Addis Ababa University, College of Health Sciences, School of Pharmacy

Department of Pharmacology and Clinical Pharmacy

Treatment Outcome of Deep Venous Thrombosis and Associated Factors among Patients in Selected Hospitals of Addis Ababa; Ethiopia, Multi-center Cross-sectional Study

By: Seble Birhane (B. Pharm)

A Thesis Submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in Partial Fulfillment for the Requirements of Master of Science Degree (MSc.) in Pharmacy Practice.

June 28, 2023

Addis Ababa, Ethiopia

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Assefa Mulu (B.Pharm, MSc, Assistant Professor)

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June 28, 2023

Addis Ababa, Ethiopia

Addis Ababa University

School of Graduate Studies

This is to certify that the thesis prepared by Seble Birhane, entitled: ***"Treatment Outcome of Deep Venous Thrombosis and Associated Factors among Patients in Selected Hospitals of Addis Ababa; Ethiopia, Multi-center Cross-sectional Study"*** and submitted in partial fulfillment of the requirements for the Degree of Master of Pharmacy in Pharmacy Practice complies with the regulations of the University and meets the accepted standards concerning originality and quality.

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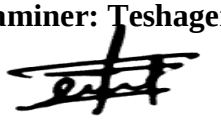
Signature  Date 22/06/2023

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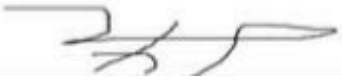
Signature  Date 22/06/2023

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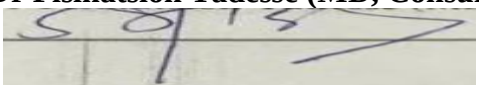
Signature  Date 23/06/2023

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Head, Department or Graduate Program Coordinator

Abstract

Background: Pulmonary embolism and deep venous thrombosis are the two most important manifestations of venous thromboembolism (VTE).Anticoagulation is the mainstay of treatment. The aim of treatment of deep vein thrombosis (DVT) is to reduce morbidity and mortality. The major outcomes of DVT are death, recurrence and major bleeding due to anticoagulation therapy.

Objective: To evaluate treatment outcome and associated factors among patients diagnosed with DVT in Tikur Anbessa Specialized Hospital, St. Paul's Hospital Millennium Medical College and Zewditu Memorial Hospital.

Methods: A retrospective cross-sectional study was conducted from October to March, 2021 among DVT patients admitted to wards of Tikur Anbessa Specialized Hospital, Zewditu Memorial Hospital and St. Paul's Hospital Millennium Medical College from July 1, 2017, to July 2020 (3 years). Patient specific data was collected by using structured data collection tool. Data were collected and entered into Epi info 4.6.0.6 and analyzed using SPSS version 25. Binary logistic regression analysis was used to determine independent predictors of DVT treatment outcome. Candidate variables associated with the outcomes of interest (P<.25 in the bivariate analysis) were included in multivariate logistic regression analysis model.

Results: The mean age of the study participants was 45.2, years (±15.36). Risk factors of DVT include immobilization (29.9%), previous surgery (27.5%), cancer (21.1), unprovoked (23), previous VTE (20.6%), infection (19.6%) and advanced age (>75 years) (8.1%). DVT recurrence rate was 22.5%. In a multivariate logistic regression analysis participants with bilateral DVT (AOR=2.8, 95%CI=1.14, 6.66), obese participants (AOR=3.3, 95%CI=1.15, 9.59), participants with hypertension (AOR=6.5, 95%CI=2.90, 14.70), participants with retro viral infection (RVI) (AOR=6.3, 95%CI=2.34, 16.94), baseline international normalized ratio (INR) (2-3) (AOR=6.6, 95%CI=2.86, 15.37) increase in likelihood of developing recurrence DVT. During the study period 2.2% of the participants died and 19.9% developed complication. Participants who had major bleeding were 4.5% with bilateral DVT (AOR=3.9, 95%CI=1.6, 9.7), participants having active cancer (AOR=6.5, 95% =2.9, 14.75) and whose age >75 years (AOR=6.8, 95%CI=2.03, 22.33) had increase risk of major bleeding than the opposite compartment.

Conclusions: In the current study, the overall DVT recurrence rate was 22.5%, which is complicated by pulmonary embolism and causes 2.2% death. Patients who presented with PE had higher rates of death compared with patients with isolated DVT. Efforts are needed to identify patients who are most at risk for VTE complications and to develop better anticoagulation strategies suitable for long-term use and improve the treatment outcomes.
Key words: Deep Vein Thrombosis, Recurrence, Risk Factors, bleeding and Addis Ababa

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List of abbreviation and acronyms

APTT… Activated partial thromboplastin time

CBC… Complete Blood Count

DM…Diabetes mellitus

DOAC…Direct oral anticoagulant

DVT…Deep vein thrombosis

HCT…Hematocrit

HGB… Hemoglobin

INR….International normalized ratio

JUMC…Jimma university medical center

LMWH… Low molecular weight heparin

NOAC… Non-vitamin K antagonist Oral Anticoagulants

PE…..Pulmonary embolism

PT…Prothrombin time

PTS…Post thrombotic syndrome

RVI… Retroviral Infection

SPHMMC… St. Paul's Hospital Millennium Medical College

SPSS… Statistical Package for Social Sciences

SPSH….St. Peter Specialized Hospital

TTR…Time in therapeutic range

TASH…Tikur Anbessa Specialized Hospital

VTE…. venous thromboembolism

VKA… Vitamin K- Antagonist

ZMH….Zewditu Memorial Hospital

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1. Introduction

1.1. Background

Deep venous thrombosis (DVT) is the presence of a blood clot in a deep vein. DVT and pulmonary embolism (PE) are the two most important manifestations of venous thromboembolism (VTE), which is the third most common life-threatening cardiovascular disease, after myocardial infarction and stroke, in the United States. According to the Centers for Disease Control and Prevention, the annual incidence of VTE is one or two per 1,000 persons and the overall mortality rate is between 60,000 and 100,000 annually. One-half of patients with DVT will have long-term complications, including post thrombotic syndrome and venous ulcers. One-third of patients with VTE will have a recurrence within 10 years (1).

DVT is a complex multifactorial disease and an important cause of preventable mortality and morbidity (2). Rates of DVT increase sharply after about age of 45 years, and are slightly higher in men than women in older age. Major risk factors for thrombosis, other than age, include exogenous factors such as surgery, hospitalization, immobility, trauma, pregnancy, and the puerperium and hormone use, and endogenous factors such as cancer, obesity, and inherited and acquired disorders of hypercoagulation (3). DVT is a major and a common preventable cause of death worldwide approximately 0.1% of the global population will develop DVT each year. There are 48 new cases of DVT per 100,000 people each year, on average, when both age and gender are taken into account; males have a higher incidence rate than females at every age (130 vs. 110 per 100,000, respectively) but first-time DVT affects both men and women equally, though men are more likely to experience recurrences of thrombosis. The prevalence of DVT increases dramatically with age, making it a disease primarily affecting the elderly (4).

A number of invasive and non-invasive approaches are possible for diagnosis of DVT (eg, contrast venography, impedance plethysmography, compression ultrasonography, D-dimer testing). In most circumstances, compression ultrasonography is the noninvasive approach of choice for the diagnosis of symptomatic patients with a first episode of suspected DVT. A negative D-dimer assay may be insufficient to rule out DVT as a stand-alone test in patient populations with a high prevalence of venous thromboembolism, and not all D-dimer assays are validated for this application.

The aim of treatment of VTE is to reduce morbidity and mortality. This is achieved by optimal therapy with anticoagulants to prevent thrombus extension and embolization. The major outcomes of venous thrombosis are death, recurrence, post thrombotic syndrome and major bleeding due to anticoagulation therapy (5).

Anticoagulation is the mainstay of VTE treatment. Patients with DVT or PE should be treated acutely with Low Molecular Weight heparin (LMW), fondaparinux, unfractionated intravenous heparin, or adjusted-dose subcutaneous heparin. Dosing requirements for LMW heparin are different for each product. The dose should be sufficient to prolong the activated partial thromboplastin time (aPTT) to 1.5 to 2.5 times the mean of the control value, or the upper limit of the normal aPTT range (6).

Treatment with LMW heparin, fondaparinux, or unfractionated heparin should be continued for at least five days and oral anticoagulation with a vitamin K antagonist should be overlapped for at least four to five days. No such overlap is required if rivaroxaban is chosen. The use of thrombolytic agents, surgical thrombectomy, or percutaneous mechanical thrombectomy in the treatment of venous thromboembolism must be individualized. Patients with hemodynamically unstable PE or massive iliofemoral thrombosis (ie, phlegmasia cerulea dolens), and who are also at low risk to bleed, are the most appropriate candidates for such treatment. Inferior vena caval filter placement is recommended when there is a contraindication to, or a failure of, anticoagulant therapy in an individual with, or at high risk for, proximal vein thrombosis or PE (7). If the use of a vitamin K antagonist is contraindicated or inconvenient, long-term therapy can be undertaken with adjusted-dose unfractionated heparin, low molecular weight heparin, fondaparinux, or rivaroxaban (8). Direct oral anticoagulants (DOACs) are preferred for their ease of use, favorable pharmacokinetics with fixed dosing, fewer drug interactions, and lack of monitoring requirements (9). DOACs exhibit comparable efficacy and significantly lower bleeding risk compared to warfarin (10).

DOACs represent a major development in treating venous thromboembolic diseases and AF. They do not need laboratory monitoring, have less drug and food interaction, and lower risk of intracranial bleeding. Their short half-life is an important advantage, particularly in preoperative management and helps to avoid bridging with parenteral anticoagulation. However, it is a concern in poorly compliant patients. Appropriate doses of all DOACs for each indication are essential for safe and efficient outcomes (11).

1.2. Statement of the problem

There is little information available in Ethiopia about the prevalence of deep vein thrombosis, treatment outcomes, or risk factors for its recurrence.

The economic burden of VTE spans from the loss of economic output due to premature mortality to the medical costs in treating the acute event and the costs of complications and long-term morbidity (2). Although case fatality was minimal during the acute episode, 15.4% of afflicted patients with acute thromboembolism died within 90 days of the incident event, emphasizing the need for effective methods to improve outcomes in this group. As treatment choices grow beyond warfarin to include direct oral anticoagulants, it is critical to document how thromboembolism therapy and outcomes improve over time (4).

The incidence of venous thromboembolism (VTE) was 5.5% in a research conducted at TASH in Addis Ababa, which was higher than the findings of other studies (12). DVT and associated complications used to be common in hospital settings, but they are also becoming more common in outpatient. A study conducted in Canada found that rates of recurrent VTE and severe bleeding after DVT and PE remain unacceptably high in the community environment (13). Approximately half of patients with DVT will develop PTS (14).

Finding from TASH and Jimma also discovered that the recurrence rate of DVT was greater than most previously published data. During the follow-up period, the recurrent DVT was complicated to PE and mortality. The total incidence rate of recurrence was 2.99 per 1000 patient days (15).

In global healthcare, deep vein thrombosis remains a significant condition, since associated morbidity is significant and has elevated healthcare-related costs (16).

According to statistics gathered in the United States, DVT contributes to the deaths of 33 percent of those affected. There are an estimated 66 percent of DVT cases that do not result in death, leads to a significant number of hospitalizations (17).

VTE is a major health problem in the Europe, with over one million VTE events or deaths per annual in the six countries examined. The estimated total number of symptomatic VTE events per annum within the six EU countries was 465,715 (404,664-538,189) cases of deep-vein thrombosis, 295,982 (242,450-360,363) cases of pulmonary embolism (PE), and 370,012 (300,193-483,108) VTE-related deaths. Almost three-quarters of all VTE-related deaths were from hospital-acquired VTE (18).

VTE is a prevalent condition, with an estimated annual incidence of 5-12 per 10,000 people (19).

In the United States, the rate of DVT hospitalization per 100,000 subjects aged 60 years increased from 581 in 2001 to 739 in 2010, with an average duration of stay of 4.7 days in 2011 (20).

From 2000 to 2006, the prevalence of PE ranged from 55.3 to 71.7 per 100,000 participants, with an incidence of 406.9 per 100,000 aged 80 and over (year 2006). In-hospital mortality increased from 20.4% to 24.9% between 2001 and 2003 (21).

The cumulative incidence of recurrent venous thromboembolism was 17.5% after 2 years of follow-up, 24.6% after 5 years, and 30.3% after 8 years and survival after 8 years was 70.2% (22).

VTE had an overall incidence rate of 131.5 per 100,000 person-years. DVT was more common in young people, while PE was more common in the elderly. In 3671, a VTE recurrence occurred. The recurrence rate peaked in the first six months at roughly 11 per 100 person years it was the same till three years, and 2 per 100 person years from year four to ten of follow-up (23).

One third of patients diagnosed with DVT/PE have a recurrence within 10 years, and up to 50% develop post-thrombotic syndrome (PTS) (24).

In 5-9% of patients, recurrent venous thromboembolism is associated with an increased risk of death. Prolonged anticoagulation, on the other hand, might raise the risk of bleeding, which can lead to an increase in mortality (25).

The frequency of recurrent DVT is rising making early identification and treatment of risk factors that predispose to recurrence critical. Since there is limited studies in Ethiopia data on prevalence, risk factors, recurrence and treatment outcomes for DVT has paramount importance (12),(15).

1.3. Significance of the study

The prevalence of deep venous thrombosis (DVT) is increasing steadily across the globe. It is anticipated that the burden in our nation will continue to expand as a result of an increase in life expectancy, the adoption of a lifestyle more typical of the western world, and the impact of a great number of accidents on its total. One of the diseases that can be avoided is DVT, if adequate screening, early identification, and treatment are utilized. As a result, it is anticipated that this research will communicate to relevant parties the necessary suggestions following an examination of the treatment outcomes. First, in Ethiopia, little is known about the treatment outcome status among DVT patients as studies done are scarce in the area. Therefore, this study generated essential data that could fill this gap. Secondly, having data regarding DVT treatment outcomes will help policy makers to effectively plan strategies that will maximize patient care. The findings of the study will initiate pharmacists to design a better anticoagulation therapy management. In addition findings will assist the hospitals and ministry of health in efforts to establish pharmaceutical care services for better patient care and improve the treatment outcomes.

2. Literature review

The short-term outcomes after a diagnosis of thromboembolism are consequential; with 15.4% of patients dying within 90 days after initial diagnosis. The study includes diverse source population, inclusion of events from both inpatient and outpatient settings, and validation of index thromboembolic events and collection of data through review of medical records. Although case-fatality during the acute episode was relatively low, 15.4% of affected patients with acute thromboembolism died within 90 days of the incident event, highlighting the need for effective strategies to improve outcomes in this population. As treatment options continue to expand beyond warfarin to include direct oral anticoagulants, it is important to document how treatment and outcomes of thromboembolism evolves over time (4).

A retrospective cross sectional study done in 2017 involving chart review using the instrument from TASH guideline on VTE prophylaxis and treatment showed the incidence of venous thromboembolism (VTE) was 5.5% which was higher than the findings of other studies conducted elsewhere and out of 200 medically admitted patients, 186 (93%) of them had at least two risk factors for VTE development. Only 75 (40%) patients received thromboprophylaxis and VTE was prevented in 61 (32.8%) patients who received prophylaxis. However, 11 (5.5%) high and highest risk categories patients developed VTE during their stay at hospital. In 128/200 (64%) study participants, the status of VTE outcome was not known since such information was not documented on patents' charts. Patients aged ≥ 60 years, lung diseases including pneumonia and having stroke in the last month, were independent predictors for development of VTE events. In this study, although all patients have at least one risk factor for VTE 37.5% of them received thromboprophylaxis and the need for implementation of existing evidence based guidelines proposed by TASH is high (12).

The medical records of residents from the Worcester area with International Classification of Diseases, Ninth Revision (ICD-9) codes consistent with possible venous thromboembolism (VTE) during 1999, 2001, and 2003 were independently validated and reviewed by trained abstractors. Patients who presented with PE or isolated DVT experienced similar rates of subsequent PE, overall VTE, and major bleeding during 3-year follow-up (5.9% vs 5.1%, 15.0% vs 17.9%, and 15.6% vs 12.4%, respectively). Mortality was significantly increased at 1-month follow-up in patients who initially presented with PE (13.0% vs 5.4%); this difference persisted at 3 years (35.3% vs 29.6%). Patients whose course was complicated by

major bleeding were more likely to experience recurrent VTE or to die at 3 years than those without these complications and patients who presented with PE had similar rates of subsequent PE or recurrent VTE compared with patients with isolated DVT. However, rates of recurrent VTE and major bleeding after DVT and PE remain unacceptably high in the community setting. Efforts are needed to identify patients most at risk for VTE associated complications and to develop better anticoagulation strategies conducive to long-term use in the community setting (13).

A multi-institutional cohort of patients diagnosed with confirmed pulmonary embolism and/or deep venous thrombosis during years 2004 through 2010 was established from four large, US-based integrated healthcare delivery systems comprised 5,497 adults with acute venous thromboembolism. Pulmonary embolism was predominantly managed in the hospital setting (95.0%) while 54.5% of patients with lower extremity thrombosis were treated as outpatients. This study provides a unique examination of the acute presentation, treatment, and outcomes of inpatients and outpatients with venous thromboembolism across four geographically diverse US-based health systems. Although most patients with thromboembolism were treated with anticoagulants, 1 in 10 people were not, frequently due to concerns for bleeding risk or poor clinical prognosis.

In meta-analysis done in 2018 with Six randomized controlled trials, including 1418 patients with DVT, demonstrated that thrombolysis in combination with anticoagulation therapy did not reduce the incidence of post thrombotic syndrome (PTS) compared with anticoagulation alone. Thrombolysis in combination with anticoagulation might increase the incidence of major bleeding. However, because of the low incidence of major bleeding, more randomized controlled trials are needed. Although anticoagulation therapy with warfarin or novel oral anticoagulants (NOACs) and compression stocking are the main treatments for DVT, approximately half of patients with DVT will develop PTS. However, a meta-analysis with 1462 patients did not demonstrate that patients with DVT could benefit from compression stockings. More effective treatments are needed to deal with DVT. As a result, thrombolysis, especially catheter-directed thrombolysis, is regarded as a last resort (14).

Three-months prospective open cohort study in 2018 was conducted among 129 patients stated more than 3/4th of study participants developed deep venous thrombosis for first time, 27(20.9%) of participants had second deep venous thrombosis admission status, and only 4(3.1%) have multiple admission status. During the 90 days follow up period of each

participants from a cohort of DVT, 34(26.4%) recurrent VTE were observed. Type of event was DVT in 28 patients (82.40%) and the rest admitted with pulmonary embolism as a result of DVT complication, which was confirmed by CT-scan. The overall incidence rate of DVT recurrence was 2.99 per 1000 patient days. Little number [6(4.7%)] of patients had confirmed complete DVT resolution within three months of treatment. During 90 days, about 25(19.4%) of them presented with bleeding incidence. Four (3.1%) patients died during the observation period giving a mortality rate of 0.35 per 1000 person-days. The result revealed that statistically significant difference ($P< 0.025$) was observed between the hospitals, as all were reported from St. Paul‘s hospital patients diagnosed with DVT, who was admitted to inpatients wards of JUMC and SPHMMC (15).

A descriptive, cross sectional analytical study in 2016 with sample of 296 medical patients admitted for at least 7 days showed the prevalence of lower limb DVT among medical patients admitted for at least 7 days was 11.1%.Patients with DVT had a lower mean body mass index (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 Prevalence of DVT of the lower limbs was 11.1 % (33/296). Prevalence of proximal lower limb DVT was 9.1%. Eighty two percent (27/33) of all patients with DVT had proximal lower limb DVT. Asymptomatic lower limb DVT was noted in 85 % (28/33) of all patients with DVT (26).

Systematic review and meta-analysis on outcomes in patients with suspected deep vein thrombosis in 2020 reviewed among patients with lower extremity DVT, 0.85% and 0% developed recurrent DVT and PE, respectively, at 3 months. Among patients with upper extremity DVT, 0.49% and 1.98% developed recurrent DVT and PE, respectively, at 3 months. No major bleeding events were reported for those anticoagulated, which is lower than in other systematic reviews. For both upper and lower extremity DVT, low pretest probability patients with a negative D-dimer had a comparable incidence of VTE at 3 months (1%) as patients with a negative ultrasound (US). At higher pretest probabilities, negative US testing with or without serial US appear to be the safer option. In this review, it summarized the outcomes of patients evaluated by various diagnostic pathways (27).

A study conducted in August 2008 at St. John’s in Canada the study was in a multi physician family medicine clinic, with sampling of all patients who received anticoagulation management by the pharmacist almost all patients were satisfied with the warfarin education

provided by the pharmacist. At least 95% of patients agreed/strongly agreed that the pharmacist completed a satisfactory job teaching the importance of warfarin adherence, why INR tests were necessary, and the risks of bleeding. Approximately 75% agreed/strongly agreed that the risk of a blood clot was explained, that dietary considerations for warfarin therapy were described, and that they were told when to see a doctor. Patients and family doctors were pleased with the pharmacist managed anticoagulation program and suggested continuation of the program. The service is highly regarded by both patients and family doctors and can complement the role of the pharmacist in a multi-physician family medicine clinic in the management of anticoagulation. The current pharmacist based anticoagulation programs in family medicine and pharmacist managed anticoagulation service showed a slightly improved INR control and better outcome for pharmacist-managed treatment relative to standard physician care, with a therapeutic time range of 73% vs. 65%, respectively (28).

A prospective cohort study in 2006 showed the prevalence of DVT among surgical intensive care unit (ICU) patients was found to be approximately 10%. This number is less than that seen in other studies which report an incidence between 25–32%. Such a low prevalence of DVT further confirmed the traditional view that DVT is not very common in Thailand patients. Among the 190 first-time admitted ICU patients with a mean acute physiology and chronic health evaluation (APACHE II) score of 9.2 ± 6.0 (range, 0–29), 20 patients had DVT (prevalence of 10.5%). Thromboprophylaxis was not given to any patient. The only independent and significant risk factor for DVT was a longer ICU stay, age, sex, APACHE II score, presence of comorbidities and operative intervention were not associated with the presence of DVT it shows that even critically ill surgical patients at high risk have a low DVT prevalence (29).

2.1. Conceptual framework

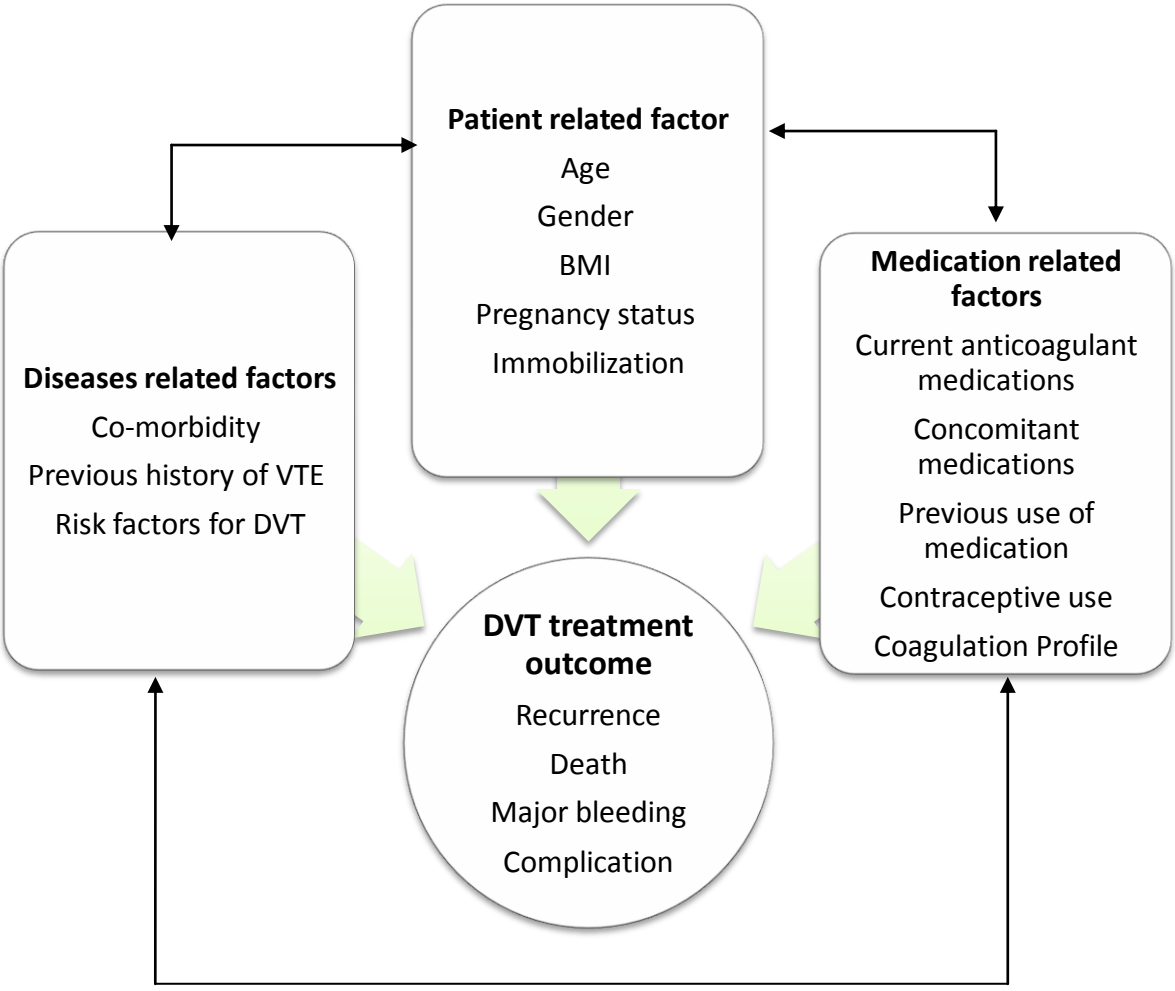

Figure 1; conceptual framework (4,12,13,15).

3. Objectives of the study

3.1. General objective

To evaluate treatment outcome and associated factors among DVT patients on anticoagulation therapy at selected hospital in Addis Ababa.

3.2. Specific objectives

To assess prevalence of recurrence among DVT patients hospitalized at SPHMMC, ZMH and TASH hospitals.

To assess prevalence of major bleeding among DVT patients hospitalized at SPHMMC, ZMH and TASH hospitals.

To assess prevalence of mortality rate among DVT patients hospitalized at SPHMMC, ZMH and TASH hospitals.

To determine predictors of recurrence among DVT patients hospitalized at SPHMMC, ZMH and TASH hospitals.

To determine predictors of major bleeding among DVT patients on anticoagulation therapy hospitalized at SPHMMC, ZMH and TASH hospitals.

4. Methods and Materials

4.1. Study area and period:

A retrospective cross sectional study was conducted from October to March, 2021 among DVT patients admitted to wards of SPHMMC, ZMH and TASH from July 1, 2017 to, July 1, 2020 (3 years). SPHMMC, TASH and ZMH are located in Addis Ababa, Ethiopia. We choose these hospitals because they are referral hospitals and patients from different parts of the country come and this gives us a chance to find diverse participants. They are tertiary hospital and we were able to find the required sample size of participants with DVT. TASH is a training center for undergraduate and post graduate medical and health science students established in 1972 E.C. TASH has more than 800 beds gives treatment service for about 370,000-400,000 patients per year. SPHMMC was established through a decree of the council of Ministers in 2010G.C, although the medical college opened in 2007 G.C. It is governed by a board under the federal Ministry of Health. The college has more than 2800 clinical, academic and administrative and support staffs that provide medical specialty services to patients who are referred from all over the country. This teaching hospital has 700 beds for inpatient service; the hospital sees an average of 1200 emergency and outpatient clients. Zewditu Memorial Hospital was built, owned and operated by the Seventh-day Adventist Church, but was nationalized during the Derg regime in about 1976. ZMH has 188 in-patient beds and serves 9,171 inpatients and 89,540 outpatients per year. Currently there are around 720 patients under regular follow up at the clinic, with an average of 30 patients seen on each clinic day.

4.2. Study Design

A retrospective cross sectional study was conducted.

4.3. Population

4.3.1. Source Population

All patients who were admitted with deep vein thrombosis at SPHMMC, ZMH and TASH were the source population for the study.

4.3.2. Study population

Target populations for this study were patients who were admitted to SPHMMC, ZMH and TASH with diagnosis of deep vein thrombosis during the study period.

4.4. Inclusion and Exclusion Criteria

4.4.1. Inclusion criteria

Patients at SPHMMC, ZMH and TASH that were diagnosed and treated for DVT both for upper and lower extremity from July 1, 2017, to July 1 2020, patient's age 18 and above and those on anticoagulants for at least 3 months or more.

4.4.2. Exclusion Criteria

Patients, who had incomplete data or medical record.

4.5. Sample size Determination and Sampling technique

4.5.1. Sample size determination

The sample size was determined by using single population proportion formula:

$$N = \frac{Z^2 p (1-p)}{d^2}$$

Where: n= sample size required

d= Marginal error of 5% (w=0.05)

Z= the degree of accuracy required (95% level of significance = 1.96)

P= prevalence of deep vein thrombosis treatment outcomes in Ethiopia 50%.

$$n= \frac{(1.96)^2 (0.5)(0.5)}{(0.05)^2} = 408$$

From the three settings we had found 1320 patients (500 from TASH, 220 from ZMH and 600 from SPHMMC) admitted with DVT during the study period. We found these data from health management information system and we computed the required samples from each study settings proportionally.

TASH= $\frac{\text{Study population*Sample size}}{\text{Total population}} = \frac{500*408}{1320} = 155$

SPHMMC= $\frac{600*408}{1320}$=185

ZMH= $\frac{220*408}{1320}$=68

4.5.2. Sampling techniques

We used systematic random sampling, to select the participants. K was calculated by 1320 /408= 3. From 1-3 participants we selected the first patient by lottery method then every 3rd patient until required sample size was obtained.

4.6. Variables

4.6.1. Dependent variable

DVT treatment outcomes.

4.6.2. Independent variables

Diseases related factors (co-morbidity, previous history of VTE and risk factors for DVT), patient related factor (age, gender, BMI, pregnancy status and immobilization) and medication related factors (current anticoagulant medications, concomitant medications, previous use of medication, use of oral contraceptive and coagulation profile)

4.7. Data collection tools and procedures

Our data collection tools were prepared by using different literatures. It contains Part I: Sociodemographics characteristics, Part II: Types of DVT, risk factors and Clinical data, Part III: DVT outcome measurement and it included (I: Assessing recurrent, II: Anticoagulation management practices and III: Assessing bleeding), Part IV: Laboratory findings, part V: List of all medications and also data regarding complications and information about the category of bleeding that happens during the treatment period based on International Society on Thrombosis and Haemostasis were all gathered from the chart(4,8,12,13,15,30). Data collection was performed by two trained data collectors, one nurse and two pharmacists. They were trained for one day about the objectives of the research and the questionnaire they were given specific instructions on how to collect information in order to obtain the most crucial data. Throughout data collection, the principal investigator was supervising. The collected data was routinely examined for accuracy and consistency.

4.8. Data quality assurance

Validity of the study was censured by a pretest performed on 5% of the study population at St. Peter specialized hospital with similar characteristics to ensure the agreement of the data abstraction format with the need of the study. Modifications were mainly made to the variables used to measure DVT treatment outcomes and were corrected and modified into the final version of the data abstraction format. All collected data was examined for completeness and consistency during data management, storage and analysis.

4.9. Data Analysis

Data were collected and entered into Epi info 4.6.0.6 and analyzed using Statistical Package for the Social Sciences (SPSS) latest version 25. Descriptive statistics such as frequency, percentage, mean, and standard deviation (SD) was used to describe demographic and clinical features, as well the outcomes. Logistic regression models were used to determine whether the Sociodemographics data, laboratory findings or co morbid conditions related to specific outcomes (recurrent DVT or major bleeding) and then candidate variables possibly associated with the outcomes of interest ($P<.25$ after bivariate analysis) were included in each logistic multivariate regression model. Variables with $P>.25$ were eliminated so that only variables with a statistically significant association with the outcome of interest were included in the final regression models.

4.10. Study outcome measures

The outcomes important to patients were considered from most recommendations are recurrent VTE, major bleeding and mortality. The primary outcome for the study was recurrence, major bleeding and death whereas the secondary outcomes included were predictor factors for major bleeding and recurrent.

4.11. Ethical consideration

Ethical approval was sought from the ethical review committee of School of Pharmacy as well as department of Internal Medicine, hematology clinic, School of Medicine from all three hospitals. Ethical clearance was obtained from AAU/CHS/SoP/ERC, letter reference number ERB/SOP/266/13/2021. In addition, permission was obtained from IRB of SPHMMC, letter reference number PCP/176/13/21, from TASH and from ZMH as well. Permission was obtained from TASH, ZMH and SPHMMC administrations to access the medication records.

4.12. Definition of terms

Recurrence: is defined as an objectively verified hospital discharge diagnosis of DVT or as a fatal complication of DVT confirmed by ultrasonography, or site of thrombosis either previously uninvolved or had interval documentation of incident DVT (15).

Major bleeding: fatal bleeding; retroperitoneal, intracranial, or intraocular bleeding; bleeding that causes hemodynamic compromise requiring specific treatment; bleeding that requires intervention (surgical or endoscopic) or decompression of a closed space to stop or control the event; clinically overt bleeding, requiring any transfusion of 1 U or more of packed red blood cells or whole blood; clinically overt bleeding, causing a decrease in hemoglobin of 3 g/dl or more (or, if the hemoglobin level is not available, a decrease in hematocrit of 10% or greater) (31).

Mortality: DVT can cause clot to move or break off and travel to the lungs (pulmonary embolism), and as a result death can happen (32).

Complication: Complications from deep vein thrombosis can be very serious. It includes pulmonary embolism (PE), chronic venous insufficiency, and post-thrombotic syndrome (32).

Improved: Adequate progress is being made toward achieving the goals of therapy and the sign symptoms are improving. The same drug therapy will be continued.

Complete resolution: The patients that took the drug therapy and finished the treatment courses had no residual diseases by Doppler ultrasound and discontinue the drug therapy.

No change: No measurable progress in achieving goals of therapy can be demonstrated at this time. No changes will be made. The same drug therapy will be continued.

Worsened: There has been a decline in health status while receiving the current drug regimen. Some adjustments in drug product selection and/or drug dosage are required.

5. Results

5.1. Socio-demographics and deep vein thrombosis characteristics of study participants

The study sample consisted of 408 men and women from the three hospitals during the three years study period and included patient that took anticoagulant medication for at least 3 months. The mean age (±SD) of the study participants was 45.2 (±15.36) years and 36.5% of the participants were in the age group of ≥51 years. More than half (58.8%) of the participants were female as shown in **Table 1** below.

Table 1: Sociodemographic characteristics of study participants with DVT at selected hospitals in Addis Ababa, July 1, 2017 to July 1, 2020

Variable (n=408)		**Frequency**	**Percent**
Age in years	18-35	116	28.4
	36-50	143	35.0
	≥51	149	36.5
	Mean age (±SD)	45.2 (±15.36)	
Sex	Male	168	41.2
	Female	240	58.8

The majority of DVT cases reported were with lower limb thrombosis (95.3%), followed by unilateral (78.7%) and proximal DVT (40.4%). Regarding the presence of sign and symptoms, more than three fourth of studied patients had pitting edema and all the studied cases had pain and swelling. Among the risk factors of DVT, 29.9% of cases were associated with immobilization, 27.5% of cases were associated with previous history surgery and the others are summarized in **Table 2** below.

Table 2: Clinical profiles of DVT patients at selected hospitals in Addis Ababa, July 01, 2017 to July 01, 2020

Variables (n=408)		**Frequency**	**Percent**
Sites of DVT	Lower limb	389	95.3
	Upper limb	6	1.5
	Both lower and upper limbs	13	3.2

DVT types	Proximal	165	40.4
	Distal	11	2.7
	Both	232	56.9
DVT involved limb	Unilateral	321	78.7
	Bilateral	87	21.3
Sign and symptoms at presentation	Pain	408	100.0
	Swelling	408	100.0
	Pitting edema	318	77.9
	Skin discoloration	233	57.1
	Local tenderness	219	53.7
Risk factors of DVT	Recent immobilization	122	29.9
	Previous surgery	112	27.5
	Active cancer	86	21.1
	Previous VTE	84	20.6
	Presence of infection	80	19.6
	Pregnancy	64	15.7
	Obesity	54	13.2
	Age>75	33	8.1
	Heart failure	23	5.6
	Stroke	18	4.4
	Prior history of trauma	17	4.2
	Genetic (anti-phospholipid antibody syndrome)	9	2.2
	Unprovoked	94	23

5.2. Co-morbidities of DVT

Co morbid disease found in the study participants were hypertension (30.4%), diabetes mellitus (11.8%), retroviral infection (11.4%), malignant disease 62(15%). Among the malignant cases breast cancer accounts (29%) followed by ovarian, cervical, rectal and liver cancers. Eighteen percent of the participants had a prior history of surgery. Abdominal surgery accounts 55.4% followed by orthopedic, brain, cardiac and breast surgery as shown in **Table 3** below.

Table 3: The distribution of comorbid disease conditions among DVT diagnosed patients at selected hospitals in Addis Ababa, July 01, 2017 to July 01, 2020

Co-morbidities (n=408)		**frequency**	**Percent**
With co morbidity		204	50
Hypertension		124	30.4
Prior history of surgery		74	18.1
Types of surgery	Abdominal	41	55.4
	Orthopedic	17	23.0
	Brain	6	8.1
	ENT	5	6.8
	Cardiac	3	4.1
	Breast	2	2.7
Cancer		62	15
List of cancers	Breast	18	29.0
	Ovarian	17	27.4
	Cervical	12	19.4
	Rectal	10	16.1
	Other *	5	8.0
RVI		59	14.4
Diabetes mellitus		48	11.8
HF		21	5.1
Dyslipidemia		13	3.2

Stroke	12	2.9
CLD	11	2.6
AF	3	0.7

*Lung, Colorectal and Liver cancer, AF: Atrial fibrillation, CLD: Chronic Liver Disease, ENT: Eye, Nose and Throat, HF: Heart Failure, RVI: Retroviral Infection.

5.3. Classes of medication patients were taking during their treatment

All of study participants were taking anticoagulants. From a total of 408 DVT patients, 204 had co-morbid conditions and were taking concurrent medications. The majority of these patients were taking antibiotics, followed by cardiovascular, vitamin K, and then antidiabetic drugs, as shown in the **Figure 2** below:

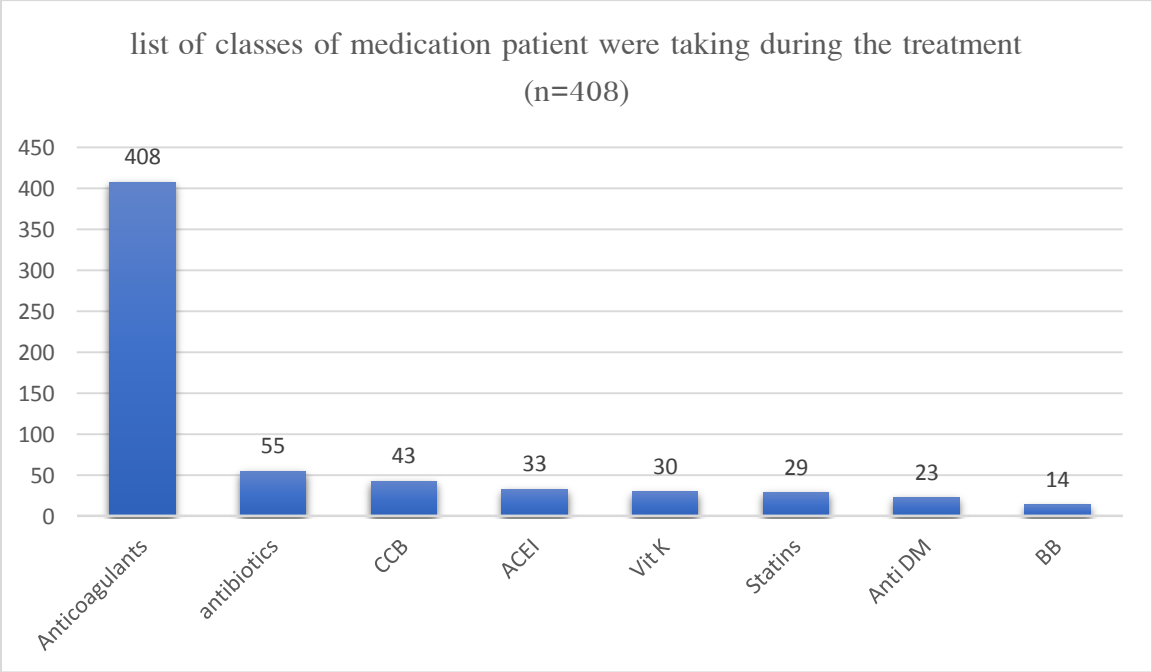

Figure 2: List of classes of medication patient were taking during the treatment at selected hospitals in Addis Ababa, July 1, 2017 to July 1, 2020

ACEI: Angiotensin Converting Enzyme Inhibitor, Anti DM: Anti Diabetics, B-blocker: Beta Blocker, CCB: Calcium channel Blocker, VIT K: Vitamin K.

5.3.1. Anticoagulant medications used for management of DVT

Majority of study participants were taking warfarin (79.4%), along with either unfractionated heparin (80.8%) or enoxaparin (19.1%) and the rest took rivaroxaban (20.6%) (**Table 4**).

Table 4: Anticoagulants medications and their respective doses used for the management of DVT patients at selected hospitals in Addis Ababa, July 01, 2017 to July 01, 2020

Anticoagulants medications		**Frequency**	**Percent**
Warfarin		324	79.4
Starting dose of warfarin	2.50 mg	61	18.8
	5.00 mg	251	77.5
	7.50 mg	12	3.7
Maintenance dose of warfarin	2.50 mg	49	15.1
	5.00 mg	116	35.9
	7.50 mg	149	46.0
	10.00 mg	10	3.0
Heparin		262	80.8
Loading dose of Heparin	5000 IU	262	100
Maintenance dose of Heparin	17500 IU	258	98.5
	20000 IU	3	1.1
	75000 IU	1	0.4
Enoxaparin		62	19.1
Rivaroxaban		84	20.6

5.4. Coagulation profile

In our study we used traditional method and it calculates the time to therapeutic range (TTR) as the proportion of in-range INR values to the total number of INR values. Our study showed that the TTR result was 53.9±17.8 and regarding INR result, a mean ± SD was 1.25±0.56, 1.62±0.72, and 1.74±0.66, seconds within 24hrs, 72hrs, 5th days respectively as shown below in (**Figure 3**).

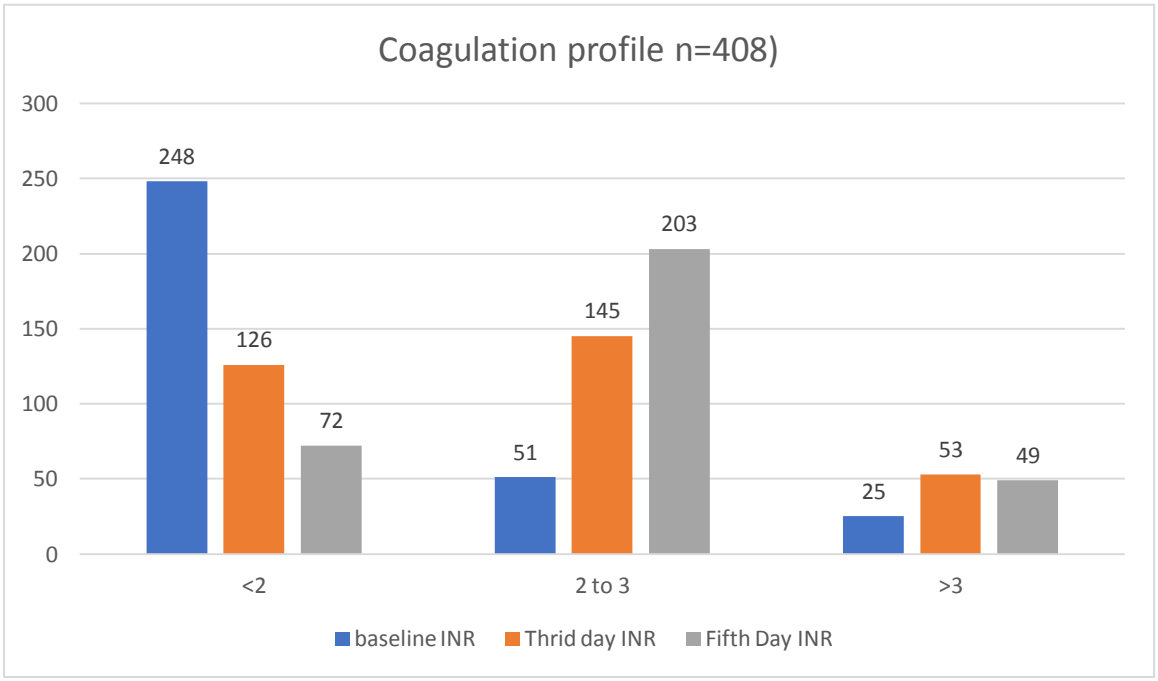

Figure 3: Coagulation profile of DVT patients at selected hospitals in Addis Ababa, July 01, 2017 to July 01, 2020

5.5. Outcomes

The primary outcomes for the study were recurrence, major bleeding and death whereas the secondary outcomes included were predictor factors for recurrent and major bleeding.

5.5.1. DVT recurrence

According to our study findings, the prevalence of recurrent DVT was 22.5%, with 20.1% accounting for second recurrences, 2% and 0.5% accounting for third and fifth recurrences, respectively. Time of recurrence after previous episode of DVT was also assessed (**Table 5**).

Table 5: The Times of recurrent DVT at selected hospitals in Addis Ababa, July 01, 2017 to July 01, 2020

If the patient has recurrent DVT when was the first DVT diagnosis in years Times of Recurrent	Frequency	Percent
<1 years	21	22.8
1-3 years	35	38
3-5 years	20	21.7
>5 years	16	17.4

5.5.2. Occurrence of Recurrent DVT on Anticoagulant therapy

Out of all DVT recurrent 83.7% developed DVT after taking warfarin with either enoxaparin or heparin and the remaining 16.3 took rivaroxaban.

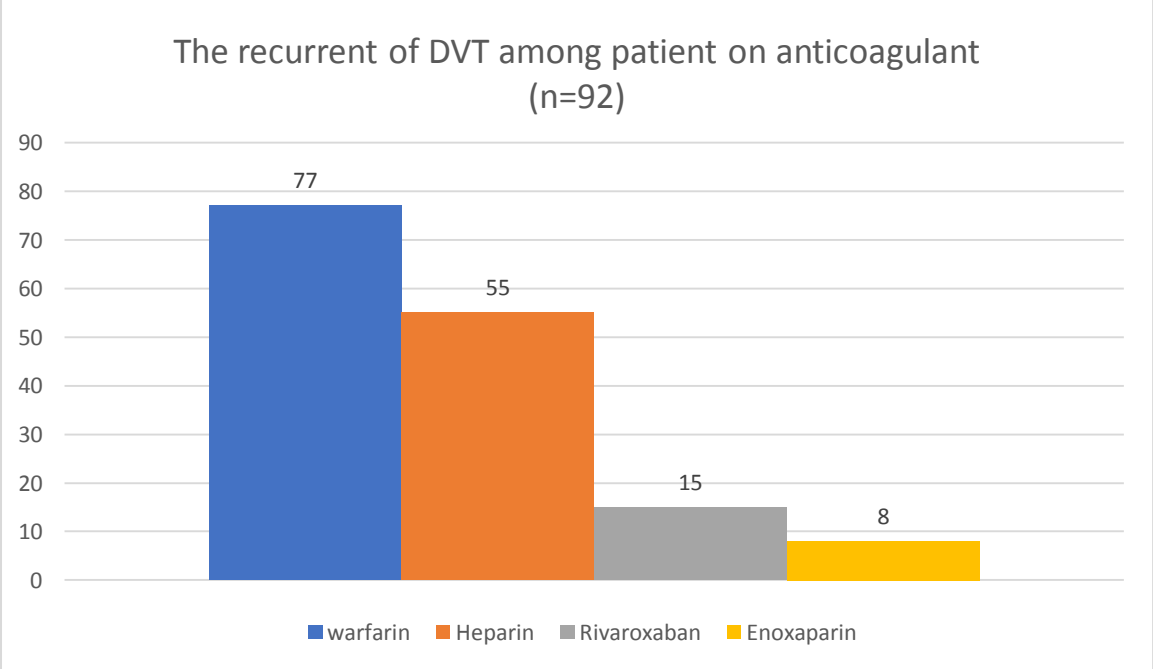

Figure 4: The anticoagulant drugs that the patient were taking at selected hospital in Addis Ababa, July 01, 2017 to July 01, 2020

5.5.3. Mortality

After taking the anticoagulants 17.9% of patients were completely resolved among patients who finished the course of treatment, 10% were worsened and 2.2% (9) died. The reported causes of death were bleeding 2o to supra-therapeutic INR (1 patient), respiratory failure (RF) 2o to septic shock and PE (1 patient), RF 2o to acute PE(2 patients), RF 2o to massive PE(1 patient), RF 2o to massive PE & hypoxia (3 patients), PE and UGIB 2o to Variceal bleeding 2o to CLD (1 patient).

5.5.4. Complication of DVT

Our study showed from all participants, 19.9% had developed complication and PE accounts 44.4% followed by PTS and chronic vein insufficiency.

5.5.5. Major bleeding

Ten percent of the study participants had bleeding during follow up and 4.5 % of them had >3% of reduction hemoglobin level or they had major bleeding. Participants with subjective findings for bleeding were 6.7%. Nose bleeding was reported by 39.3 % of patients who complained of bleeding (**Figure 5** and **Table 6**).

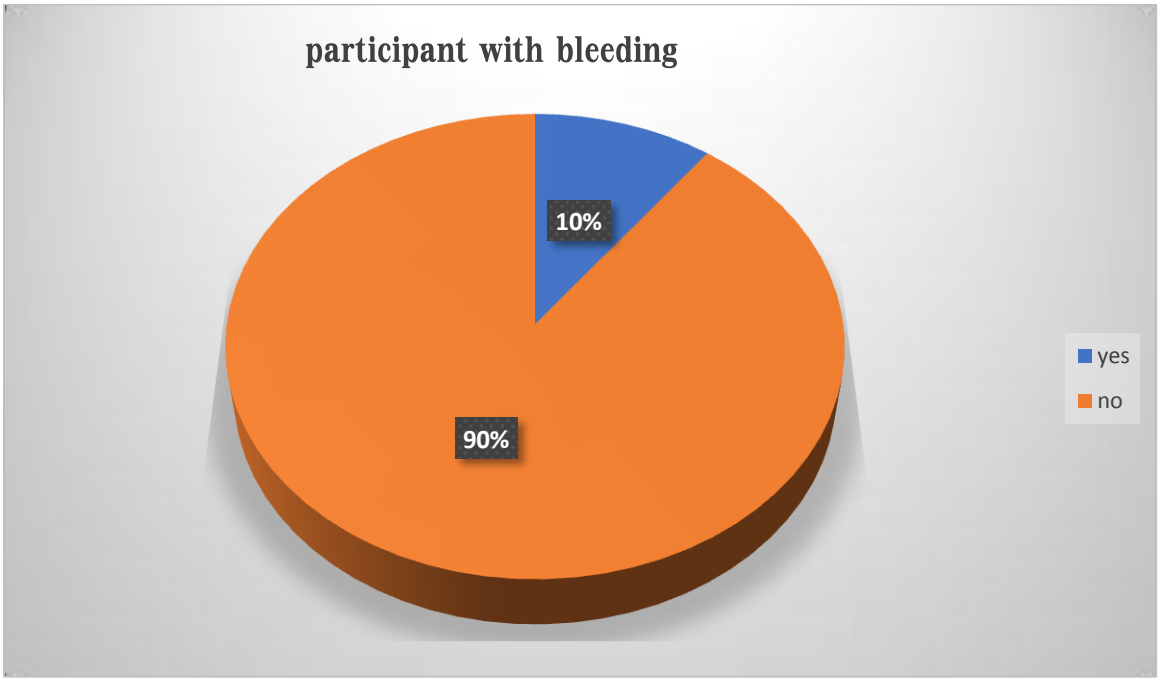

Figure 5: Bleeding status of the study participants on anticoagulant therapy at selected hospital in Addis Ababa, July 01, 2017 to July 01, 2020

Table 6: Bleeding status of the study participants using International Society on Thrombosis and Haemostasis guideline at selected hospital in Addis Ababa, July 01, 2017 to July 01, 2020

Variable	**Frequency**	**Percent**
Bleeding during follow up	42	10
Patients with major bleeding	19	4.5
Subjective findings of bleeding	28	6.7
The list of subjective finding of bleeding		
Nose bleeding	11	39.3
Active vaginal bleed	6	21.4
GI bleeding	4	14.3
Gum bleeding	3	10.7
Hematuria	3	10.7
Urethral bleeding	1	3.6

5.5.6. Occurrence of major bleeding among patients on anticoagulant therapy

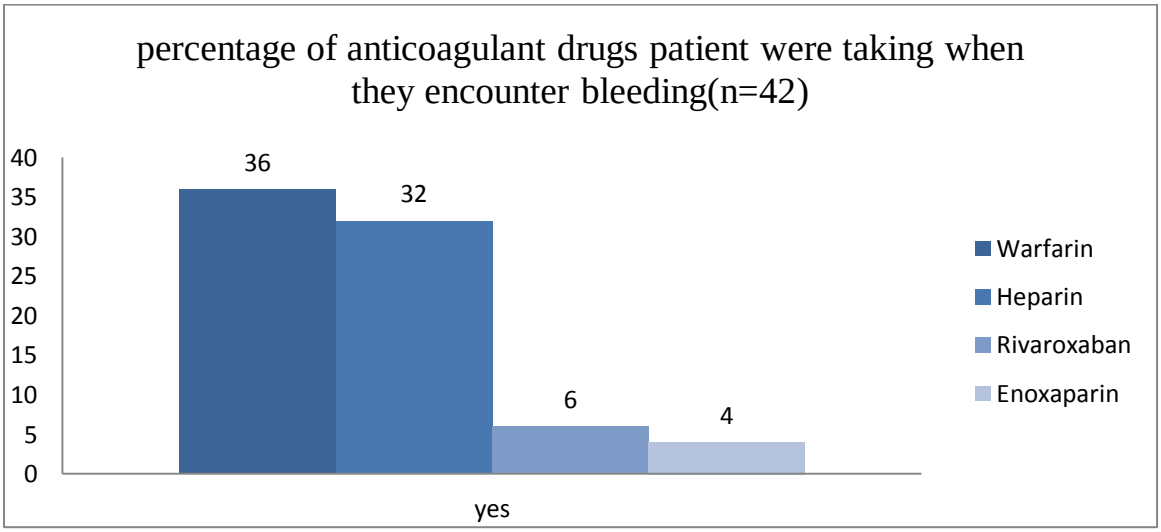

Figure 6: Percentage of anticoagulant drugs patients were taking when bleeding occur at selected hospital in Addis Ababa, July 01, 2017 to July 01, 2020

5.5.7. Over all treatment outcomes of DVT

Table 7: DVT treatment outcomes at selected hospital in Addis Ababa, July 01, 2017 to July 01, 2020

Variable		**Frequency**	**Percent**
Patient develops recurrent DVT		92	22.5
Number of recurrent DVT			
Two		82	20.1
Three		8	2.0
Five		2	.5
Current status of DVT			
Improved		210	51.5
No change		75	18.4
Complete resolution		73	17.9
Prophylaxis after complete resolution		20	27.4
Worsened		41	10.0
Death		9	2.2
Cause of death	RF 2^o to massive PE	4	44.4
	RF 2^o to acute PE	2	22.2
	Others*	3	33.3
Developed complication		81	19.9
Types of complication	PE	36	44.4
	PTS	31	38.3
	Chronic venous insufficiency	14	17.3

*Bleeding 2^o to supra-INR, RF 2^o to PE + septic shock and UGIB & hypoxia 2^o to Chronic Liver Diseases, PE: Pulmonary Embolism, PTS: Post Thrombotic Syndrome, RF: Respiratory Failure, UGIB: Upper Gastrointestinal Bleeding.

5.6. Predictors of recurrent DVT

The association of independent variables with the dependent variable was investigated using multivariate logistic regression model. On bivariate logistic regression analysis, age 36-50 and ≥51 years, female gender, bilateral DVT, presence of infection, obesity, previous surgery, recent immobilization, hypertension, RVI, patient that developed complication and level of base line INR had statistically significant association with DVT recurrence.`

The result of the multivariate logistic regression analysis showed that, bilateral DVT, obesity, hypertension, RVI, having complication, and base line INR were statistically associated with DVT recurrence. Accordingly, participant having bilateral DVT had 2.8 folds increased likelihood of recurrence than unilateral DVT (AOR=2.8, 95%CI=1.14, 6.66) and obese participant were 3.3 folds increased likelihood of recurrence than normal body mass index (AOR=3.3, 95%CI=1.15, 9.59) and participants with hypertension had 6.5 times recurrence DVT than none hypertensive patient (AOR=6.5, 95%CI=2.90, 14.70) and RVI patient were 6.3 folds increase recurrence of DVT than the opposite compartment (AOR=6.3, 95%CI=2.34, 16.94). Participant that developed complication and lower baseline INR was also statistically significant **(Table 8)**.

Table 8: The result of bivariate and multivariate logistic regression analysis of predictor factors for DVT recurrence among study participants at selected hospital in Addis Ababa, July 01, 2017 to July 01, 2020

Variables	**Recurrence DVT**		**COR (95%CI)**	**P-value**	**AOR (95% CI)**	**P-value**
	Yes	**No**				
Age of the study participant						
18-35	15(8.6%)	101(91.4%)		1		1
36-50	41(28.7%)	102(71.3%)	2.7(1.41, 5.19)	0.003	1.5(0.59, 3.84)	0.383
>=51	36(24.2%)	113(75.8%)	2.1(1.11, 4.15)	0.023	0.79(0.29, 2.17)	0.652
Sex of the study participants						
Male	25(14.9%)	143(85.1%)		1		1
Female	67(28%)	173(72%)	2.2(1.33, 3.69)	0.002	0.59(0.28, 1.25)	0.171
Types of deep vein thrombosis						
Unilateral	43(13.6%)	278(86.6%		1		1
Bilateral	49(56.3%)	38(43.7%)	8.3(4.89, 14.19)	0.000	**2.8(1.14, 6.66)**	0.024
Presence of local tenderness						
Yes	56(25.6%)	163(74.4%)	1.5(0.91, 2.34)	0.117	0.64(0.32, 1.29)	0.218
No	36(19.1%)	153(80.9%)		1		1
Presence of infection						
Yes	48(60%)	32(40%)	9.7(5.59, 16.76)	0.000	1.2(0.37, 2.92)	0.944
No	44(13.4%)	284(86.6%)		1		
Obesity						
Yes	37(68.5%)	17(31.5%)	11.8(6.22, 22.49)	0.000	**3.3(1.15, 9.59)**	0.027
No	55(15.6%)	299(84.4%)		1		1
Previous surgery						
Yes	46(41.1%)	66(58.9%)	3.8(2.32, 6.19)	0.000	0.68(0.27, 1.68)	0.410
No	46(15.6%)	250(84.4%)		1		1

Recent immobilization						
Yes	48(30.4%)	74(60.6%)	3.6(2.19, 5.79)	0.000	0.94(0.42, 2.15)	0.893
No	44(16.4%)	242(84.6%)		1		1
Hypertension						
Yes	65(52.4%)	59(47.6%)	10.5(6.17, 17.82)	0.000	**6.5(2.90, 14.70)**	0.000
No	27(9.5%)	257(90.5%)		1		1
Retroviral infection						
Yes	46(79.3%)	12(20.7%)	23.3(11.69, 46.44)	0.000	**6.3(2.34, 16.94)**	0.000
No	46(13.2%)	303(86.8%)		1		1
Patient develop complication (PE, PTS and chronic vein insufficiency)						
Yes	48(58.5%)	33(41.5%)	9.3(5.42, 16.14)	0.000	**3.7(1.60, 8.75)**	0.002
No	44(13.5%)	283(86.5%)		1		1
Use of heparin in DVT management						
Yes	55(20%)	220(80%)		1		1
No	37(28.4%)	96(71.6%)	1.5(0.95, 2.49)	0.078	0.70(0.34, 1.46)	0.345
Base line International Normalized Ratio						
<2	49(14.9%)	280(85.1%)		1		1
2-3	19(37.3%)	32(62.7%)	3.4(1.78, 6.16)	0.000	**6.6(2.86, 15.37)**	0.000
>3	24(85.7%)	41(14.3%)	34.3(11.4, 103.12)	0.000	5.3(0.98, 28.25)	0.052

5.7. Predictors of major bleeding

The strength of association between the independent variable and major bleeding was measured using 95% confidence interval and odds ratio. Accordingly, DVT type, presence of active cancer, DM and age above 75 years were associated with major bleeding by bivariate logistic regression analysis.

Multivariate logistic regression analysis showed that patients with bilateral DVT had 3.9 folds increase in major bleeding than unilateral DVT (AOR=3.9, 95%CI=1.6, 9.7) and participants having active cancer disease had 6.5 folds increase in major bleeding than those with no active cancer (AOR=6.5, 95% =2.9, 14.75). Participants whose age >75 years had 6.8 folds increase in major bleeding than those age below 75 years (AOR=6.8, 95%CI=2.03, 22.33) (as shown in **Table 9** below).

Table 9: The result of bivariate and multivariate logistic regression analysis of predictor factors associated with major bleeding among study participants at selected hospital in Addis Ababa, July 01, 2017 to July 01, 2020

Variables	**Major bleeding**		**COR (95%CI)**	**P-value**	**AOR (95% CI)**	**P-value**
	Yes	**No**				
Sex of the study participants						
Male	14(8.3%)	154(91.7%)		1		1
Female	28(11.7%)	212(88.3%)	1.5(0.74, 2.85)	0.278	0.821(0.35, 1.94)	0.653
Types of Deep vein thrombosis						
Unilateral	16(4.4%)	305(95.6%)		1		1
Bilateral	26(29.9%)	61(70.1%)	8.1(4.11, 16.05)	0.000	**3.94(1.6, 9.701)**	0.003
pitting edema						
Yes	35(11%)	283(89%)	1.5(0.63, 3.42)	0.376	0.74(0.26, 2.13)	0.573
No	7(7.8%)	83(92.2%)		1		1
active cancer						
Yes	28(32.6%)	58(67.4%)	10.6(5.27, 21.39)	0.000	**6.54(2.90, 14.75)**	0.000
No	14(4.3%)	308(95.7%)		1		1
Diabetes mellitus						
Yes	18(47.5%)	30(62.5%)	8.4(4.10, 17.19)	0.000	1.4(0.42, 4.70)	0.577
No	24(6.7%)	336(93.3%)		1		
Age >75 years						
Yes	19(57.6%)	14(42.4%)	20.7(9.25, 46.64)	0.000	**6.8(2.03, 22.93)**	0.002
No	23(6.1%)	352(93.9%)		1		1

6. Discussion

Recurrence of deep vein thrombosis occurred at a rate of 22.5%. Nine participants (2.2%) died and 19.9% of patients developed complications, PE accounted for 44.4% of these complications, followed by PTS and chronic vein insufficiency. Forty two participants (10%) had bleeding episodes, and 4.5% of participants had major bleeding (a hemoglobin level reduction of more than 3%).

A DVT incident was high in the age greater than 35 years. There were similar results in studies that were done in Addis Ababa and Jimma too (15,30). Among the sign and symptoms general swelling was the most common presenting symptom detected in all patients included in the study and it was corresponding to findings done in Singapore general hospital (33) and Queen Mary Hospital in Hong Kong (34). Similarly both in our and these studies pain and tenderness were the next commonly encountered manifestations.

Our study showed that 95.3% of the patients were having DVT in their lower limbs, only 4.7% of them had the DVT in the upper extremities, and this was in line with a study done in Zambia (26) where 82% of all patients with DVT had proximal lower limb DVT which is also noted in other studies (33,34). Unilateral limb involvement was seen in (78.7% of the patients) and the remaining (21.3%) had bilateral lower limb involvement. Higher percentages of unilateral involvement were reported in other studies (30,33).

Another research that was done in Tikur Anbessa Specialized Hospital (30) showed that the majority of the patients were females accounting for 65.4% of the total population. This is similar to our finding that showed preponderance (58.5%). However in another study conducted in Duhok Azadi Hospital (35) showed that the majority of participants were males accounting for 59.37%. This variation can be explained by the fact that the study didn't include patient with already diagnosed DVT they picked clinically suspected cases and examine them and include those who had positive Doppler finding for DVT.

Our finding showed the most common risk factors found for DVT development were longer hospital stay (immobilization) (29.9%), previous surgery (27.5%), unprovoked DVT (without any risk factors) (23%), active cancer (21.1%), previous VTE (20.6%), acute infection (19.6%), pregnancy (15.7%), heart failure (5.6%), prior history of trauma (4.2%), genetic (Anti-phospholipid syndrome) 2.2%, and age ≥ 75 years (8.1%). According to a study done in Addis Ababa (30) the most commonly noted risk factors for DVT were malignancy of any

kind (30.9%) and prolonged immobilization (19.8%). The difference can be the current study is a multi-center study. Likewise in another study in America, the CVRN VTE Study (4) found that cancer was also a common co morbid condition, affecting 36.4% of all patients. Recent immobility and/or injury were found in 41.9% of the cohort and 22.8% of patients with the event classified as unprovoked The finding with unprovoked risks was similar to our findings the variation could be due our study classified the immobility but the CRVN study puts them in general category. In contrary a study in Nigeria (36) showed only 2% were unprovoked where ours showed 94 (23%) of the patients and this variation might be due to smaller sample size used in their study.

The prevalence of recurrent DVT in our finding was 22.5% and this was comparable to study done in Addis Ababa and Jimma (15) which showed DVT recurrence rate of 26.4% slightly higher than our finding this might be due to our study was multi center and had more sample size and variation in the follow up period. It is also comparable to study conducted in USA (26.1 %) and South Africa (21.5%) (37,38). The result of the multivariate logistic regression analysis showed that, bilateral DVT, obesity, hypertension, RVI, having complication, and base line INR were statistically associated with DVT recurrence and from the recurrent DVT cases (22.5%), 20.1% had second, 2% had third, and 0.5% had fifth recurrences, respectively. One study showed patients who had both proximal and distal DVT had a higher recurrence rate than those who only had proximal or calf DVT. Higher recurrence rates were also associated with unprovoked DVT and age >65 years (37). Hansson et al. tracked 738 patients with DVT for 3.7-8.8 years in a cohort trial and discovered that the cumulative incidence of recurrent VTE was 21.5% in 5 years. Proximal DVT, malignancy, and prior thromboembolism history were found to be independent risk variables for the VTE recurrence in their multivariate survival analysis (38). In a different study, White et al. monitored 37,000 DVT patients for 6 months and suggested that factors such as age, cancer, surgeries, and length of hospitalization are associated with DVT recurrence (39). In other study baseline co morbidities of arrhythmia, congestive heart failure, and chronic kidney disease was significantly associated with recurrent VTE in 6.1% of these patients and these variations might be due to larger sample size in their study (40).

In our study, participants with hypertension had 6.5 times recurrence DVT than those who hadn’t. In a Meta analysis their review found that 3 major risk factors for VTE and its recurrence was obesity, cigarette smoking, and hypertension (41) this difference with our

study was in one variable and cause could be in our study we couldn't investigate the cigarette smoking because it is retrospective.

According to a review conducted to confirm that hypertension and DVT has a correlation after orthopedic surgery, (42) stated that hypertension may promote DVT and may be a significant risk factor for DVT occurrence, however the relationship is not clear. Most of the studies showed diabetes mellitus co morbidity was an independent predictor of developing DVT recurrence and was eight times more among patients living with DM (15) and also similar data from previous study found that diabetes mellitus was associated with a threefold increase in the likelihood of developing recurrent DVT (43).

Similar to ours another study showed development of recurrent deep venous thrombosis was strongly associated with post-thrombotic syndrome (22) aligning with ours participants with complication had 3.7 fold increase in developing recurrent DVT.

HIV infection has been widely recognized as risk for a prothrombotic illness, and this link has now been demonstrated by a vast number of studies, with VTE rates among HIV-infected individuals ranging from 0.19% to 7.63% each year. In comparison to the general population of the same age, HIV infection is associated with a two to tenfold greater risk of venous thrombosis (44). In our study RVI patient had 6.3 folds increase in recurrent DVT than the opposite compartment.

Some risk factors demonstrated a strongest association with VTE such as, low CD4+ cell count especially in the presence of clinical AIDS, protein S deficiency, and protein C deficiency. Whereas other risk factors are still controversial like protease inhibitor therapy, presence of active opportunistic infections and presence of antiphospholipid antibodies, including anticardiolipin antibodies and lupus anticoagulant.

In our finding bilateral DVT were associated with 2.8 folds increase in recurrent DVT. Patients with bilateral DVT are more likely to develop pulmonary embolism (33.8% vs. 20.8%). They were older (median age 69 years) than those with unilateral DVT. Furthermore, individuals with bilateral DVT have a higher mortality rate (9.1% vs. 5.2%), but no higher recurrence rate was seen (45).

Increase risk of DVT recurrent due to obesity were also seen in a large cohort study of VTE patients, researchers discovered that 4 years after stopping anticoagulation therapy, the adjusted HR of recurrence was 1.3 (95% CI, 0.9-1.9) (P=0.20) among overweight patients

and 1.6 (95% CI, 1.1-2.4) (P=0.02) among obese patients compared to patients of normal weight (46). Similarly in our finding obese participant were found to have 3.3 folds increased likelihood of recurrence than normal body mass index (AOR=3.3, 95%CI=1.15, 9.59).

Although anticoagulation therapy with warfarin or novel oral anticoagulants (NOACs) is the main treatments for DVT, approximately most of the patients with DVT develop complication and recurrence (14). More effective interventions are needed to deal with DVT. Our finding showed 92 patients that were on or already finished treatment developed recurrent DVT.

Our study found that 9 (2.2%) of the participants died during the study period. PE and other complications were the causes of death. In our study, the mortality associated with clinically recognized PE is comparable to that observed in the Worcester Venous Thromboembolism Study. Patients who presented with PE had a significantly higher overall death rate than those who presented with isolated DVT (13). Both in our study and Labropoulos et al. also showed strong links between PE and death. A frequent cause of death was PE (37). The foundation of treatment for most patients with venous thromboembolism is anticoagulation. Patients with pulmonary embolism should be risk stratified to determine whether advanced treatment, such as thrombolysis or embolectomy, will benefit them (41).

Result from our data showed that from all the participants, 19.9% patients had developed complication and from those who developed complication, PE accounts 44.4% followed by PTS with 38.3% and chronic vein insufficient 17.3%. CDC reported that 33% to 50% of people who have experienced a DVT will experience long-term complications (post-thrombotic syndrome), which include swelling, pain, discoloration, and scaling in the affected limb (47). Another follow up study in Sweden showed during the two-month to seven-year follow-up period, 26% of the study population developed post-thrombotic syndrome, recurrent DVT occurred in 12% of the patients, and pulmonary embolism occurred in 9% (38).

Our finding stated that 4.5% had a major bleeding characterized by hemoglobin decrease by equal and greater than 3, and DVT type, presence of active cancer, DM and age above 75 years had an association with major bleeding. Bilateral DVT had 3.9 folds increase major bleeding than unilateral DVT and participant having active cancer disease had 6.5 folds increase in major bleeding than those who hadn’t and participants whose age is above 75years had 6.8 folds increase the major bleeding than age below 75 years. Our finding was

also supported by another study done in University Hospital of Padua, Italy (48). In comparison to individuals without cancer, people with established venous thrombosis are more likely to experience major bleeding and recurrent thromboembolic complications.

Some investigations, including ours, have indicated that age greater than 75 years is related with an increased risk of bleeding, hence this parameter has been incorporated in the calculation of bleeding risk scores (49,50). Sixty five patients (12%) experienced major bleeding, and in 10 patients (2%), tragically, resulted in their deaths. Age 65 years or older, a history of stroke, gastrointestinal bleeding in the past, a serious comorbid condition (recent myocardial infarction, renal insufficiency, or severe anemia), and atrial fibrillation were five independent risk factors for major bleeding that predicted major bleeding in the participants (51).

In contrast, other studies stated no relationship with age or cancer but an INR of 8.5, a history of recent gastrointestinal lesions, and a history of recent trauma and prior noncompliance known to the medical staff were identified as independent risk factors for bleeding and major bleeding in a multivariate analysis and the variation could be in this study participants were included with INR of 5 or above and larger sample size and longer follow up duration (52).

Yet, there is general agreement that the increased risk of bleeding in the elderly is a multifactorial phenomenon (poor drug elimination, a greater likelihood of drug interactions due to the higher number of concomitant medications). Major bleeding incidents can be dangerous, as they have been shown to have a greater case fatality rate when related to VKA therapy than recurrent VTE itself. Numerous initiatives to increase the safety of VKA therapy, including as strict INR monitoring by specialized clinics and genotype-guided dosing approaches, were mainly ineffective. Recent research, however, has shown that NOACs have advantages over VKAs in terms of a decreased bleeding risk, with equivalent efficacy (53).

7. Strength and Limitations

The study uses larger sample size compared to others; we tried to corporate main outcomes of DVT (recurrent, mortality, complication, major bleeding and predictor factors for recurrent and major bleeding) that has not been addressed in other studies. There are limitations to this study's design as we used retrospective cross-sectional chart reviews. There was evidence of incomplete recording by providers or a lack of information about pertinent findings like subjective findings for bleeding were not available in most cases and most of the dates of the INR results were also not available but despite these drawbacks, the study offered helpful information and developed the necessary recommendations.

8. Conclusions

In the current study, the overall DVT recurrence rate was 22.5%, which is complicated by pulmonary embolism post thrombotic syndrome and chronic vein insufficiency and causes 2.2% death. Patients who presented with PE had higher rates of death compared with patients with isolated DVT. Recurrent VTE and major bleeding rates after DVT and PE, on the other hand, remain high. Efforts are needed to identify patients who are most at risk for VTE complications and to develop better anticoagulation strategies that are suitable for long-term use.

9. Recommendations

For health care professionals

- Patients should be educated and screened for DVT recurrence in the first three years following the initial DVT because our research indicated that recurrence rates were high during that time. Patients should also be urged to go to the hospital at the early experience of the symptoms.
- Close laboratory monitoring should be done for patient age older than 75 years old and for those with active cancer.
- Participants with PE complication should be able to get more advanced treatment in order to avoid mortality because in our finding participants with PE had high mortality incidents.

For researchers

- We recommend a prospective study that can monitor patients who have experienced DVT and precisely document the predictor factors and therapeutic approaches applied to determine the treatment outcomes. This will increase the healthcare system's ability to improve the outcomes.

For policy makers

- The country's health minister and PFSA should work and collaborate with the relevant parties on importing the DOACs in order to prevent the unwanted outcomes of DVT, which include recurrence, death, complications, and major bleeding, and mostly patients are taking warfarin due to the drugs availability and affordability.

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11. ANNEX II: Data collection tool

<table>
<tr><td colspan="3">PART I: Socio-demographic characteristics of patients</td></tr>
<tr><td colspan="2">1. Card Number_____
2. Date of Admission _____/_____/___
3. Age (yrs):_____</td><td>4. Gender: ☐Male ☐ Female
5. Weight (kg)_____ Height(cm)_____</td></tr>
<tr><td colspan="3">Part II: Types of DVT, risk factors and Clinical data</td></tr>
<tr><td colspan="2">6. DVT sites:</td><td>7. Types of DVT</td></tr>
<tr><td>☐ Upper Extremity</td><td>☐ Lower Extremity</td><td rowspan="2">☐ Unilateral ☐ Bilateral
☐Acute ☐ Chronic</td></tr>
<tr><td>☐ Proximal DVT
☐ Distal DVT</td><td>☐ Proximal DVT
☐ Distal DVT</td></tr>
<tr><td colspan="3">8. Are the sign and symptoms present:</td></tr>
<tr><td colspan="2">☐ Pitting edema
☐ Skin discoloration
☐ Pain</td><td>☐ Swelling
☐ Local Tenderness
☐ Other specify: _____</td></tr>
<tr><td colspan="3">9. What are the risk factors associated</td></tr>
<tr><td colspan="2">☐ Age >75
☐Presence of an acute infectious disease
☐ Pregnancy
☐ Active cancer
☐ Obesity (BMI >30 kg/m2)
☐ Surgery
☐ Recent immobilization ≥3</td><td>☐ Stroke
☐ History of major bleeding
☐ Use of estrogen-containing OCP or HRT
☐ RVI
☐ Previous VTE
☐chronic lung diseases
☐ Family history of VTE
☐ Others</td></tr>
</table>

days ☐ Heart failure ☐ Prior history of trauma	☐ Unprovoked
10. Co morbidity ☐ Cancer ☐ Atrial Fibrillation ☐ Diabetes ☐ Hypertension ☐ Dyslipidemia ☐ Previous stroke ☐Heart failure ☐CLD ☐Renal failure ☐CAD ☐HIV/AIDS ☐Other, specify_____	**11. Diagnosis /type of cancer** ☐ Colorectal ☐ Rectal ☐ Breast ☐Ovarian ☐ Lung ☐ Liver ☐ Cervical ☐ Other, specify: _____ **12. Prior history of surgery:** ☐ Yes ☐ No **13. If‘ ‘Yes‘‘ type of surgery** ☐ Orthopedic ☐ Abdominal surgery ☐ Cardiac surgery ☐ Other specify: _____
14. Was the patient on another blood thinning drug? With dose? ☐ Warfarin, dose_____ ☐ Aspirin, dose: _____ ☐ Clopidogrel, dose_____ ☐ Other specify, dose _____	**15. Was the patient on any other that has drug interaction with warfarin mention them with dose?**

Part III: DVT outcome measurement
I: assessing recurrent
16. Did the patient develop recurrent DVT? ☐ Yes ☐ No
17. When was the first time the patient developed the DVT?
18. How many times did the patient develop DVT? ☐ first time ☐ second time ☐ _____time
19. Current status of the patient: ☐ Worsened ☐ Improved ☐ Complete resolution ☐ No change.
20. For how long did the patient take the anticoagulants the last time diagnosed with DVT and which anticoagulant was used?
21. Did the patient take prophylaxis after completing the first treatment? ☐ Yes ☐ No
22. Did the patient developed Complication ☐ Yes ☐ No If yes what is the complication ☐
23. Time to event (days from admission date) ☐ Bleeding ☐ INR ≥ 2_ ☐ Death ☐ Recurrence
24. Did patient develop any side effect while taking the anticoagulant medication? ☐Yes ☐ No If yes what was the side effect developed and due to which drug ☐

II: Anticoagulation management practices recommended by the ACCP guidelines		
Guidelines	**Yes**	**No**
25. Was the treatment with LMW heparin , fondaparinux , or unfractionated heparin started at the first day?	☐	☐
26. Was the INR ≥2.0 for ≥24 hours before stopping parenteral anticoagulation:	☐	☐
27. Was oral anticoagulation with a vitamin K antagonist overlapped with LMW heparin, fondaparinux, or unfractionated heparin for at least four to five days?	☐	☐
28. Did the patient needed to take vitamin K at any time during his treatment?	☐	☐
if dabigatran , rivaroxaban , apixaban initiated the above questions are not needed		
III: International Society on Thrombosis and Haemostasis guideline to assess the Bleeding		
29. Did the patient have bleeding during his follow up?	☐	☐
30. Did the patient have any subjective findings of bleeding? 30.1. What were the findings?		
31. Did the patient hemoglobin decrease during his follow up 31.1 How much? _____	☐	☐

32. Did the patient have clinically overt bleeding, requiring any transfusion of 1U or more of packed red blood cells or whole blood during his follow up?	☐	☐
33. Did the patient have a decrease in hematocrit during his follow up? 33.1 How much? _____	☐	☐

Part IV: Serial coagulation profile

Parameter	**Days/Weeks/Months**									
	1	2	3	4	5	6	7	8	9	10
INR										
APTT										
PT										
	11	12	13	14	15	16	17	18	19	20
INR										
APTT										
PT										
	21	22	23	24	25	26	27	28	29	30
INR										
APTT										

PT										

Complete blood count(CBC):														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Platelet Count															
Hemoglobin															
Hematocrit															

PART V: List of all medications the patients were taking that are written in the chart

S. No	**Name of drug(s) Dosage regimen at start (dose, frequency, route)**	**Indication**	**Date**	
			Start	**Stop**