Assessment of complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

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A thesis submitted to Department of Pharmacology and Clinical pharmacy, School of Pharmacy in partial fulfilments of the requirements for the degree of masters of pharmacy in pharmacy practice (M.Pharm).

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This is to certify that the thesis prepared by Teklu Gebrehiwot entitled, *'**Assessment of complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia'*** and submitted in partial fulfilment of the requirement for the degree of masters of pharmacy in pharmacy practice complies with the regulation of the university and meets the accepted standard with respect to originality and quality.

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Abstract

Anticoagulant therapy is one of the most common form of medical treatment. The most common anticoagulant therapy complications are bleeding and thromboembolic complications. Bleeding is the primary complication. Factors that can affect the complications include age, gender, comorbidities, intensity of anticoagulant effect, length of therapy and concomitant drugs. The objective of the study was to assess complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital. A prospective longitudinal study design involving patient follow-up and chart review was conducted from November to June 2014. Chi-square test and Linear Mixed Model regression were employed to examine the relationships and associations between variables. The incidence of complications of anticoagulant therapy was found to be 60 (26%). Bleeding was the most common reported 27 (12.4%) (5.2% major, 10.7% minor), followed by thromboembolism 12 (7.1%), bruising 10 (5.9%), heparin induced thrombocytopenia 9 (5.3%) and skin necrosis 8 (4.7%). Sex, concomitant drugs, intensity of INR/aPTT values, usual trend of coagulation treatment and having coagulation profiles from different laboratory sites had been associated with complications. However, age, comorbidities, length of therapy, number of anticoagulants and anticoagulant therapy related factors were not significant risk factors. The findings of this study indicated that patient on anticoagulant therapy at medical wards were at higher risk of bleeding followed by thromboembolic complications. Availability of coagulation laboratory reagents at Tikur Anbessa Specialized Hospital and preparing guidelines on anticoagulant therapy harmonized with the laboratory values is recommended.

Key words: Complication, bleeding, thromboembolism, skin necrosis, bruising, HIT, INR, aPTT, anticoagulants

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List of Abbreviations

- 2LL	-2 restricted log Likelihood
ACCP	American college of chest physician
AF	Arterial fibrillation
aPTT	activated partial thromboplastin time
CI	Confidence interval
CRVHD	Chronic rheumatic valvular heart disease
DVT	Deep vein thrombosis
GI	Gastrointestinal
HIT	Heparin-induced thrombocytopenia
HIV	Human immunodeficiency virus
INR	International normalized ratio
LMM	Linear Mixed Model
LMWH	Low molecular weight heparin
NSAID	Non-steroidal anti-inflammatory drugs
PE	Pulmonary embolism
PF4	Platelet factor 4
PT	Prothrombin time
PT-INR	Prothrombin time- international normalized ratio
PTR	Prothrombin time ratio
SPSS	Statistical package for social sciences
TASH	Tikur Anbessa Specialized Hospital
TTR	Time in therapeutic range
U/ml	Unit/milli-liter
UFH	Unfractionated Heparin
VKA	Vitamin K Antagonists
VTE	Venous Thromboembolism

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1. Introduction

1.1. Background

Anticoagulant therapy is one of the most common medical interventions which is the mainstay of treatment and prevention of thrombosis in diverse clinical settings. [1] Warfarin and heparin are the most frequently prescribed anticoagulant drugs in clinical practice. [2, 3] Warfarin is widely used oral anticoagulant where the required dose varies within individuals, between individuals and depends on several factors. [4] On the other hand, its immediate onset of action, relatively short half-life, simple laboratory monitoring, ability to be reversed and low cost lend heparin to its broad use. [3] Activated partial thromboplastin time (aPTT) used to monitor heparin therapy and Prothrombin time-international normalized ratio (PT- INR) used to monitor warfarin therapy are the most commonly performed haemostasis tests. [5-7]

Bleeding is the primary complication of anticoagulant therapy, and is a risk of all anticoagulants even when maintained within usual therapeutic ranges. [1, 2] Thromboembolic complications have been also associated with both warfarin and heparin therapy. [2] The risk of thromboembolic or bleeding events depends largely on the time frame during which patients are outside the therapeutic range of prothrombin time (PT). [8] Skin necrosis [2], Heparin-induced thrombocytopenia (HIT) [9, 10] and bruising [5, 11] are also among the complications of anticoagulant drug therapies.

Bleeding complications are classified as major or minor bleedings. Even though, there are different ways of classifying bleeding, in most studies major bleeding is defined as fatal, intracranial bleeding, bleeding that required at least 2 units of blood transfusion or frozen free plasma, an emergency procedure either to terminate bleeding or remove a hematoma. All other bleedings are classified as minor. Thromboembolic complications like ischemic stroke or deep vein thrombosis are deemed present only if they are validated by imaging studies. [12] In patients on anticoagulation therapy, a strong correlation has been shown between high time in therapeutic range (TTR) and a reduction in complications such as bleeding and thrombosis. [8, 13] Increasing intensity of anticoagulation is one of the major risk factors for bleeding complication of warfarin.[14,15] Other

factors for anticoagulant-induced complications are patient characteristics (age, comorbidity and patient gender), concomitant use of drugs that interfere with haemostasis, drug metabolism and length of anticoagulant therapy. [15]

1.2. Statement of the problem

The main drawbacks of anticoagulation are the risk of bleeding events. The criteria for defining the severity of bleeding varied considerably between studies, accounting in part for the variation in the rates of bleeding complication reported. Much efforts have been devoted to improve the safety, however, bleeding complication still remains high. [12]

The reference range for PT and aPTT assay varies depending on the tissue thromboplastin reagents and instrument combinations each laboratories use. Thus, laboratories need to establish their own reference PT and aPTT ranges by measuring plasma of healthy volunteers. [16] These substantial variability in reagents used produce different results that have established doubt in relation to clinical practice.

The optimal therapeutic range of INR is not the same for all indications. It is likely to be influenced not only by the indication for its use, but also by patient characteristics. European experts tend to recommend higher INR ranges than do North American experts. [17] In addition, the optimal therapeutic range 2.5-3.5 in PT-INR recommended by the American Heart Association for patients in different anticoagulant indications in western countries was too high in Japanese [18] and Chinese patients [19], thus it remains uncertain whether the efficacy of anticoagulant therapy derived from western data could be extrapolated to different countries. On top of that, there have been various reports claiming the optimal clinical range should be set at 1.6-2.8 and 2.0-3.0 is desirable for high-risk cases of thromboembolism. [18]

Oral anticoagulants have a delayed onset of action and risk of thromboembolism is high during initiation. The dose required to achieve INR in the therapeutic range varies between and even within patients. [20] The use of the same fixed dose of oral anticoagulant for all patients is unachievable

because the responsiveness of different patients to anticoagulant especially warfarin is highly variable.[4] Moreover, aPTT which is used to monitor unfractionated Heparin (UFH) therapy depends significantly on patient's weight, age and gender.[7] So considering age and accurate measurement of their weight is not yet practiced to obtain optimal aPTT response to heparin therapy.

Anticoagulant therapy related complications are inevitable and lead to both substantial morbidity and expenses. [21] Unfortunately, there is little evidence to guide the management of those complications. The effects of UFH can be readily reversed with protamine sulphate and vitamin K is a specific antidote for warfarin. About 60% of the anticoagulant effect of low molecular weight heparin (LMWH) can be neutralized by protamine sulphate. In contrast, there are no specific reversal agents for any of the newer anticoagulants like rivaroxaban. The use of novel anticoagulants is further complicated by a lack of easily available laboratory tests to measure their levels and thereby optimize their clinical benefit and safety. [1, 22]

Bleeding rates reported under clinical trials which were acceptably low may be a poor guide to observed rates in real-life practice [23] intensified by the inconsistency among classification schemes in clinical studies. [17] The true incidence of bleeding depends on how bleeding was defined, how the indications were treated (in the type, timing and dose of antithrombotic agents) and on other factors such as how the study was designed.[22] In addition, there is a great controversy about factors that affect the incidence of complications. Studies had been done on quality of warfarin therapy management in out-patients [24], assessment of deep vein embolism (DVE) prophylaxis [25] and drug related problems of deep vein thromboembolism (DVT) management [26] at TASH. But, the incidence of complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital (TASH) was not known. Therefore, the present study was carried out to assess the incidence of complications, risk factors and type of complications reported due to anticoagulant therapy at medical wards of TASH. The findings would have contribution to the existing body of knowledge in the area and improves anticoagulant therapy management.

1.3. Literature review

1.3.1. Indications of anticoagulant therapy

The actual indications of anticoagulants are the same in all age groups.[4] Although anticoagulants do not directly dissolve pre-existing clot, they prevent thrombus extension and indirectly decrease clot burden by allowing the natural fibrinolytic system to proceed normally.[27] DVT prophylaxis, venous thromboembolism (VTE) treatment, Arterial fibrillation (AF) and valvular heart disease were the major clinical situations that warrant the introduction of anticoagulant therapy. Even though the duration of anticoagulant therapy remains a matter of debate in many situations [4], in patients with DVT or pulmonary embolism (PE) the length of therapy is UFH or LMWH overlap with warfarin for at least 5 days to maintain therapeutic level INR values of 2.0 to 3.0 and continue with warfarin for 3 to 6 months.[27, 2]

1.3.2. Complications of anticoagulant therapy

The normal INR range for a healthy human being is 0.8-1.2. [28] The goal of anticoagulant therapy is to keep the INR in the therapeutic range (2.0-3.0). Patients with sub-therapeutic INR values (INR < 2.0) are at increased risk for thrombosis because, if INR is too low, blood clots quickly and raise the chance of thrombosis. On the other hand, patients with supra-therapeutic INR (INR > 4.0) are at increased risk for bleeding owing to INR gets too high, it takes too long for blood to clot raising the chance of bleeding. Therefore, the quality of anticoagulation determines both thromboembolic and bleeding complications.[28-30]

PT evaluates the extrinsic and common pathway of coagulation (factor II, V, VII, X and fibrinogen).[5, 6] Deficiencies of these factors (most notably VII) and vitamin K or liver disease will prolong PT [6, 31] which increase the risk of bleeding. Deficiency of any of the intrinsic pathway coagulation factors (VIII and IX) [6] or sample taken from a heparinised catheter or cannula [31] causes prolongation of aPTT which could increase the risk of bleeding. In a clinical trial [7], the dose of heparin was adjusted according to a nomogram to achieve a target aPTT range of 60 to 85 seconds for standard aPTT reagents which correlates with the recommendation of the college of American

pathologists; individual laboratories should define the aPTT therapeutic range as the range that corresponds to a heparin concentration of 0.2 to 0.4 U/mL by protamine titration or 0.3 to 0.7 U/mL by anti–factor Xa analysis. With this approach, aPTT serves as a surrogate marker for UFH concentration.[7, 32] In fact, a fixed aPTT therapeutic range of 1.5-2.5 times the control value has become widely accepted for monitoring UFH therapy. [3, 32, 33]

Bleeding complications

Bleeding, especially intracranial bleeding is the most dreaded complication of anticoagulant therapy. [4] In a total of 102 Japanese patients [18], bleeding complications developed in 26 (25.5%) patients with 3 (2.9%) major and 23 (22.5%) minor, on the other hand, in a study in Nepal 15.7% patients had 141 bleeding events (3.8% major and 11.9% minor). [14] In a study [34] on recurrent VTE and bleeding complications in patients with cancer, 17 bleeding events occurred. Similarly, in a multi-center Study [35] on risk factors for complications of chronic anticoagulation, 1332 bleeding events (4 fatal, 31 life-threatening, 226 serious, and 1071 minor) were reported. In a study in Italy, 153 (7.6%) of (5 (0.25%) fatal, 23 major (1.1%), and 125 minor (6.2%)) bleeding complications occurred. [36]

Thromboembolic complications

Thromboembolic disease affects approximately 15% of cancer patients including superficial and deep venous thrombosis, pulmonary emboli, thrombosis of venous access devices, as well as arterial thrombosis and embolism. [37] In the evaluation of risk factors for stroke/embolism in AF study among 46 complications, 9 were thromboembolic events. [38] In a population-based retrospective cohort study in USA, the cumulative incidence of thromboembolic events was 13.1%. [39] From prospective follow-up study, patients with cancer and venous thrombosis, 20.7% patients with cancer develop recurrent VTE as compared to 6.8% in patients without cancer during anticoagulant treatment. [34] Although adequately dosed vitamin K antagonists are effective in patients with malignant disease, the incidence of thrombotic complication remains higher than in patients without malignancy.[40] In a case-control study, patients with aPTT ratio smaller than the cut-off value of

0.87 had a 2- to 3-fold increased relative risk of VTE, independently of inherited thrombophilic abnormalities.[41] In a similar study, the risk of thromboembolic complication at a prothrombin time ratio (PTR) less than 1.3 was 3.6 times higher than at a PTR of 1.3 to 1.5. [35]

Warfarin-induced skin necrosis

Skin necrosis is a rare but debilitating complication of anticoagulant therapy. It has been reported to affect 1:100 to 1:10,000 patients receiving warfarin and other VKAs and mainly observed between 3rd and 8th day of warfarin therapy, especially in patients with protein C and protein S deficiency. [2, 42] In the management of warfarin induced skin necrosis discontinuation of warfarin and reinstitution of heparin was complicated by a rapid decrease in platelet count consistent with HIT and its associated risk of platelet activation and thrombosis.[42]

Heparin-induced thrombocytopenia

Heparin induced skin necrosis and heparin induced thrombocytopenia are among the complication of heparin therapy. Heparin induced skin necrosis is an allergic immune reaction involving a complex of antibody, heparin, platelet factor 4 (PF4) and platelet begins within 1-2 days after starting heparin injections. Symptoms include redness, pain and swelling or blisters develop under the skin black-red center appears due to skin necrosis at injection sites with only about 3 cm diameter. [43]

Heparin induced thrombocytopenia is a serious potentially catastrophic and life endangering complication of heparin therapy usually occurring after 5-14 days of continuous heparin therapy. [9, 10, 44-47] It is an immune-mediated syndrome presenting as isolated thrombocytopenia or thrombocytopenia with thrombotic complications. It is caused by the binding of antibodies to complex of heparin with PF-4 and forms a highly antigenic heparin-PF-4 complex, which leads to the generation of specific immunoglobulin G heparin-PF-4 antibodies (also called HIT antibodies). HIT antibodies may activate the platelets via Fcy receptor causing the release of highly coagulable micro-particles which promote thrombosis both venous and arterial as well as less commonly necrotizing skin lesion. [44, 45, 47] More than 50% patients with isolated HIT are at risk for developing

thrombosis primarily venous thromboembolism.[48] From a meta-analysis, HIT occurs in 1-3% of all patients received UFH and in 0.3% to 0.8% of patients received LMWH. [9]

Bruising

Bruises are large areas of subcutaneous bleeding [5] caused by the escape of blood from damaged blood vessels into subcutaneous tissues. [11] Even though overlap exist with bleeding, easy bruising is commonly associated with thrombocytopenia or platelet disorders unlike bleeding which is associated with coagulation disorders. Easy bruising may be due to ecchymoses, purpura and petechiae whereas bleeding can be due to epistaxis, gastrointestinal, rectal bleeding, gingival bleeding hemarthrosis, haematuria, menorrhagia and prolonged bleeding during surgery or tooth extraction.[5] In the determination of the effect of subcutaneous injection of heparin duration on bruising, the percentage of bruising occurrence was 64% with 10 seconds and 42% in 30-seconds injection duration. In addition, the size of the bruising was smaller in the 30-second injection. [49]

1.3.3. Contributing factors for the complications of anticoagulant therapy

Socio-demographic (age and gender), presence of comorbidity, anticoagulant therapy-related risk factors and concomitant drugs have been anticipated to be associated with complications of anticoagulant therapy in many studies.

Socio-demographic and clinical characteristic of patients

An increasing body of evidence supported age as an independent risk factor for major bleeding. Major bleeding occurred more frequently in patients >75 years of old (5.1%) than in younger patients (1%). [4, 15] On the other hand, warfarin use was independently associated with higher risk of stroke, particularly in patients >75 years of old. [50] In two more studies, older patients were more likely to have more medical problems, to be taking more medications, and the anticoagulant response to warfarin was exaggerated with advanced age. [51, 52] In similar studies, on aPTT response and UFH dosing advanced age, female gender, and patient's with higher weight were associated with higher risk of bleeding. [7, 22] In a prospective study of patients with AF on warfarin therapy,

women had higher annual rates of thromboembolism off warfarin than did men (3.5% versus 1.8%).[53]

Comorbidities particularly recent surgery or trauma and renal failure were risk factors for heparin-induced bleeding.[15, 22] Impaired kidney function was associated with increased risk of stroke and bleeding due to anticoagulation. [50] Many other disease conditions; hypertension [14], cerebrovascular disease, and ischaemic stroke, history of myocardial infarction [54], serious heart disease and malignancy [15, 34] have been associated with bleeding during warfarin therapy.

In a study on dose dependent fatal complication of warfarin in pregnant women with mechanical heart valves, 27 fatal complications (22-spontaneous abortions, 2-warfarin embryopathies, 1-stillbirth, 1-ventricular septal defect and 1-growth retardation) were reported in a dose dependent manner (> 5mg had 22 and < 5 mg had 5 complications). [55] In a prospective randomized multi-center trial, [56] the occurrence of thromboembolic events was due to the INR values was <1.5 and the presence of additional risk factors such as hypertension, diabetes, post-operative infection, and a history of cancer which increased the risk of thromboembolic events, even when the recommended INR target range was 2.5–3.5.

Anticoagulant therapy related risk factors

UFH is usually delivered by continuous intravenous infusion and therapy is monitored by measuring aPTT. Traditional or physician directed dosing of UFH often leads to sub-therapeutic aPTT results due to inconsistence dosing of UFH. Conversely, validated dosing nomograms are generally favored by reducing time to achieve therapeutic anticoagulation that may be important in reducing the risk of recurrent VTE. [27] There is a strong relationship between the intensity of anticoagulant therapy and the risk of bleeding in patients with DVT, tissue heart valves, mechanical heart valves, ischemic stroke and AF. [15, 17] Increased INR values had significantly reduced the risk of ischaemic stroke. In contrast, the risk for intracranial bleeding increased particularly at levels above 3.0. Hence, INR range between 2.0–3.0 seems to offer the optimal compromise between

stroke protection and bleeding complications.[57] In randomized clinical trial, the frequency of major bleeding in patients targeted on INR 2.0 to 3.0 has been less than half the frequency in patients randomly assigned to warfarin therapy targeted at INR >3.0. [15]

Since the pharmacodynamics response of warfarin delays, initiation of warfarin therapy alone is challenging. Administration of warfarin loading doses (7.5 mg or more per day) often reach a supratherapeutic INR level that can place a patient in hypercoagulable state, increase the patient's risk of bleeding and prolonged hospital stay. These complications have been attributed to excessive depression and depletion of factor VII and protein C in the early therapy. [4, 17] A loading dose of warfarin greater than 10 mg is not recommended. [17] The American college of clinical pharmacy supports an induction dose rather than a large loading dose for initiation of therapy. The induction dose was ranged from 2 to 5 mg of warfarin per day and adjusted according to the patient's INR. [58] On the other hand, in a clinical trial compared 10-mg with 5-mg dosing nomogram of warfarin initiation, patients in the 10-mg group achieved a therapeutic INR 1.4 days earlier than in the 5-mg group. The 10-mg warfarin initiation nomogram was superior than 5-mg nomogram because it allows more rapid achievement of a therapeutic INR. [59] Statistical analysis have showed that there was significant association between dose adjustment and INR range. Out of 1103 total INR readings, 749 were outside target range among which there were 238 (31.8%) INR reading in which dose adjustment was not done. When the INR was above target range 82.4% of times dose adjustment was done. Whereas, when the INR was below target range dose adjustment was done only 61.8% of times. [14]

In a study in the assessment of anticoagulant complications and aPTT, the risk of bleeding was higher with increased aPTT and lower with decreased aPTT values. For aPTT between 60 and 100 seconds, there was approximately 1% increase in the risk of bleeding for every 10-second increase in aPTT. The aPTT range of 50 to 70 seconds was suggested as optimal therapeutic for intravenous heparin. [7] In addition, on comparing how well aPTT correlates with heparin, laboratory-based aPTT decisions agreed with heparin concentration 82% while, bedside aPTT decisions agreed 64%-

65%.[32] In a retrospective time-series study, the rate of bleeding complications using PT ratio to guide therapy was 6.7% as compared with 2.9% using INR. The total complication rate was significantly lower in patients monitored with INR (2.9%) as compared with PT (6.7%). [60]

Concomitant use of aspirin with warfarin has been associated with a higher frequency of bleeding, even in patients treated with a mean INR of 1.5.[15] In another study, in patients received at least three additional medications (22.2%) and those received fewer than three (3.4%) a significant difference in the total incidence of bleeding complications was reported. [54] Administration of tramadol, antiplatelets, heparin and NSAIDs, anticonvulsants, high dose inhaled steroids, and antibiotics are the common drugs that can cause warfarin-associated bleeding and bruising by inhibiting platelet function or increasing the INR levels. [6, 17, 31, 61]

Vitamin K plays an important role in human physiology as a cofactor for the synthesis of blood-coagulation proteins (factor IX, VII, X and prothrombin) and regulatory proteins (protein C and protein S). [30] It is important to use vitamin K only when recommended because inappropriate administration of vitamin K was associated with warfarin resistance [58] which was described as the inability to prolong the prothrombin time or raise the INR into the therapeutic range when the drug was given at the normal prescribed dose. [62] When such resistance develops, it is difficult to achieve a therapeutic INR in a timely manner, which may result in an increased risk of clotting events or thrombosis. [58] In the case of vitamin K deficiency associated bleeding smaller dose of vitamin K reverses the effect of warfarin. [62]

2. Objectives

2.1. General objective

To assess the complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

2.2. Specific objectives

- To determine the incidence of complications of anticoagulant therapy.
- To identify types of complications of anticoagulant therapy at medical wards of TASH.
- To identify potential risk factors with the complications of anticoagulant therapy.

3. Methods

3.1. Study setting and period

This study was carried out at medical wards of internal medicine department of TASH, Addis Ababa, Ethiopia. TASH is one of the federal referral and teaching hospitals in Ethiopia owned by government established in 1973. It is located in Addis Ababa and affiliated with College of Health Sciences, Addis Ababa University. The services of hospital are divided as outpatients, inpatients and emergency services. Internal medicine department has five medical wards (B5, B8, CB, D8 and medical adult intensive care unit) with different service providing capacity. The study was conducted from April 01–June 31, 2014 at medical wards of TASH where anticoagulant therapy were prescribed for admitted patients.

3.2. Study design

A prospective longitudinal study design involving patient follow up (observation) and progressive chart review was carried out to assess the incidence of complications and contributing factors.

3.3. Source population and study subject

The source population of the study were all patients who had attended their medical care at medical wards of TASH during the study period. On the other hand, the study subjects were all patients who were on anticoagulant therapy at medical wards of TASH during the study period and fulfilled the inclusion criteria.

3.4. Eligibility criteria

3.4.1. Inclusion criteria

All patients admitted to the medical wards of TASH whose age greater than or equal to 18 and received anticoagulant drugs during the study period were included as participant of the study.

3.4.2. Exclusion criteria

Patients on prophylactic dose of anticoagulants during the study period were excluded from the study. Patients on prophylactic dose of anticoagulant were excluded because the presence of

complications in the prophylactic dose is rare and needs separate study. Patients less than 18 years old were also excluded from the study for ethical considerations.

3.5. Sampling method and sample size calculation

The required sample size was calculated by using a single proportional sample size formula considering the following assumptions; 95% confidence level, margin of error (0.05), since no study had done about the incidence of complications anticoagulant therapy in Ethiopia and other African countries for this study, it was assumed that 50% of participants had complications.

$$n = (Z\alpha/2)^2\, p\,(1-p)/\, d^2$$
$$= (1.96)^2\,(0.5)\,(0.5)/\,(0.05)^2$$
$$= 384.14 = \sim 384$$

During the data collection the average number of patients on anticoagulant therapy per week were 15. The expected total number of participants for the total study period (3 months) were 15 (patients/week) X 4 (weeks/month) X 3 months = 180. Since the size of source population was less than 10,000, adjustment was done to correct for the required sample size.

Corrected sample size = Nxn/ (N+n) = (180*384)/ (180+384) = 122, was the corrected sample size. Where N= was the size of source population and n= was the non-corrected sample size. To compute for non-respondents 10% (=12) of the total sample size was added. Thus a total of 134 study subjects were the required sample size but the actual sample size collected were 176 then after 169 were analysed.

All participants who fulfilled the inclusion criterion were included in the study without sampling since small number of patients was on anticoagulant therapy drug the study period.

3.6. Study variables

Independent variables

- Socio-demographic characteristics
- Comorbidity
- Anticoagulant therapy related risk factors

- Intensity of INR/aPTT values
- Variation of laboratory sites
- Coagulation treatment modifications
- Concomitant drugs
- Length of anticoagulant therapy

Dependent variable

- **Complications** (bleeding, thromboembolism, heparin induced thrombocytopenia, anticoagulant induced-skin necrosis and bruising)

3.7. Data collection procedure and management

3.7.1. Data collectors

Two pharmacists were recruited and trained on how to approach participant patients, what information to collect, secure their consent, create awareness about the objective of the study and how to contact the principal investigator.

3.7.2. Data collection instrument

A follow up data abstraction format was developed by compiling a number of questions adapted from similar study materials, review of relevant literature and articles that could address the objective of the study. Pre-test of the data abstraction format was carried out on 15 patients which were not included in the final analysis before the actual data collection started and modification was done based on feedback from the pre-test.

Data abstraction format **(Annex. II)** was generally designed to include information about socio-demographic characteristics, comorbidity (ischemic stroke, history of myocardial infarction, serious heart disease, history of bleeding, hypertension, pregnancy, cancer and others), anticoagulant therapy related risk factors (intensity of anticoagulant effect, indication and dose adjustment of anticoagulant therapy, inappropriate use of vitamin K, and others), concomitant drugs, variation of laboratory sites and the usual trend of coagulation treatment practice in the study setting.

Data was collected and medical records were scrutinized in order to pursue all complications and potential risk factors of anticoagulant therapy on each follow-up days.

3.7.3. Data quality assurance

To assure the quality of data, data collectors were trained, every activities were followed by principal investigator for the completeness of data collection, terms used were made clear and corrections were given during the pre-test step before staring the main study. All completed data were examined and intensively cleaned before analysis.

3.8. Data analysis procedure

Data was checked and cleaned for completeness and consistencies then coded, entered using Epi-Data version 3.1 and analysed using SPSS version 21. Simple descriptive analysis was used to show the frequencies and percentage of variables. Cross tabulation chi-square test and Linear Mixed Model (LMM) analysis were done to obtain the relationships, intercepts, slopes, F-test and the confidence interval of statistical associations. The strength of statistical associations were measured by estimate of the intercept and 95% confidence intervals. Statistical significance was declared at $P<0.05$ and variables which shown statistical significant association ($P < 0.05$) in the LMM were included in the final fit model. Linear mixed model use intercept and slope to interpret the fixed and random effects of the variables. Intercept is interpreted as the difference in magnitude whereas difference in the rate of changes is expressed as the slope of the variables in comparison.

3.9. Ethical consideration

Ethical clearance approval was obtained from Addis Ababa University, College of Health Sciences, school of pharmacy and school of medicine, department of internal medicine research review committees. Participants of the study were asked for consent before taking part in the study and confidentiality of responses were assured.

3.10. Operational definitions

Activated partial thromboplastin time: Is a performance indicator measuring the efficacy of both the intrinsic and common coagulation pathways used to detect abnormalities in blood clotting and monitoring the treatment effects of unfractionated heparin.

Heparin induced thrombocytopenia: Is a 50% decrease in platelet from baseline. [9, 10]

Incidence: Is the number of complications during the study period observed in patients at risk of developing complications**.**

International normalised ratio: It is the ratio of a patient's PT to a normal (control) sample, raised to the power of international sensitivity index values used to determine the clotting tendency of blood in warfarin therapy.

Major bleeding: Is a nature of bleeding which requires interventions (medical treatment, medical evaluation, or at least 2 Units of blood transfusion therapy to maintain a haemoglobin value) [12, 17]

Minor bleeding: Bleeding that was reported but did not require additional testing, visits or medical intervention like changes in medication type, dose or frequency. [17]

Prothrombin time: Is the time it takes plasma to clot after the addition of tissues factors. It is used to measure the extrinsic and common coagulation pathways.

Sub-therapeutic range: INR < 2.0, where patients are at increased risk for thrombosis. [30]

Supra-therapeutic range: INR > 4.5, where patients are at increased risk for bleeding. [29, 30]

Therapeutic range: INR in the optimal range between 2.0 and 3.0. [30]

Time in therapeutic range: Is the fraction of the number of INR/ PT or aPTT values within therapeutic ranges to the total number of INR/ PT or aPTT tests. [17]

4. Results

Hundred seventy six patients were recruited and seven of them were excluded from the analysis because of the exclusion criteria. Four were on prophylactic dose of heparin and three were below 18 years old thereby, getting the number of participants to be 169.

4.1. Socio-demographic characteristics

The age of participants ranged from 18 to 85 years, with 85 (50.3%) less than or equal to 40 years, 55 (32.5%) from 41 to 64 years, 20 (11.8%) from 65-74 years and 9 (5.4%) were greater than or equal to 75 years old. Among the 169 patients, 92 (54.4%) were female whereas, 77 (45.6%) were male (Table 1).

Table 1. Socio-demographic characteristic of patients on anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Socio-demographic characteristics	Frequency	Percent
Age range		
≤40	85	50.3
41-64	55	32.5
65-74	20	11.8
≥75	9	5.4
Sex		
Male	77	45.6
Female	92	54.4

4.2. Clinical characteristic of the patients

Among the participants of the study 133 (78.7%) of them were on treatment and the remaining 36 (21.3%) were on secondary prevention protocol of anticoagulant therapy. The most common indications for anticoagulant therapy were VTE 113 (66.9%) followed by CRVHD 69 (40.8%) and stroke 15 (6.7%). The least common indications were atrial thrombosis 9 (4.0%), coronary artery disease 10 (6.0%) and others 8 (3.6%). From the total participants 154 (91.1%) had comorbidities.

Congestive heart failure 47 (30.3%), cancer 41 (26.5%) and hypertension 38 (24.5%) were the most common comorbidities. A 76 (49.0%) of participants had multiple comorbidities as compared with the total comorbidities (Table 2).

In the assessment of the number of anticoagulant indications, 121 (71.6%) patients had one, 43 (25.4%) had two, 4 (2.4%) had three and 1 (0.6%) had four indications (Fig.1). On the other hand, among patients with comorbidity 56 (33.1%) had one, 56 (33.1%) had two, 29 (17.2%) had three comorbidities, 13 (7.7%) had more than three comorbidities and (15, 8.9%) had no comorbidities (Fig. 2).

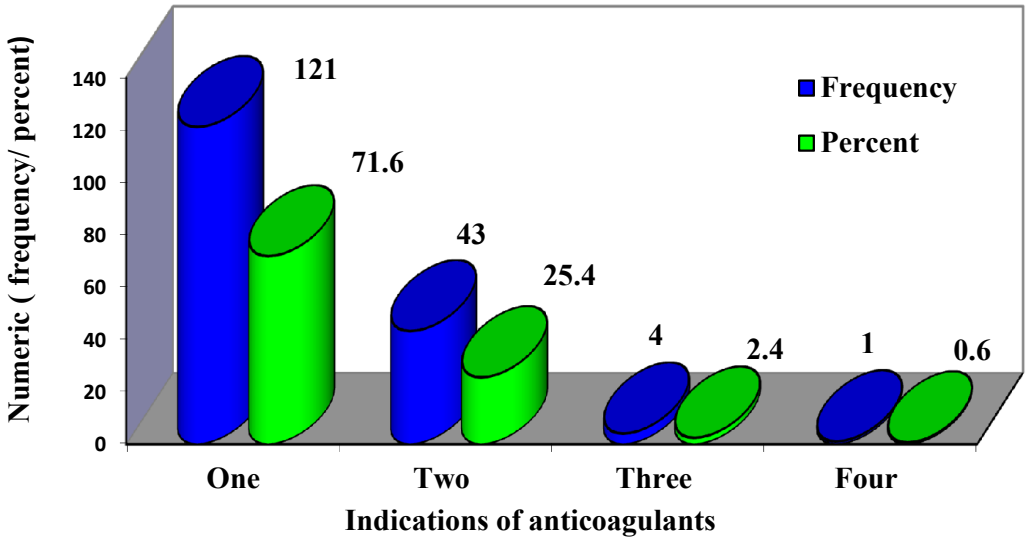

Figure 1. Number of indications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

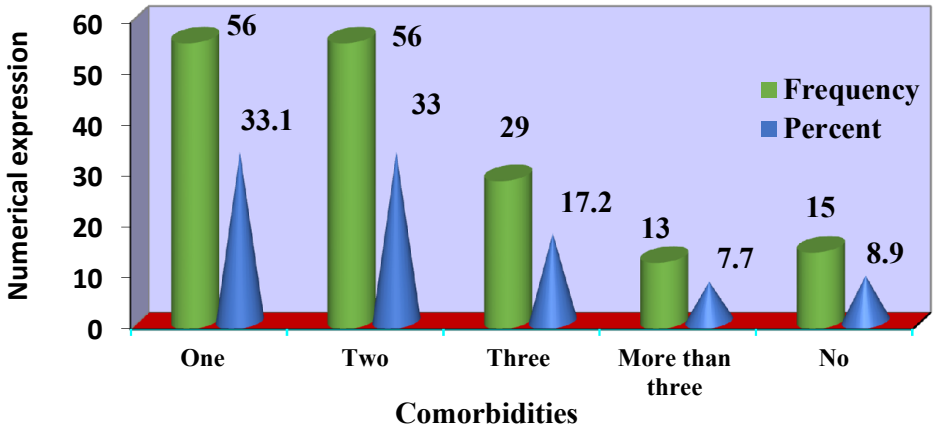

Figure 2. Number of comorbidities patients on anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Table 2. Clinical characteristic of patients on anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Clinical characteristics	Frequency	Percent
Type of therapy		
Treatment	133	78.7
Secondary prevention	36	21.3
Indication of anticoagulant therapy (type)		
Venous thromboembolism (VTE)	113	66.9
Chronic Rheumatic Valvular Heart disease (CRVHD)	69	40.8
Stroke	15	8.9
Coronary artery disease (CAD)	10	6.0
Atrial Thrombosis (Left and Right)	9	5.3
Others*	8	4.8
Total	224	132.5
Co-morbidity (#)		
Yes	154	91.1
No	15	8.9
Co-morbidity (type)		
Congestive Heart Failure	47	30.3
Cancer	41	26.5
Hypertension	38	24.5
Community acquired pneumonia	28	18.1
Diabetes Mellitus	21	13.5
Tuberculosis of different types	21	13.5
Anaemia	18	11.6
Renal insufficiency	16	10.3
HIV	13	8.4
History of Ischemic stroke/ myocardial infarction	9	5.8
Recent surgery	9	5.8
Liver disease	8	5.2
Others**	76	49.0
Total	345	222.6

**(superior sagittal sinus thrombosis, portal vein thrombosis, ventricular thrombosis, antiphospholipid syndrome and thrombotic in superior vena cava)*

*** (urinary tract infection, shock, plural effusion, asthmatic, pancytopenia, dyslipidaemia, seizure, thyrotoxicosis, etc.)*

4.3. Distribution of anticoagulant drug therapy

During the follow up period of the study, the frequencies of anticoagulant drug use were 73 (13.0%) heparin only, 225 (40.0%) warfarin only, 195 (35.0%) both heparin and warfarin, 12 (2.0%) enoxaparin only and 9 (2.0%) warfarin and enoxaparin. Nevertheless, 51(9.0%) of the total follow up periods patients had interrupted anticoagulant therapy. (Fig.3).

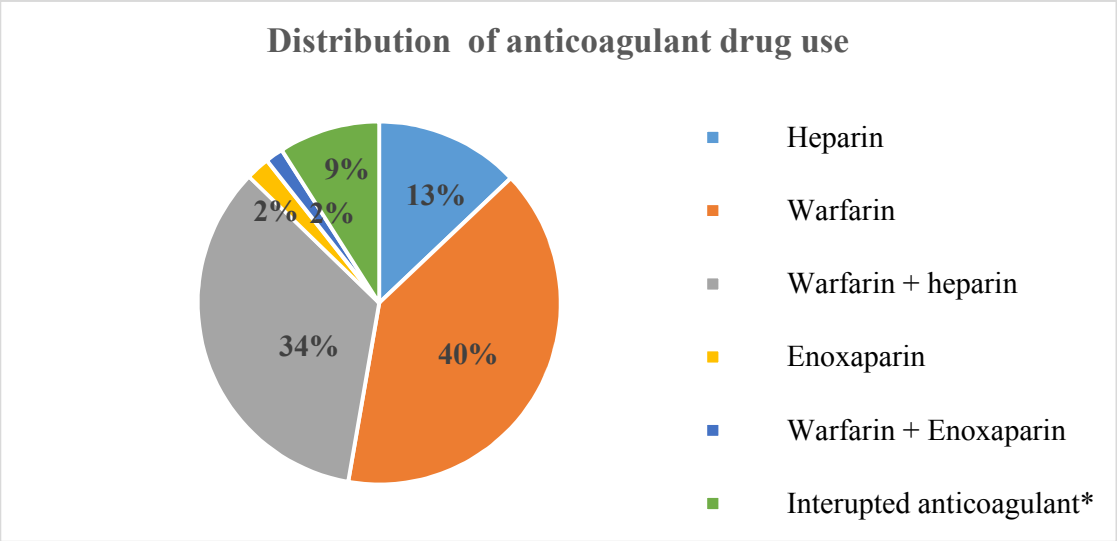

Figure 3. Frequencies of anticoagulant drug use at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014. This figure shows the distribution of anticoagulant drug use during the follow up. *When patients were not on anticoagulants due to discontinuation or holding.

The length of therapy of the study patients on heparin were 42 (32.8%) less than 5 days, 48 (37.5%) of them were on heparin for 5-10 days, furthermore, 32 (25.0%) of them were within 10-30 days and 6 (4.7%) patient were on heparin for greater than 30 days. On the other hand, the duration of therapies on warfarin less than 5 days, 5-10 days, 10-30 days, greater than 30 days were 17 (11.7%), 36 (24.9%), 75 (51.7%) and 17 (11.7%), respectively. In the case of enoxaparin 9 (64.3%) patients had less than 5 days length of therapy, 5 (35.7%) had between 5-10 days length of therapy and no data were obtained for greater than 10 days on enoxaparin therapy (Table 3).

Table 3. Length of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Length of anticoagulant therapy	Frequency	Percent
Heparin		
Less than 5 days	42	32.8
5-10 days	48	37.5
10-30 days	32	25.0
Greater than 30 days	6	4.7
Warfarin		
Less than 5 days	17	11.7
5-10 days	36	24.9
10-30 days	75	51.7
Greater than 30 days	17	11.7
Enoxaparin		
Less than 5 days	9	64.3
5-10 days	5	35.7

Note: the length of therapy given above includes bridge therapies like heparin and warfarin and enoxaparin and warfarin.

4.4. Coagulation profiles of study participants

From the total 169 patients, 165 of them had coagulation profile recorded as INR and aPTT. During the study period 565 INRs and 551 aPTTs values were recorded. The mean INR values was 2.71± 0.09 (ranged from 0.67 to 23.09). In contrast, the mean aPTT values were 78.65±4.06 (ranged from 13.1 to 337.20). A comprehensive range of INR values were prepared based on ACCP [17] and 37 (6.5%), 123 (21.8%), 158 (28.0%), 109 (19.3%), 69 (12.2%), 44 (7.8%), 11 (1.9%) and 14 (2.5%) had INR values ≤1.2, between 1.2-1.5, 1.5-2.0, 2.0-3.0, 3.0-4.5, 4.5-9.0, 9.0-10.0 and greater than 10.0 values, respectively. Among the INR values 318 (56.3%) were below range, 126 (22.3%) were above the range and only 121 (21.4%) were within the therapeutic range (Table 4).

Among the aPTT values, 106 (18.7 %) were ≤ 26 seconds, 66 (12.0 %) were between 26-30 seconds, 151 (27.4 %) were between 30-50 seconds, 58 (10.5%) were between 40-50 seconds, 82 (14.9%)

were between 50-100 seconds and 91 (16.5%) had aPTT values prolonged more than 100 seconds (Table 4).

Table 4. Coagulation profiles of patients on anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Coagulation profile		Mean, frequency	Percent
INR range (min- max)†		0.67-23.09	
Mean (n= 565)		2.71± 0.09	
aPTT range (min- max)†		13.1-337.20	
Mean (n=551)		78.65±4.06	
INR range	≤1.2	37	6.5
	1.2-1.5	123	21.8
	1.5-2.0	158	28.0
	2.0-3.0	109	19.3
	3.0-4.5	69	12.2
	4.5-9.0	44	7.8
	9.0-10.0	11	1.9
	≥10.0	14	2.5
aPTT Range	≤ 26	103	18.7
	26-30	66	12.0
	30-40	151	27.4
	40-50	58	10.5
	50-100	82	14.9
	≥ 100	91	16.50
INR Laboratory result values			
	Below therapeutic range	318	56.3
	Within therapeutic range	121	21.4
	Above therapeutic range	126	22.3

(min-max)† = minimum and maximum

4.5. Contributing factors for complications of anticoagulant therapy

In this study, hypercoagulable state, sub-therapeutic INR/aPTT values, supratherapeutic INR/aPTT, dose adjustment, loading dose, dug-drug interactions, no current laboratory values, inappropriate use of vitamin K and others were some of the anticoagulant related factors identified that could affect the complications of anticoagulant therapy. Among the participants, 156 (92.3%) of them had one or more anticoagulant therapy related contributing factors. Hypercoagulable state were observed in (32, 18.9%) patients, on the other hand, the number of patients with sub-therapeutic INR/aPTT level (135, 79.9%), supra-therapeutic INR/aPTT level (69, 40.8%), no dose adjustment (142, 84.0%), no loading dose (5, 3.0%), drug-drug interactions (134,79.3%), no updated laboratory values (96, 56.8%), inappropriate use of vitamin K (7, 4.1%) and other anticoagulant therapy related factors (treatment shifting with no reason, on anticoagulant treatment before admission, drug-food interactions, in appropriate diagnosis and financial problems) (23, 3.6%) were factors that may affect the complications of anticoagulants (Table 5 and 6).

In the assessment of contributing factors for complications, the presence of concomitant drugs were seen in 151 (89.3%) patients with 86 (50.9%) of them were on more than three concomitant drugs that could interact with anticoagulant drugs. Similarly, in the assessment of variability of laboratory sites, among participants, 86 (50.9%) of them had their coagulation profile from one site, 53 (31.4%) from two sites, 20 (11.8%) from three sites and 6 (3.5%) had their coagulation profiles from four different laboratory sites (Table 5). It is not surprising to say that the usual trend of coagulation treatment done by medical practitioners might affect the complications of anticoagulant therapy. During the study period 111 (65.7%) of the patients had treatment modification in a total of 232 cases included: discontinuation of the drug (82, 48.5%), holding the dose (61, 36.1%), reducing dose (33, 19.5%), increasing dose (22, 13.0%) and treatment shift (13, 7.7%) (Table 5 and 6).

Table 5. Qualitative assessment of contributing factors for the complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Variables	Frequency	Percent
Anticoagulant therapy related factors		
Hypercoagulable state	32	18.9
Sub-therapeutics INR/aPTT level	135	79.9
Supra-therapeutics INR/aPTT level	69	40.8
Dose adjustment not done	142	84.0
Loading dose not given	5	3.0
Inappropriate use of Vitamin K	7	4.1
Drug-drug interactions	134	79.3
No updated laboratory values	96	56.8
Others*	23	13.6
Total	643	418.9
Treatment modification		
Discontinuation of the drug	82	48.5
Holding the dose of the drug	61	36.1
Reducing the dose	33	19.5
Using alternative dosing	5	3.0
Increasing the dose	22	13.0
Restarting the dose	6	3.6
Treatment Shifting	13	7.7
Others**	10	5.9
Total	232	137.3

* *(no bridging at the same time, absence of coagulation profile, treatment shifting with no reason, on anticoagulant treatment before admission, warfarin toxicity when PT is greater than aPTT, drug-food interactions, in appropriate diagnosis, no laboratory result after changing drugs, financial problems)*

** *(wrong treatment for aspirin with warfarin, wrong diagnosis restarting bridging therapy, providing vitamin K intravenous and 4 units of frozen free plasma for major bleeding, holding and discontinue for unconfirmed diagnosis, changing therapy without updated coagulation profile, providing vitamin K 1 mg)*

Table 6. Quantitative assessment of contributing factors for complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Variables	Frequency	Percent	Cumulative percent
Anticoagulant therapy related factors			
One	13	7.7	7.7
Two	68	40.2	47.9
Three	52	30.8	78.7
More than three	23	13.6	92.3
No	13	7.7	100.0
Concomitant drugs use			
One	13	7.7	7.7
Two	27	16.0	23.7
Three	25	14.8	38.5
More than three	86	50.9	89.3
No	18	10.7	100.0
No. of treatment modifications			
One	34	20.1	20.1
Two	48	28.4	48.5
Three	23	13.6	62.1
More than three	6	3.6	65.7
No	58	34.3	100.0
No. laboratory sites			
One	86	50.9	50.9
Two	53	31.4	82.3
Three	20	11.8	94.1
Four	6	3.5	97.6
No laboratory results	4	2.4	100.0

4.6. Complication of anticoagulant drug therapy

The total incidence of complications of anticoagulant therapy in relation with the total time of the participants at risk of developing complications were 60 in 26% patients. Bleeding complications accounted for 27 (12.4%), with 9 (5.3%) major and 18 (10.7%) minor bleedings. Thromboembolism was the second with 12 (7.1%), followed by skin necrosis, HIT and bruising 8 (4.7%), 9 (5.3%) and 10 (5.9%), respectively. From this study bleeding complication had the highest incidence of complications, whereas skin necrosis had the lowest incidence (Fig. 4 and 5).

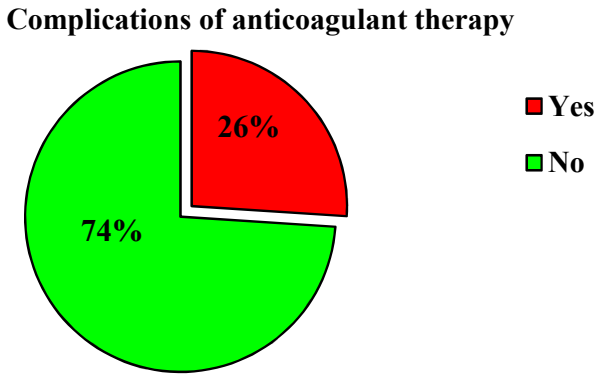

Figure 4. Incidence of complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014.

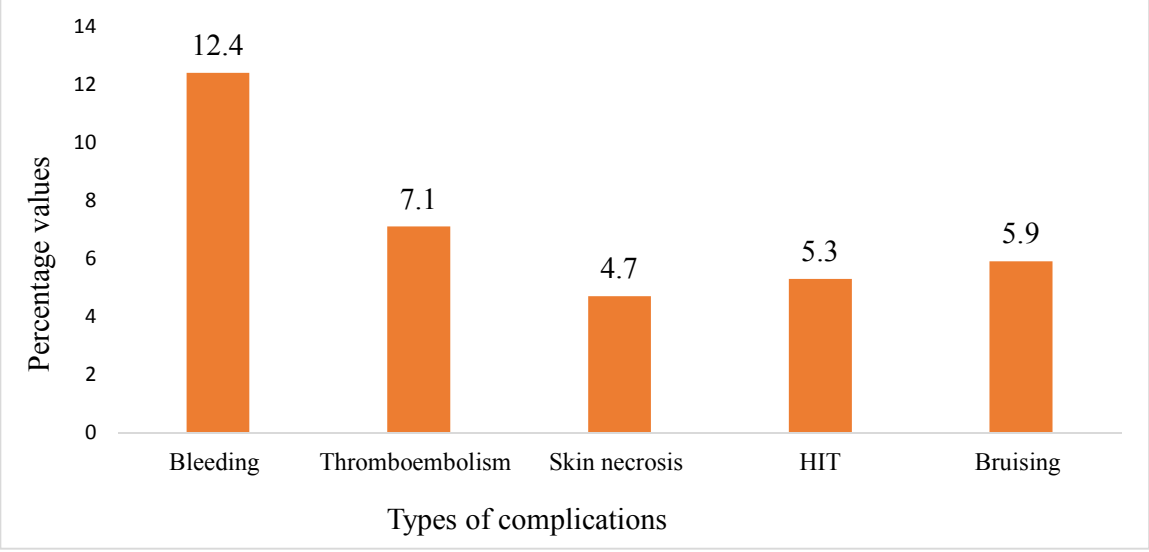

Figure 5. Types of complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

As shown in Table 7, bleeding complications were reported as 13 (7.6%) epistaxis, 1 (0.6%) intracranial bleeding, 2 (1.2%) gingival bleedings, 6 (3.6%) gastrointestinal bleedings, 2 (1.2%) genitourinary bleeding and 3 (1.8%) other bleeding complications. On the other hand, 6 (3.5%) stroke and 6 (3.6%) recurrent VTE were thromboembolic complications.

Table 7. Incidence of bleeding and thromboembolic complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Type of complications	Frequency	Percent
Bleeding		
Epistaxis	13	7.6
Intracranial bleeding	1	0.6
Gingival bleeding	2	1.2
Gastrointestinal bleeding	6	3.6
Genitourinary bleeding	2	1.2
Others*	3	1.8
Severity of bleeding		
Minor bleeding	18	10.7
Major bleeding	9	5.3
Recurrent thromboembolism	12	7.1
Stroke	6	3.5
Recurrent VTE	6	3.6

** (active bleeding from trauma, bleeding from the wound site, sputum blood tingled due to high INR)*

4.7. Relationship between independent variables and complications

The result of cross tabulation between coagulation profiles and complications had shown that patients in INR range values from 1.2 to 1.5 and from 1.5 to 2.0 had the lowest incidence of complications 27 (22.0%) and 51 (32.3%), respectively. In addition to that, increasing INR values were significantly correlated with increasing complications which was statistically significant at

the estimated correlation coefficient of 22.54 at P=0.001, 95% degree of confidence. As the INR values increased, the incidence of bleeding complication was increased where, the highest incidence was reported when the INR values were greater than 10.0. However, thromboembolic complication was decreased as INR values increased. The highest thromboembolic complication was reported, when the INR values was between 1.5-3.0. (Table 8).

In a similar way, aPTT values ranged from 30 to 40 second of coagulation time was correlated with the lowest likely incidence of complication which was statistically significant (X^2=23.67, P<0.001) with 95% degree of confidence. More thromboembolic complication was attained with aPTT values less than 26 second whereas change in bleeding complications was likely similar with increased aPTT values. Increased aPTT values was correlated with decreased thrombosis. (Table 8).

In addition to coagulation profile values, being female sex (X^2=4.53, p=0.033), number of coagulation treatment modifications (X^2= 10.16, P= 0.001), coagulation profile results from different laboratory sites (X^2= 15.26, P= 0.002) were correlated with the presence of complications which were statistically significant at 95% degree of confidence. On the other hand, age (X^2= 0.52, P=0.771), number of anticoagulant drugs used (X^2= 0.353, P=0.553), anticoagulant therapy related factors (X^2 =0.19, p= 0.667), comorbidities (X^2= 0.55, P= 0.457), concomitant drugs (X^2= 5.40, P=0.067) and length of anticoagulant therapy (X^2= 7.59, P= 0.055) were not correlated with the incidence of complications (Table 9).

Table 8. Correlation between coagulation profiles and complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Coagulation profiles	N (%) types of complications						Chi-square (X^2)	P-value
	Bleeding	Thrombo embolism	Skin necrosis	Bruising	HIT	Total (yes)		
Intensity of INR values								
INR ≤ 1.2	7 (53.8%)	3 (23.1%)	1 (7.7%)	8 (61.5%)	1 (7.7%)	13 (35.1%)	22.54	0.001
INR 1.2-1.5	15 (55.6%)	7 (25.9%)	2 (7.4%)	3 (11.1%)	11 (40.7%)	27 (22.0%)		
INR 1.5-2.0	26 (51.0%)	14 (27.5%)	14 (27.5%)	9 (17.6%)	11 (21.6%)	51 (32.3%)		
INR 2.0-3.0	21 (52.5%)	11 (27.5%)	7 (17.5%)	4 (10.0%)	10 (25.0%)	40 (36.7%)		
INR 3.0-4.5	18 (60.0%)	6 (20.0%)	7 (23.3%)	4 (13.3%)	6 (20.0%)	30 (43.5%)		
INR 4.5-9.0	12 (57.1%)	1 (4.8%)	5 (23.8%)	5 (23.8%)	2 (9.5%)	21 (47.7%)		
INR 9.0-10.0	4 (80.0%)	0 (0.0%)	0 (0.0%)	2 (40%)	0 (0.0%)	5 (45.5%)		
INR ≥ 10.0	10 (90.9%)	0 (0.0%)	2 (18.2%)	2 (18.2%)	1 (9.1%)	11(78.6%)		
Intensity of aPTT values (seconds)								
aPTT ≤ 26	6 (57.1%)	9 (32.1%)	1 (3.6%)	5 (17.9%)	8 (28.6%)	28 (27.2%)	23.67	0.000
aPTT 26-30	9 (60.0%)	4 (26.7%)	6 (40.0%)	2 (13.3%)	0 (0.0%)	15 (22.7%)		
aPTT 30-40	25 (50.0%)	12 (24.0%)	11 (22.0%)	3 (26.0%)	4 (28.0%)	50 (33.1%)		
aPTT 40-50	8 (57.1%)	2 (14.3%)	1 (7.1%)	0 (0.0%)	5 (35.7%)	14 (24.1%)		
aPTT 50-100	21 (60.0%)	3 (12.5%)	9 (25.7%)	6 (17.1%)	4 (11.4%)	35 (42.7%)		
aPTT ≥ 100	27 (56.3%)	10 (20.8%)	10 (20.8%)	7 (14.6%)	1 (22.9%)	48 (52.2%)		

x^2= estimated correlation coefficient

Table 9. Correlation of independent variables and complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Variables		Complications		Chi-square (X^2)	P-values
		Yes	No		
Age	≤ 40	23 (27.1%)	62 (72.9%)	0.52	0.771
	41-64	15 (27.3%)	40 (72.7%)		
	≥ 65	6 (20.7%)	23 (79.3%)		
Sex	Male	14(18.2%)	63 (81.8%)	4.53	0.033
	Female	30 (32.6%)	62 (67.4%)		
Number of anticoagulants	1	14 (23.3%)	46 (76.7%)	0.35	0.553
	>1	30 (27.5%)	79 (72.5%)		
Anticoagulant related factors	No	23 (28.4%)	58 (71.6%)	0.19	0.667
	Yes	19 (25.3%)	56 (74.7%)		
Comorbidity	No	28 (25.0%)	84 (75.0%)	0.55	0.457
	Yes	13 (31.0%)	29 (69.0%)		
Treatment modification	No	19 (23.2%)	63 (76.8%)	10.16	0.001
	Yes	16 (55.2%)	13 (44.8%)		
Concomitant drugs	< 3	9 (22.5%)	31 (77.5%)	5.40	0.067
	≥ 3	34 (30.6%)	77 (69.4%)		
Variability of laboratory sites	No	1 (5.6%)	17 (94.4%)	15.26	0.002
	1	14 (15.9%)	74 (84.1%)		
	2	17 (33.3%)	34 (66.7%)		
	≥ 3	13 (50.0%)	13 (50.0%)		
Length of therapy (days)	No	0 (0.0%)	4 (100%)	7.59	0.055
	<5	9 (15.3%)	50 (84.7%)		
	5-10	27 (29.0%)	66 (71.0%)		
	10-30	32 (28.6%)	80 (71.4 %)		
	> 30	10 (43.5%)	13 (56.5%)		

x^2= estimated correlation coefficient

A linear mixed model was done for all independent variables in order to identify their association with the dependent variable incidence of complications. The model of fit for each variables was determined by using -2 restricted log Likelihood (-2LL) the smaller- is- better from the information criteria displayed when the linear mixed model runs. Different covariance types were used to obtain the best fit model for each variables expressed as estimated fixed effects. As shown in table 10,

female sex (F= 4.600, P= 0.033, CI= - 0.277 (-)-0.012), at least three coagulation treatment modifications (F= 6.069, P= 0.001, CI= 0.207-0.586), coagulation profile results from at least three different laboratory sites (F= 5.591, P= 0.001, CI= 0.056-0.944), intensity of INR values (F=4.536, P < 0.001, CI= -0.445 (-) -0.170), intensity of aPTT values (F= 4.676, P < 0.001, CI= -0.457 (-)-0.158) and concomitant uses of at least three drugs (F=2.788, p= 0.024, CI= 0.0342- 0.467) were statistically associated with the incidence of complications at 95% degree of confidence. On the other hand, age (F=0.256, P= 0.504, CI= -0.134-0.266), comorbidity (F=1.279, P= 0.283, CI= -0.274-0.370), length of therapy (F= 2.565, P= 0.055, CI= 0.068 - 0.496), anticoagulant related factors (F= 0.504, P= 0.605, CI= -0.162-0.391) and the number of anticoagulant drugs (F= 0.353, P= 0.553, CI= -0.181- 0.097) were not statistically associated with the presence of complications of anticoagulant therapy.

Table 10. Linear mixed model analysis of factors associated with complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Variables	F- test	P-values	95% CI
Age	0.256	0.504	-0.135-0.266
Sex	4.600	0.033	-0.277(-)-0.012
Comorbidity	1.279	0.283	-0.274- 0.370
Coagulation treatment modifications	6.069	0.001	0.207- 0.586
Anticoagulant related factors	0.504	0.605	-0.162- 0.391
Number of anticoagulant drugs	0.353	0.553	-0.18 - 0.097
Concomitant drug use	2.788	0.064	0.034- 0.467
Variability of laboratory sites	5.591	0.001	0.056- 0.944
Length of therapy	2.565	0.055	0.068-0.496
Intensity of INR values	4.536	0.000	-0.447 (-) - 0.170
Intensity of aPTT values	4.676	0.000	-0.457 (-) - 0.158

Finally, among the independent factors statistically associated with the presence of complications of anticoagulant therapy were selected for the final fit model of the LMM. Variables that were not

statistically associated in the multi analysis were rejected and the analysis was rerun until the last best model with smaller-is-better model fit using the information criteria -2LL was attained. Length of therapy was not statistically associated with the incidence of complications and the model was not best fit according the information criteria of -2LL then it was dropped out from the model. The analysis was rerun to attain the best final model fit. In this study the mean estimated overall fixed effect of the incidence of complication was increased to 0.462 as the variables were added in to the model. From Table 11, the incidence of complications of anticoagulant therapy due to female sex was 0.163 more than that of due to males at 95% confidence levels. The current usual practice of coagulation treatment with at least three modifications in patients on anticoagulant therapy was positively associated with the incidence of complications ($F=10.06$, $p<0.001$,) and 0.236 more than those with no coagulation therapy modification done.

In a similar way, concomitant use both less and more than three drugs were statistically associated with the incidence of complications ($F= 5.14$, $P=0.048$, 95% CI = 0.002-0.324) and ($F= 5.14$, $P= 0.003$, 95% CI= 0.081-0.380), respectively. Participants with coagulation profile results at least from three different laboratory sites had 0.188 more incidence of complications than participants with coagulation profile results from one laboratory site which was statistically significant ($F= 7.885$, $P<0.001$, 95% CI= -0.290 (-)-0.086). According to the final model of LMM, INR range 1.2-1.5 had 0.214 lower incidence of complications than INR values ≥ 4.5 ($F=1.718$, $P= 0.007$, 95% CI (-0.368 (-)-0.060). On the other hand, aPTT values between 40-50 second had 0.241 lower incidence of complications as compared with aPTT values greater than 100 seconds which was statistically significant ($F= 2.340$, $P= 0.001$, 95% CI= -0.384 (-)-0.098) (Table 11).

Table 11. Linear mixed model final fit model analysis factors associated with complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Variables		Estimates	F- test	P-values	95% CI
Sex	Male	-0.163	18.572	0.000	-0.237(-)-0.089
	Female	0		0	0
Usual trend of treatment	1	0.040	10.061	0.520	-0.083 -0.163
	2	-0.030		0.579	-0.137-0.077
	≥ 3	0.236		0.000	0.119 -0.352
	No	0		0	0
Concomitant drugs	<3	0.163	5.140	0.048	0.002-0.324
	≥ 3	0.231		0.003	0.081-0.380
	No	0		0	0
Variability of laboratory	1	-0.014	7.885	0.456	-0.025 -0.013
Sites	2	-0.043		0.392	-0.143 -0.056
	≥ 3	-0.188		0.000	-0.290 (-) -0.086
	No	0		0	0
Intensity of INR values	≤ 1.2	-0.169	1.718	0.101	-0.371 -0.033
	1.2-1.5	-0.214		0.007	-0.368 (-) -0.060
	1.5-2.0	-0.142		0.251	-0.285-0.021
	2.0-3.0	-0.091		0.219	-0.236- 0.054
	3.0-4.5	-0.053		0.477	-0.200 -0.094
	≥ 4.5	0		0	0
Intensity of aPTT values	≤ 26	-0.082	2.340	0.239	-0.218 -0.054
	26-30	-0.142		0.059	-0.290 -0.005
	30-40	-0.099		0.093	-0.215-0.016
	40-50	-0.241		0.001	-0.384(-) -0.098
	50-100	-0.096		0.163	-0.230 -0.039
	≥ 100	0		0	0

4.8. Trends of coagulation profiles and complications of anticoagulant therapy

From Figure 6, the minimum mean of aPTT value during follow up days was 46 second at the first day. The difference between consecutive means was large in the aPTT values and generally the trend looked rapidly increased from 1st day to the 7th day. In addition to that, aPTT coagulation profile had the highest mean value at the 6 -7th days of follow up.

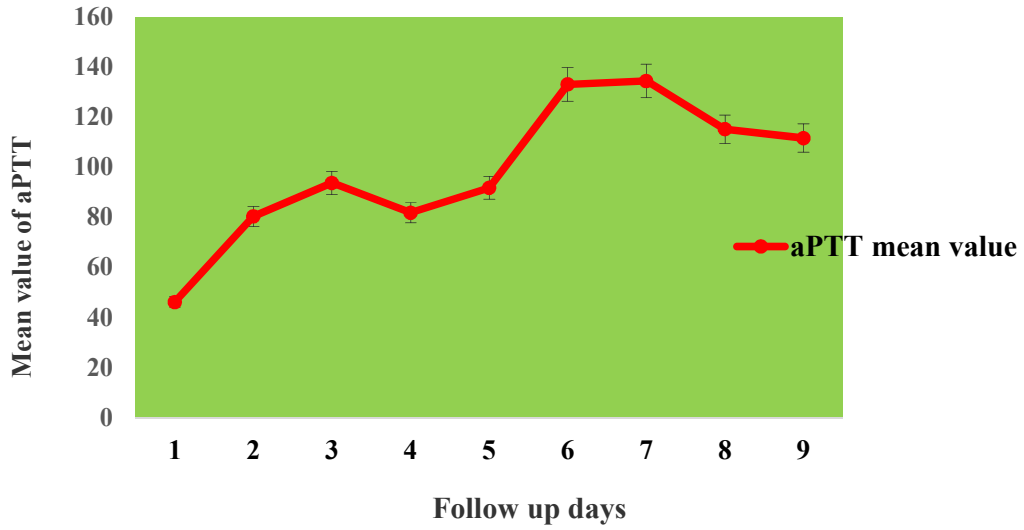

Figure 6. Mean sequential aPTT value of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Similarly, the minimum mean of INR value during follow up days was 1.91 at the first day. The highest mean INR value of 3.57 was reported at the 3rd follow up day (Fig. 7). The number of complications was also manipulated based on follow up days. The highest number was during the 3rd day on follow up and was continuously decreased from the 4th -7th follow up days (Fig. 8).

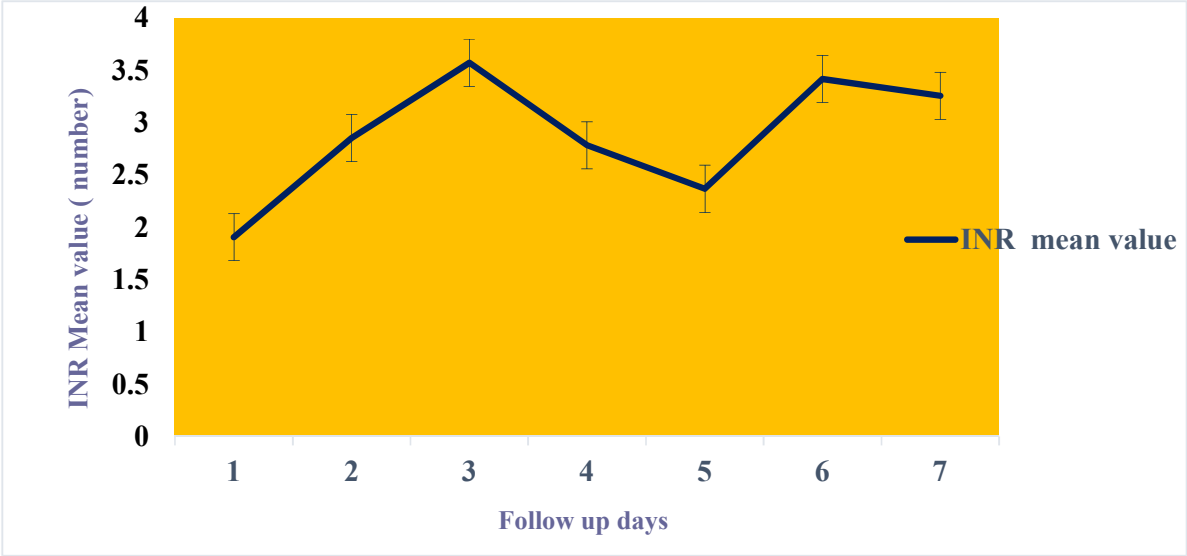

Figure 7. Mean sequential INR coagulation profile values of anticoagulant therapy at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

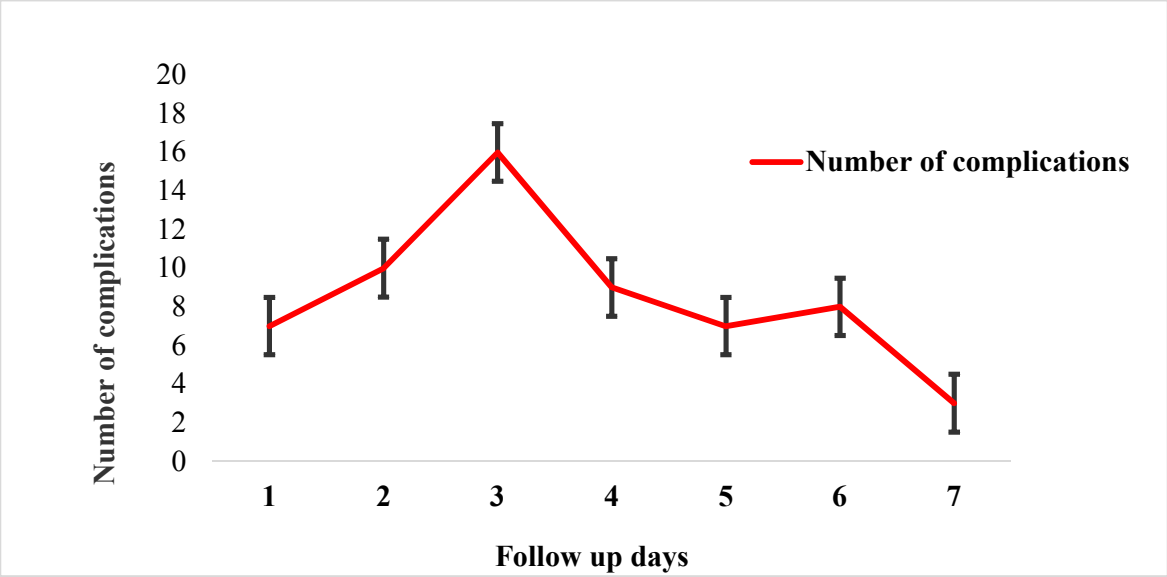

Figure 8. Number of complications of anticoagulant therapy on follow up days at medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

4.9. Assessment of interventional needs of anticoagulant therapy

In addition to spot recommendation suggested for the medical practitioners during the presence of complications, assessment of interventional need was done to minimize the incidence of complications as well as manage those complications that had happened. Almost all 166 (98.2%) patients need one or more interventional recommendations based on the presence of comorbidity, type of anticoagulant used, intensity of anticoagulant therapy and coagulation laboratory results. 128 (75.7%) patients need setting INR/aPTT target goals, 10 (5.9%) providing loading dose, 10 (5.9%) anticoagulant treatment shifting, 160 (94.7%) of the them need dose adjustment, 139 (82.2%) counselling on drug-drug interactions, 90 (53.3%) reloading when aPTT less than 50 seconds, 15 (8.9%) restarting the dose of the previous drug and 50 (29.6%) patients with other recommendations were also obtained from the result. So, based on the result more than 90% of patients had dose adjustment and drug-drug interaction counselling problems on the other hand, the practice of proving loading dose was appropriate in more than 90% patients (Table 12).

Table 12. Interventional need assessment for anticoagulant therapy at wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2014

Interventional need assessment	Frequency	Percent
Interventional need (#)		
Yes	166	98.2
No	3	1.8
Interventional need (types)		
Setting INR/aPTT target goal	128	75.7
Providing loading dose	10	5.9
Dose adjustment	160	94.7
Counselling on drug-drug interaction	139	82.2
Restarting the dose of the drugs	15	8.9
Reloading when aPTT values < 50 second	90	53.3
Treatment shifting anticoagulant drugs	10	5.9
Other recommendations assessed*	50	29.6
Total	602	356.2

**(Bridging warfarin with heparin, checking coagulation profile, decreasing the dose as every other day bases, holding heparin, increase the dose of warfarin, loading with heparin and taking current coagulation profile, providing vitamin K for warfarin complicated)*

5. Discussion

The present study was undertaken to identify incidence, types of complications and risk factors for the complications of anticoagulant therapy at medical wards of TASH. Warfarin, heparin and enoxaparin are anticoagulant drugs mostly used for anticoagulation in Ethiopia. Bleeding, thromboembolism, skin necrosis and heparin induced thrombocytopenia are some of the complications of anticoagulant drugs.

In this study, the most common indications of anticoagulant therapy were VTE 113 (66.9 %) followed by CRVHD 69 (40.8%). In a population-based retrospective cohort study in Minnesota USA [39], the primary indications of anticoagulant were VTE (39%), stroke or transient ischemic attack (21%), AF (11%) and coronary artery disease (7%). More indications were reported with DVT and AF as well as lower indication for stroke in comparison with the study in USA. The presence of more VTE and CRVHD indications might be correlated with the incidence of thromboembolic complications.

In the present study, the incidence of complications was 60 in 26% of patients. In a study done by Wehinger et.al[38] in the evaluation of risk factors for stroke/embolism in AF patient's, 46 complications (14.6%) occurred. Similarly, in a study in USA [39] the three months cumulative incidence of bleeding and thromboembolic was 8.3%. In comparison with the number of complications in the AF study, the reason more complications reported might be due to the inclusion of different indications rather than AF only. In addition to that HIT, skin necrosis and bruising complications were included that raised the number of complications. Although changing the dose of anticoagulant therapy was employed to decrease the incidence of complications, still it is higher and needs greater commitments among professionals in preparing working guidelines on specific indications.

Bleeding was the primary complication accounted for 27 (12.4%) with 9 (5.3%) major and 18 (10.7%) minor bleeding. In a study in Nepal [14] a total of 141 bleeding events occurred in 15.7% patients with (3.8%) major and (11.9%) minor bleedings. In a prospective cohort study in Italy [36], 153 (7.6%) with 28 (1.4%) major and 125 (6.2%) minor and in a multi-center study [35], 1332 bleeding events occurred. Similarly from Japanese study [18], 3 (2.9%) major bleeding, such as cerebral and GI bleeding and 23 (22.5%) patients with minor bleeding complications such as nasal, gingival or subcutaneous bleeding were reported. In a post-valve surgery study [14] on warfarin therapy epistaxis was the most common bleeding event (16.8%). Unlike the above studies, in this study, intracranial bleeding, GI bleeding, incidental nasal bleeding and active bleeding from trauma were considered as major bleeding since more than 2 units of blood or frozen free plasma were given during the incidence [17, 18] and epistaxis or nasal bleeding, gingival, genitourinary bleeding were among the minor bleedings described. Epistaxis was the most common bleeding event. The difference in types and incidence of bleeding might be due to difference in study settings (out patients, inpatients and special anticoagulant clinics), in therapeutic ranges of indications, common comorbidities, defining the type of bleeding, duration of anticoagulant therapy and sample size included.

The second type of complication was thromboembolism with the incidence of 12 (7.1%) included; stroke with transit attack stroke and hemiparesis 6 (3.5%), recurrent DVT 4 (2.4%), recurrent PE 2 (1.2%). In a study on warfarin in post-valve surgery [14], 5 thromboembolic complications (Transient ischemic attack of limbs-1, hemiparesis-3, acute left limb ischemia-1) developed in 5 patients. From prospective follow-up study, 20.7% patients with cancer developed recurrent VTE as compared to 6.8% in patients without cancer. [34] Among 46 complications in AF study, 9 were thromboembolic events. [38] In the current study, the incidence of thromboembolic complication was higher than post-valve surgery and AF studies, this might be due to hypercoagulability owing to defective naturally occurring anticoagulant mechanisms or heightened levels of procoagulant factors due to shorten aPTT. It is being increasingly appreciated that hypercoagulability is one of the triggers that may

alter the balance of haemostasis. In particular, increased levels of fibrinogen, II, VIII, IX and XI coagulation factors recently emerged as independent risk factors of VTE. Trying to minimize the fear of bleeding complications, physicians often withhold or discontinue anticoagulation and antiplatelet therapy, which in turn lead the patient to be in sub-therapeutic range and develop further ischemia or thrombosis might be the second reason. The third justification could be poor assessment of patient's platelet level which leads to the presence of higher HIT, where in this study, the presence of higher HIT could support the higher incidence of thromboembolism. Furthermore, the dose of anticoagulants used might be high, since higher intensity of anticoagulant therapy might not be a protective for the development of secondary thromboembolism. Difference in study setting might be also another reason for the difference in the incidences.

In this study, the incidence of HIT was stated as 9 (5.3%). From a meta-analysis, HIT occurred in 1% to 3% of all patients on UFH and in 0.3% to 0.8% of patients on LMWH. [10] But, in this study, the incidence was higher than the meta-analysis. This could possibly be due to difference in defining the event among the studies and inappropriate recording of baseline platelet counts. Based on this result, having baseline platelet count for all participants could end up with more mild HIT incidences. This is in fact related with increase in thromboembolic and skin necrosis complications.

Skin necrosis is one of the rare debilitating complications of anticoagulant therapy that has received less attention. In the current study, the incidence of skin necrosis was 8 (4.7%). Even though, the report was underestimated in many case reports and articles, the incidence of skin necrosis was stated as 0.01% to 1%. [2, 42] In this study, the incidence was higher than the expected. The reason might be the assessment of skin necrosis was done on all anticoagulants (warfarin and UFH) rather than individuals, in addition to, switching between heparin and warfarin since both of these drugs were associated with the presence of skin necrosis. Heparin-induced skin necrosis is commonly seen in patients with HIT which can activate the clotting process resulting in clots in small blood vessels of the skin. The presence of higher female participants and higher dose of anticoagulant use might be additive justifications that could increase skin necrosis. Patient's susceptibility might

be another reason since patients with lupus anticoagulant, hypersensitivity to heparin, antiphospholipid antibodies, protein C or S deficiency, antithrombin or factor VII deficiency and hereditary or acquired thrombophilias had been shown to be more susceptible for skin necrosis. [43] Misdiagnosis between skin necrosis and bruising might be also the other reason since symptoms of skin necrosis and bruising have similarities. The discontinuation of heparin therapy in most cases had implications for the lower incidence of heparin induced skin necrosis but, in this study inappropriate use of heparin like (treatment shift from UFH to enoxaparin, using higher dose of UFH) might be the reason for the increase in the incidence. It is so far, important early recognition and prevention of skin necrosis since continued treatment may precipitate life-threatening complications in other organ systems.

Bruising was one of complications of anticoagulant therapies reported with 10 (5.9%) incidences. In a study done by Zaybak et al [49] the effect of subcutaneous injection duration of heparin on bruising, the percentage of bruising occurrence was 64% with 10-second and 42% in the 30-second injection durations. The reason for the lower incidence in this study might be due to duration of heparin injection was not taken into consideration and failure in distinguishing between skin necrosis and bruising, where some bruising might be reported as skin necrosis.

In the assessment of risk factors for the complications of anticoagulant therapy using LMM analysis, age was not significantly associated (F= 0.256, P=0.504, 95% CI=-0.135-0.266). An increasing body of evidence supports that age >75 years as an independent risk factor for major bleeding. [4, 15] On the other hand, warfarin use was independently associated with a higher risk of stroke in patients >75 years old. [50] In another studies, anticoagulant response to warfarin was overstated with advanced age. [51, 52] In one more study, aPTT response and UFH therapy advancing age was associated with higher risk of bleeding. [7] In contrast, in a retrospective multicenter study, [63] age was not associated with risk of bleeding. Similarly with the multicenter study in this study, the effect of age was not statistically associated with the incidence of complications. This could be due to marginal age range of study participants were lower and smaller number of patients were greater

than 75 years old. The other reason might be younger ages are less likely to have more problems and take many medications that can interact and affect the incidence of complications.

In this study, LMM has shown that sex was found to be significantly associated with the incidence of complications (F= 4.60, P= 0.033, 95% CI= -0.27 (-) -0.012). Being female sex was more likely to complicate than male from anticoagulant therapy. In two studies [40, 53], female sex was an independent risk of thromboembolism than did men. In another studies [7, 22], female gender was associated with higher risk of bleeding. This study was consistence with the above studies where, female sex was an independent risk factor for the presence of complications. In line with this women appear to be more commonly affected than men from skin necrosis. So, female sex can influence the decision to use anticoagulant drug therapy.

The presence of concomitant drugs was one of the independent risk factors for the complication outcome of anticoagulant therapy. In the current study, concomitant drugs (F=2.788, p= 0.024, 95% CI= 0.0342-0.467) were significantly associated with the incidence of complications. The presence of at least three concomitant drugs was more likely to complicate than less three concomitant drugs. This result was consistent with the study done by Hughes et al [54] indicated incidence of bleeding events in patients taking at least three additional medications (22.2%) was significant higher than less than three (3.4%). In this study, 50.9% patients had at least three additional drugs. The presence of three concomitant drugs increases the chance of availability of drugs that can change the pharmacokinetic properties of anticoagulant drugs so that prolongation and shortening of coagulation profiles will end up with complications.

In the current study, the presence of comorbidities was not associated with complications (F= 1.279, P= 0.283, 95% CI= -0.274-0.370). There were a good lines of evidence that comorbidities; particularly recent surgery or trauma and renal failure were risk factors of bleeding [15], impaired kidney function was associated with increased risks of stroke and bleeding. [15, 50] Hypertension [14, 54], cerebrovascular disease [15, 54], ischemic stroke and history of myocardial infarction [54], malignancy

[15, 34, 40] and pregnancy [55] had been also associated with bleeding and thromboembolic complications during anticoagulant therapy. Unlike to the above studies, a multi-center retrospective study [63] had shown that hypertension was not associated with risk of bleeding. In this study, even though the suspected comorbidities were indicated, the correlation as well as association of the presence of more than three comorbidities and complications was not significant. This might be due to the number of each suspected independent comorbidities was not enough to produce significant association or the presence of many other comorbidities that do not affect the complications of anticoagulant therapy. So greater emphasis should be given to individual effects of the suspected comorbidities rather than the presence of more than three comorbidities.

In this study, in the LMM analysis, the presence of at least three anticoagulant treatment related risk factors (Table 6) did not shown a significant difference with less than three factors in the incidence of complications (F= 0.504, P= 0.605, 95% CI= -0.162-0.391). This could be due to the number of each contributing factors were small to produce a significant association with the complications. On the other hand, most of these factors were assessed based on the assumption that the optimal therapeutic ranges and management protocols used in other studies were applicable in the same way in the current study setting. Therefore, it was one point forward for the identification and refection of the optimal coagulation profiles and management protocols of anticoagulant drugs. This is because the result of this analysis was an indication that patients who were sub-therapeutic based on other studies and guidelines might be in the therapeutic ranges so that the presence of complication was decreased. It is important to address the issue of optimal therapeutic ranges of commonly used coagulation profiles and the recommend anticoagulant drug management protocols.

In the assessment of number of coagulation treatment modifications, 111 (65.7%) patients had one or more anticoagulant drug treatment corrections (Table 5 and 6). Practicing at least three of the usual trends in the study setting was statistically associated with complication (F= 10.06, p <0.001) as compared with no coagulation therapy modification done. This might be due to higher percentage of discontinuation and holding of anticoagulant drugs practiced which were not appropriate. In a

study conducted by Sridhar et al [64] discontinuation of warfarin was associated with the risk of recurrent TVE and stroke. Traditional or physician directed dosing of heparin often leads to sub-therapeutic aPTT values. [27] Therefore, setting a standard coagulation profile ranges and preparing institutional anticoagulant management guidelines might be needed to minimize the incidence of complications due to usual trend of anticoagulant therapy.

In the present study, cross tabulation chi-square had shown that, the highest incidence of bleeding was observed in INR values > 10.0 and the highest incidence of thromboembolism was found in the INR values < 1.5. In a randomized clinical trial [15], retrospective analysis in Netherland [40] highest incidence of bleeding was found in the INR values > 3.0. In addition, from the Netherland study [40], highest incidence of recurrence thromboembolism was found in the INR values < 2.0. In comparison with the above studies in this study, the highest incidence of bleeding was observed at higher INR values but, the highest incidence of thromboembolism was at lower INR value than that of the study in Netherland. These results were biologically plausible because lower INRs have been associated with high levels of thromboembolic events and higher INRs have been associated with high levels of bleeding. The significant difference in the INR ranges of the incidences might be due to genetic variation of patients that leads to variation in pharmacokinetics and pharmacodynamics anticoagulants, the study designs, dietary intake and compliance of participants.

In this study, TTR of INR values was 21.4% whereas, 78.6% of INRs were out of the optimal INR ranges (2.0-3.0). This result was very low when compared with that of China [13] (50%), Sweden [13] (76.2%), Ethiopia TASH outpatients [24] (34%) and Western studies [12] (61- 66%). In patients on anticoagulation, a strong correlation has been found between high TTR and a reduction in complications.[13] From the current study, TTR at the medical wards was lower than TTR at the outpatients of TASH even though both results were sub-optimal. It is known that the optimal therapeutic range of INR is not the same for all indications. In this study, INR range ≥ 4.5 had been significantly associated with the presence of complications (F=1.718, P=0.007, 95%). Even though INR range of 2.0-3.0 had not been associated with the highest incidence of complications, INR

range 1.5-2.0 seems to be with the lowest incidence of complications according to the correlation. The optimal therapeutic INR range 2.5-3.5 recommended by the American Heart Association for patients in different anticoagulant indications in western countries was too high in a Japanese [18] and Chinese [19] patients as the therapeutic range. Hence, it still remains uncertain whether the optimal therapeutic range of anticoagulant therapy derived from western data could be extrapolated into different genetic makeup group of peoples with different risk factors of complications. Therefore, a randomized clinical trial or large scale multi-center cohort study should be done to determine the optimal therapeutic INR range for Ethiopia.

In the current study, the intensity of aPTT value was statistically associated with the incidence of complications. The aPTT values greater than 100 seconds was more likely for the presence of complications (F= 2.340, P= 0.001, 95% CI= 0.098 - 0.384) as compared with aPTT values 40-50 seconds. In a study conducted by Granger et al [7] the risk of bleeding increased dramatically beyond aPTT values of 60 to 70 seconds and lower with decreased aPTT values. In a case-control study, patients with aPTT ratio smaller than the cut-off value had 3-fold increased relative risk of VTE. [41] The difference in aPTT values in the above studies could be due to the difference in laboratory sites involved in the study that could have different heparin concentration agreements. Since aPTT values depends on weight, age and sex of participants [7, 22] those might be the reason that leads to the differences. In this study the dose of heparin therapy was not based on weight that might be associated with lower aPTT values, while different studies used weight based heparin to maintain aPTT values within range. To definitively address the issue of optimal aPTT range, patients would need to be randomized to various aPTT target ranges.

In addition, participants with coagulation profile results at least from three different laboratory sites was more complicated from anticoagulant therapy than results from the same laboratory site. This result was logically expected and the reason might be laboratory sites could possibly affected by analytical factors like tube used to collect sample and distance, technical skill and analytical

methods led to different coagulation references thereby, change in the management of coagulation based on their results might end-up with complications.

In the assessment of trends of complications, INR and aPTT during the follow up, at the 3rd day, highest number of complications was reported consistent with higher mean values of INR and aPTT. This might be due to the delay in action of warfarin therapy, coagulation profile results from difference laboratories and usual practice of coagulation treatment at the medical wards. Therefore, INR and aPTT values might be used to predict risk of complications and effects of anticoagulant drugs.

6. Limitations

- This study was not a multi-center study addressing different patient comorbidities (surgical, orthopaedic, paediatric and gynaecology wards) that may have different incidence of complications so this incidence does not reflect the overall incidence of anticoagulant therapy at TASH.
- Data from the outpatient clinics (haematology and cardiac) was not incorporated into the study due to difference in study settings, setup barrier in data collections and over crowed patients.
- The sample size of participants was not maximum to make generalization due to renovation of the surgical wards. Therefore, caution should be exerted in extrapolating the results for clinical use.
- The data collection system was very difficult to record all points at the time of follow up with inconsistence of diagnosis and clinical practice of the medical practitioners. This might have impact on incidence and associated factors of complications.

7. Conclusions

In general, the study found that significant number of patients had anticoagulant therapy related complications with more pronounced incidence of bleeding followed by thromboembolism, which could be attributed to the presence concomitant drugs, intensity of INR/aPTT values, number of coagulation treatment modifications, patients with coagulation profile results from at least three different laboratory sites and being female gender. However, the type of therapy, age, presence of comorbidities, number of anticoagulants, length of anticoagulant therapy, anticoagulant therapy related factors and number of indications of anticoagulant were not contributing factors for the complications. These findings highlight the need for greater understanding of the risk factors of complications of anticoagulant therapy at medical wards. Furthermore, increased incidence of skin necrosis, heparin induced thrombocytopenia complications needs a great concern and warrants further investigation.

8. Recommendations

Based on the results found the following points are recommended

- Assessment of the incidence of complications should be done at multi-center of TASH including surgical, paediatric and oncology wards.
- It is also recommended to prepare anticoagulant drugs use algorithm and INR/aPTT value ranges optimal for the specific indications of anticoagulants.
- Availability of coagulation profile laboratory reagents at TASH and preparing guidelines on anticoagulant therapies harmonized with the laboratory values is recommended.
- A randomized clinical trial or a large scale prospective cohort study should be done to determine the optimal therapeutic ranges of coagulation profiles at difference study settings at national levels.

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Annexes

Annexe I: Consent form and information sheet

Addis Ababa University, School of Pharmacy, Department of Pharmacology and Clinical pharmacy study on 'Assessment of complications of anticoagulant therapy at medical wards' of Tikur Anbessa Specialised Hospital, Addis Ababa, Ethiopia.

Greeting:

Hello, my name is_____. I am here today to collect data on complications of anticoagulant therapy at medical wards of Tikur Anbessa Specialised Hospital. The study is being conducted by Mr. Teklu Gebrehiwot from Addis Ababa University, School of Pharmacy Department of Clinical pharmacy and Pharmacology, post graduate program.

The purpose of this study is to determine and identify the incidence of complications and associated risk factors of anticoagulant drug therapy prescribed at medical wards. This is a prospective longitudinal cohort follow up study, so I request you to take part in this study and respond genuinely since your cooperation and willingness is greatly helpful in identifying complications and risk factors for the complications of anticoagulant drug therapy.

Your name will not be written in the data abstraction follow up format and will never be used in connection with any information you tell us. There is no possible risk associated with participating in this study except the time spent on follow up. All information given by you will be kept strictly confidential. Your participation is voluntary and you are not obligated to participate in the follow up study. If you feel discomfort with this study, it is your right to drop out any time you want. If you have questions regarding this study or would like to be informed of the results after its completion, please feel free to contact the principal investigator.

Address of the principal investigator:

Teklu Gebrehiwot

Cell phone: +251- 0910-334-253

E-mail: tekluu2020@yahoo.com

Are you willing to participate in this study?

1. Yes - …….. Continue to the follow up data abstract form
2. No - …… Skip to the next participant

Annexe II: Data abstraction follow up format

Addis Ababa University, College of Health Sciences,

School of pharmacy, Department of Pharmacology and Clinical pharmacy

Data abstraction format for assessment of complications of anticoagulant drug therapy

At medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

Part 0: General Information

001. Data abstraction follow up format code number: _____ admission date _____

002. Unit/ward: _____ Type of Therapy: _____

003. Date of starting: _____/____/_____ last follow-up date: _____/_____/___

Part 1: Socio demographic condition (✓)

101**:** Respondents age in years **1)** 18-40 **2**) 41-64 **3)** 65-75 4) > 75

102: Gender of the respondent? 1) Male 2) Female

PART II: Complications of anticoagulant drug therapy

201. Indication of anticoagulant therapy? 1. One 2. Two 3. Three 4. More than three

1. Deep vein thrombosis (DVT)
2. Chronic rheumatic valvular heart disease (CRVHD)
3. Atrial Fibrillation (AF)
4. Pulmonary embolism (PE)
5. Stroke or transient ischemic attack
6. Myocardial infarction (MI)
7. Coronary artery disease (CAD)
8. Others _____
9. Others _____

202. Comorbidity disease 1. One 2. Two 3. Three 4. More than three 5. No

1. Hypertension
2. Congestive Heart Failure
3. Cancer (malignancy)
4. Ischemic stroke
5. Diabetes Mellitus
6. Recent (surgery or trauma)
7. Renal insufficiency
8. History of myocardial infarction
9. History of bleeding
10. Pregnant woman
11. Liver disease
12. Community acquired pneumonia
13. Retroviral infection
14. Anemia _____
15. Others _____
16. Others _____

203. Type of anticoagulants drug therapy? 1. One 2. Two 3. Three

Drug name	Therapy starting date	Loading/starting Dose	Maintenance Dose	Date dose changed done	Adjustment of dose given	Date discharged
UF Heparin						
Warfarin						
Enoxaparin						

204. Length of anticoagulant therapy

Drug name	Less than 5 days	5-10 days	10-30 days	Greater than 30 days
UF Heparin				
Warfarin				
Enoxaparin				

205. Concomitant drugs? 1. One 2. Two 3. Three 4. Greater than three 5. No

1. Aspirin
2. Tramadol
3. Ceftriaxone
4. Cimetidine
5. Digoxin
6. Carbamazepine
7. Metronidazole
8. Azithromycin
9. Amiodarone
10. Simvastatin
11. Clopidegol
12. Rifampin
13. INH
14. Diclofenac
15. Others _____
16. Others _____

206. Variability of laboratory sites? 1. One 2. Two 3. Three 4. More than three 5. No

207. Data on repeated measurement of the coagulation profiles

Days	INR Values	aPTT values	Reference value of aPTT of laboratory institution	Platelet Count	Laboratory institution	Anticoagulant drugs used	Complication reported (yes/No)
Day1							
Day2							
Day3							
Day4							
Day5							
Day6							
Day7							
Day8							
Day 9							
Day 10							

208. Complications of anticoagulants reported? 1. One 2. Two 3. Three 4. More than three 5. No

1. Bleeding (major____or minor___)
2. Recurrent thromboembolism
3. Heparin induced thrombocytopenia (HIT)
4. Skin necrosis
5. Bruising
6. Others_____

209. Bleeding complications from question 208? 1. One 2. Two 3. Three 4. No

1. Epistaxis
2. Menorrhagia
3. Intracranial haemorrhage
4. Nasal bleeding
5. Gingival bleeding
6. GI bleeding
7. Others_____
8. Others _____

210. Recurrent thromboembolism

1. Transient ischemic attack
2. Recurrent DVT
3. Recurrent PE
4. Stroke
5. Others_____
6. Others_____

211. Probability of heparin induced thrombocytopenia (HIT) baseline PLT_____

1. >50% fall or platelet nadir 20-100 $x10^9/L$
2. 30-50% fall or nadir platelet 10-19 $x10^9/L$
3. <30 % fall or nadir platelet $<10x10^9/L$

212. Anticoagulant drug therapy related problems? 1. One 2.Two 3.Three 4. More than three 5.No

1. Hypercoagulable state
2. Supratherapeutic INR/aPTT level
3. Sub-therapeutic INR/aPTT level
4. Inappropriate use of vitamin K
5. Drug-drug interaction
6. No dose adjustment
7. Loading dose not given
8. No current laboratory results
9. Others_____
10. Others_____

214. The usual trend of coagulation treatment? 1. One 2. Two 3. Three 4. More than three 5.No

1. Discontinue the medication
2. Holding the medication
3. Reducing the dose of the drug
4. Increasing the dose of the drug
5. Using alternative dosing system
6. Restarting the dose of drugs
7. Shifting between drugs
8. Others _____

215. Recommendation need assessment? 1. One 2. Two 3. Three 4. More than three 5.No

1. Setting goals of INR/aPTT values
2. Providing loading dose
3. Providing dose adjustments
4. Drug- drug interaction counselling
5. Restarting the dose of the drug
6. Reloading for aPTT < 50 seconds
7. Shifting between drugs
8. Others_____