USS modality Iliac…….. …….. Femoral…… …….. Popliteal…… ……	 1 0 1 2 3
30	Right lower limb	Is DVT present? Yes…….. No…….. If DVT present ,anatomical location & USS modality Iliac…….. …… Femoral…….. …….. Popliteal…….. ……..	 1 0 1 2 3

Overall Comment

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Appendix 2: Information and consent form

You are being asked to participate in this research study. The study is being conducted by Dr Charles Mwandama a Master of Medicine student in the department of Internal Medicine. The research study is one of the requirements to obtain a Masters degree in Internal Medicine.

Purpose of study

The purpose of this study is to determine how common DVT is in medical patients admitted to the University Teaching Hospital. DVT is the formation of blood clots in the deep blood vessels of the legs or arms. When blood clots form in deep blood vessels, they may cause your leg to become swollen and very painful. The blood clot may also move to the lungs and cause shortness of breath that may result into death. Formation of DVT can be prevented by giving medicines that prevent clot formation. This study will help to identify patients who are prone to developing DVT and may require medicine to prevent clots formation and associated complications.

Procedure

If you agree to take part in this study, you will be asked a number a questions to determine likelihood of you developing DVT. Other circumference of the lower part of your legs will be measured .It addition a number of blood tests including HIV test will be done if not already done. An ultra sound scan of your legs will be done to physically see if you have any blood clots in your legs.

Potential risks and discomforts

The procedures involved in this study have very minimal risks. Slight discomfort will be experienced from needle pricks during collection of blood samples.

Potential benefits to participant

This study may increase ability to diagnose DVT and to potentially to reduce DVT-related complications. If you are found to have DVT, your treating doctor will be notified so that you will be given treatment as per current hospital practice of care.

Contact Details

If you have any questions regarding this study, you may contact the principal investigator, Dr Charles Mwandama at the *department of Internal Medicine University Teaching Hospital* or the UNZA Biomedical Research Ethics Committee at the *University of Zambia.*

Payment for participation in the study

You will not be paid for participating in the study.

Confidentiality

All information collected during this study will be kept confidential under lock and key. Only the researcher and supervisor will have access to the information. If you volunteer to take part in the study you can withdraw at any point without any consequences. You will continue to receive treatment as per current hospital standard of care.

Signature of research participant

I have read the information above on this study. I agree to take part in the study…….

Signature/Thumb print……..

Date……..

(**If participant is unable to consent, next of kin can consent**)

Signature/Thumb print of next of

kin……..

Date……..

Witness………

Signature……

Date……

Signature of Researcher

Name of researcher……

Signature……

Date……..

Consent and Information form in Nyanja
Pepala la chiziwiso ndi cibvomekedzo

Inu mwapempedwa ku tengako mbali mu punziro lamene a dotolo Charles Mwandama ali ku chita ku fikiliza mapunziro a kuya a Masters of Medicine

Lingaliro la punziro

Lingaliro la punzirori ndi ku funa ku ziba mwamene matenda a kuyuma kwa magazi mu mizipe za mukati (Deep Vein Thrombosis) ali o churuka mu antu odwala ali mu chipatala cha University Teaching Hospital (UTH).

Aya matenda yamayamba ngati magazi ayuma mumizipe za mumendo ndi manja. Yaka Yuma, yalengesa kwendo kapena kwanja kuvimba naku baba kwambiri. Magazi a mene ya Yuma yanga pite ku m pwapwa ndi kulengesa kubvutika mu kupema kwamene kunga lengese kufa. Ku letsa matenda aya kuli mankwala munga mwe. Punziroli liza tandiza mwamene tinga zibe amene anga nkale ndi matenda aya naku funikira mankwala yanga letse ku Yuma kwa magazi ndi mabvuto yo bwelapo.

Zocitika mu punziro

Ngati mwa vomela kutengaku mbali mu punziro iri, muza funsidwa mafunso kotero kuti ti one ngati mu oneka kutu munga nkale nayo matenda aya. Tiza pima kuzungulila kwa kwendo yanu, ndi kupima zina za magazi pamodzi ndi HIV ngati mukalibe ku pimisa. Pambuyo ka izi tiza chita Ultra sound ya mendo yanu ku ti tione ngati kuli magazi yo yuma mu mendo yanu.

Kodi Ku li zoyofya ku tengako mbali mu punzilori?

Zochitika mu punziroli zilibe zoyofya, ku baba potenga magazi ndi ye kuza pezeka chabe.

Zopezamo

Punziroli liza ti tandiza ku ziba mo pezera matenda aya ndi ku chepetsa mabvuto yake. Ngati mwapezeka kuti muli ndi matendaya a dotolo anu aza uzidwa ndipo mankwala aza kupatsani kulinga ndi zonze zoyenera.

Lamya

Ngati muli ndi mafunso pa punziroli, munga tumile a dotolo Charles Mwandama ku chigawo cha *department of medicine mu UTH* kapena a chigawo cho yanganira ma punziro otero *UNZA biomedical ethics committee pa UNZA*

Malipiro pa kupezeka mu punziro

Simu ka pasidwa ndalama po tenga ko mbali mupunziro

Chisinsi

Zonse ziza tengedwa mu punziro iri tiza sunga mwa chisinsi. Oyenderetsa punziroli ndiye a za ziwa chabe zo chitika. Ngati pambuyo pa ku bvomera kutengako mbali mu punziro mwa funa ku leka, munga leke kopanda chilango ngakale a dotolo anu aza pitiliza muku yanga ni monga masiku onse.

Chizindikiro

Otengako mbali:

Signature (kufwatika): _____

Date: _____

Mboni ka pena oimirira odwala

Signature (kufwatika): _____

Date_____Chizindikiro

Oyenderetsa punzilo

Signature olo kufwatika _____

Dzina: _____

Appendix 3: Table 3.Variables and statistical analysis

Name of variable	Type of variable	Data type	Statistical analysis
Age	Independent	Continuous	t- test
Sex	Independent	Categorical	Chi-square test
Current history of Swelling leg	Independent	Categorical	Chi-square or fisher's exact test
Recently bed ridden for at least 3 days	Independent	Categorical	Chi-square or fisher's exact test
Paralysis	Independent	Categorical	Chi-square or fisher's exact test
Major surgery within the last 12 weeks	Independent	Categorical	Chi-square or fisher's exact test
Previously documented DVT	Independent	Categorical	Chi-square or fisher's exact test
Contraceptive use	Independent	Categorical	Chi-square or fisher's exact test
Puerperium	Independent	Categorical	Chi-square or fisher's exact test
Documented malignancy	Independent		Chi-square or fisher's exact test
Entire leg swelling on physical examination	Independent	Categorical	Chi-square or fisher's exact test
Calf swelling on physical examination	Independent	Categorical	Chi-square or fisher's exact test
Pitting edema confined to swollen leg	Independent	Categorical	Chi-square or fisher's exact test
Localized tenderness of swollen limb	Independent	Categorical	Chi-square or fisher's exact test
Collateral superficial veins	Independent	Categorical	Chi-square or fisher's exact test

Clinical diagnosis	Independent	Categorical	Chi-square or fisher's exact test
HIV test	Independent	Categorical	Chi-square or fisher's exact test
BMI	Independent	Continuous	t-test
White cell count	Independent	Continuous	t-test
Hemoglobin	Independent	Continuous	t-test
Platelet count	Independent	Continuous	t-test
CD4 count	Independent	Continuous	t-test
Wells score	Independent	Continuous	t-test
DVT present on compression USS	Dependent	Categorical	Chi-square or fisher's exact test
Anatomical location of DVT if present	Dependent	Categorical	Chi-square or fisher's exact test

Appendix 4: Ethical Approval

THE UNIVERSITY OF ZAMBIA

BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
Telegrams: UNZA, LUSAKA
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P.O. Box 50110
Lusaka, Zambia

Assurance No. FWA00000338
IRB00001131 of IORG0000774

27th February, 2015.

Our Ref: 009-03-14.

Mr. Charles K. Mwandama,
University Teaching Hospital,
Department of Internal Medicine,
P/Bag RW 1X,
Lusaka.

Dear Mr. Mwandama,

RE: RESUBMITTED RESEARCH PROPOSAL: **"THE PREVALENCE OF DEEP VENOUS THROMBOSIS AND ASSOCIATED RISK FACTORS IN MEDICAL PATIENTS ADMITTED TO THE UNIVERSITY TEACHING HOSPITAL" (REF. No. 009-03-14)**

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 19th February, 2015. The proposal is approved.

CONDITIONS:

- This approval is based strictly on your submitted proposal. Should there be need for you to modify or change the study design or methodology, you will need to seek clearance from the Research Ethics Committee.
- If you have need for further clarification please consult this office. Please note that it is mandatory that you submit a detailed progress report of your study to this Committee every six months and a final copy of your report at the end of the study.
- Any serious adverse events must be reported at once to this Committee.
- Please note that when your approval expires you may need to request for renewal. The request should be accompanied by a Progress Report (Progress Report Forms can be obtained from the Secretariat).
- **Ensure that a final copy of the results is submitted to this Committee.**

Yours sincerely,

M.M.Mbewe (mrs)
CHAIRPERSON

Date of approval: 27th February, 2015. **Date of expiry:** 26th February, 2016.