

Republic Of Yemen
Ministry Of Higher Education
& Scientific Research
21 September University of
Medical & Applied Science
Faculty of Clinical Pharmacy



Evaluation of Heparin Use in Hospitalized Patients of Surgery Ward at 48 Model Hospital

A Study Research

**Submitted to the Faculty of Clinical Pharmacy University of 21 September in
Partial Fulfillment of the Requirements of the Degree of
Bachelor in Faculty of Clinical Pharmacy**

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2022

بسم الله الرحمن الرحيم

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سورة الزمر : الآية (٩)

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Dedication

TO OUR FAMILIES

TO OUR PROFESSORS AND DOCTORS

TO OUR FRIENDS AND COLLEAGUES

Acknowledgment

First and last, all thanks to **Allah** for his strength,
kindness and support to complete this work.

I would like to acknowledge my
Supervisor/Assistant **Prof. Ali Alyahwai**
who was the soul and activator for our team research.

Special thanks for **48 Model Hospital**
Who kept no effort to support success of this research work.
Special thanks for Chief of 21 September University of Medical
& Applied Science

Medical Council / **Prof. Mojahed Measar**
Special thanks for all employees in pharmacy Deanery specially
Dr. Abdulmalik Abodonia

Lastly thanks for all students in my college.

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List of Abbreviation

VTE	Venous Thromboembolism"
PTS	Postthrombotic Syndrome
GP	Glycoprotein
vWF	Von Willebrand Factor
CBC	Complete Blood Count
PT	Prothrombin Time
INR	International Normalized Ratio
aPTT	Activated Partial Thromboplastin Time
DVT	Deep Vein Thrombosis
ESR	Erythrocyte Sedimentation Rate
WBC	White Blood Cell
DOACs	Direct Oral Anticoagulants
CrCl	Creatinine Clearance
UFH	Unfractionated Heparin
LMWH	Low-Molecular-Weight Heparin
PE	Pulmonary Embolism
P-GP	P-Glycoprotein
FDA	Food And Drug Administration
HIT	Heparin-Induced Thrombocytopenia
ABW	Adjusted Body Weight
ACT	Activated Clotting Time

Abstract:

Background: Considering the high prevalence and risk of Deep Vein Thrombosis (DVT) in hospitalized patients and the existence of different prophylaxis methods in these patients, the necessity of evaluating the rational administration of heparin and mechanical prophylaxis is one of the important priorities. The present study aimed to evaluate the consistency of the Heparin administration in comparison to guidelines in patients admitted to 48 typical Hospital.

Amis of study: Monitoring heparin dose in 48 hospital in surgery ward, Assessment dose of heparin for patients with chronic disease, Evaluation for heparin dose as prophylaxis or treatment according to guideline, Detection interaction between heparin and other medication and reduce adverse effect during uses of heparin.

Methods: In this prospective study drug use evaluation, 80 hospitalized patients receiving venous thrombosis prophylaxis were enrolled, of which patients were selected from surgical wards. The demographic and clinical data of patients were collected using patients and clinical records of them. We used the checklists based on the Caprini Questionnaire for patients in surgical wards to evaluate whether patients had received heparin prophylaxis and mechanical DVT prevention according to guidelines . Then the obtained data was analyzed by using descriptive statistics SPSS version 21.

Results: In the surgical ward 80 patients admitted to surgical wards, 70 (87.5%) were males patients and 10 (12.5%) were females, most of them less than 40 years old 67 (83.8%)patients. Most of patients were using heparin (5000 U per 12hr) as prophylaxis 76 (95.0%). Drug prophylaxis was administered in surgical wards in 78 (97.4%) patients according to the guideline.

Conclusion: Most of patients males admitted to surgery ward was using heparin as prophylaxis without comorbidity or chronic disease, and most of them have elevated in platelets count because transfusion of blood or platelets.

Chapter-1

1.Introduction:

Venous thromboembolism includes DVT (deep vein thrombosis) and PE (pulmonary embolism), which have significant complications and mortality in hospitalized patients. Unprovoked VTE is when a specific cause and background are not found, and this indicates the influence of environmental factors and vice versa. Provoked VTE is when we have a specific background and risk factor, such as malignancy or immobility. The main prophylaxis of VTE is anticoagulants that the duration of prophylaxis treatment varies from 3 to 6 months depending on the underlying disease and risk factors ^[1].

Thromboprophylaxis reduces the risk of VTE in patients. While most studies show that thromboprophylaxis reduces the risk of death in surgical patients, the reason for this difference between surgical and internal patients is not known but is probably due to the high incidence of comorbidities in internal patients ^[2] It identified three major factors influencing deep vein thrombosis in the form of impaired blood flow (Due to lack of proper venous pumping resulting from impaired muscle contraction), vascular damage (due to activation of vasoactive amines or attributable to external layers on the organs) and increased coagulation (due to stimulation of thrombogenic factors following injury, including increased platelet aggregation and adhesion) ^[3,4]. Given that venous thrombosis can lead to dangerous and occasionally fatal complications, its prevention is very important, especially in hospitalized patients who are at risk for major risk factors for venous thrombosis. So, in recent years, various mechanical and pharmacological treatments have been used in hospitalized patients to prevent venous thrombosis; these include unfractionated heparin and low molecular weight heparin ^[5, 6].

Based on studies, mechanical prevention methods such as mechanical pressure are relatively ineffective, and they are not effective alone. ^[7] Therefore, further research on increasing the effectiveness and reducing the side effects of prophylactic use of anticoagulants as a more effective treatment than mechanical methods is a topic of discussion among researchers and physicians ^[8, 9] However, despite the introduction of guidelines and systems for calculating the risk of venous thrombosis in patients, the use of these cases has not become common among physicians, and in some cases, not following these guidelines not only endangers the lives of patients but can also lead to a loss of costs and drug reserves following the improper administration of anticoagulants ^[10, 11].

Due to the high prevalence and risk of DVT and PTE in hospitalized patients and also the existence of different prophylaxis methods in these patients, the need to evaluate the rational use of prophylaxis with heparin or enoxaparin is one of the important priorities in terms of reducing costs and rationalizing prophylaxis. ^[12] It gets more important when these drugs are among the most expensive drugs in the hospital due to high consumption, so the aim of this study was to investigate the rational use of heparin/enoxaparin and mechanical prophylaxis for thromboembolic events in DVT prophylaxis regimens in patients admitted to 48 Hospital during three months.

1.1. Definition:

1.1.1. Thromboembolism:

A thrombus is a blood clot attached to the vessel wall composed of platelets, fibrin, and clotting factors that may partially or completely occlude the lumen of a blood vessel and compromise blood flow and oxygen delivery to distal tissue. It is often provoked by prolonged immobility and vascular injury and most frequently seen in patients hospitalized for a serious medical illness, trauma, or major surgery. ^[13]

VTE can also occur with little or no provocation in patients who have an underlying hypercoagulable disorder. Although VTE may initially cause few or no symptoms, the first overt manifestation of the disease may be sudden death from PE, which can occur within minutes, before effective treatment can be given ^[14,15,16].

A history of VTE is a significant risk factor for recurrent thromboembolic events. Postthrombotic syndrome (PTS) is a complication of VTE that occurs due to damage to the vein caused by a blood clot and leads to development of symptomatic venous insufficiency such as chronic lower extremity swelling, pain, tenderness, skin discoloration, and ulceration. The treatment of VTE is fraught with substantial risks. Antithrombotic therapies (thrombolytics and anticoagulants) require precise dosing and meticulous monitoring, as well as ongoing patient assessment and education. Well-organized anticoagulation management services improve quality of care and reduce overall cost ^[17].

A systematic approach to drug therapy management reduces risks, but bleeding remains a common and serious complication. Therefore, preventing VTE is paramount to improving outcomes. When VTE is suspected, a rapid and accurate diagnosis is critical to making appropriate treatment decisions. The optimal use of antithrombotic drugs requires not only an in-depth knowledge of their pharmacology and pharmacokinetic properties but also a comprehensive approach to patient management. ^[18,19]

1.1.2. Coagulation:

Blood coagulation is the process by which liquid blood changes into semisolid blood clots. It helps preventing blood loss from damaged blood vessels. When a blood vessel is damaged, small blood particles called platelets immediately form a plug at the site of injury. Shortly after, blood proteins, called coagulation factors or clotting factors, respond in a complex cascade to strengthen the platelet plug. Later, the wound heals and the platelet plug is broken down ^[20].

1.2. Epidemiology:

The true incidence of VTE in the general population is unknown because many patients, perhaps more than 50%, have no overt symptoms or go undiagnosed. An estimated 2 million people in the United States develop VTE each year, of whom 600,000 are hospitalized and 60,000 die. The estimated annual direct medical costs of managing the disease are well over \$1 billion. The incidence of VTE nearly doubles in each decade of life older than 50 years of age and is slightly higher in men. As the population ages, the total number of DVT and PE cases continues to rise ^[21,22,23].

1.3. Pathophysiology of Thromboembolism:

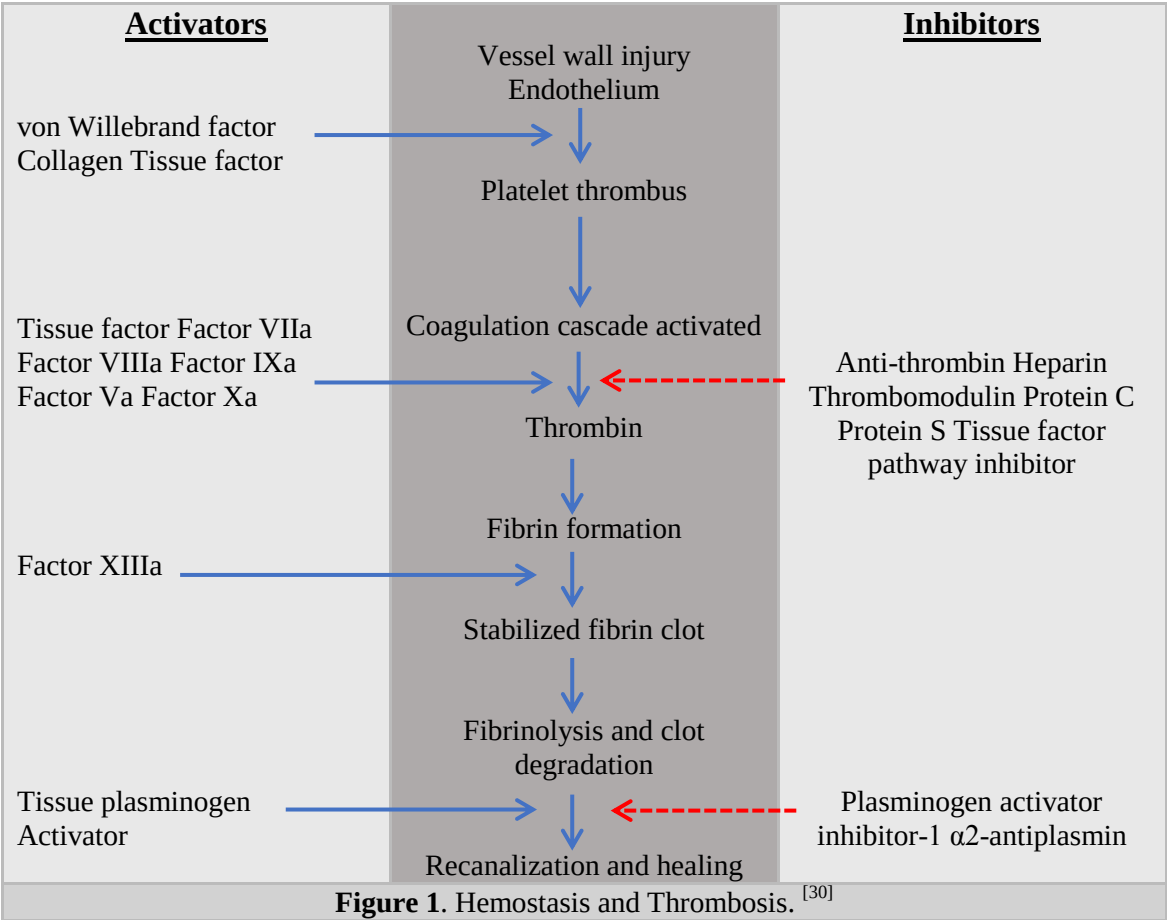
Hemostasis, the arrest of bleeding following vascular injury, is essential to life. Within the vascular system, blood remains in a fluid state, transporting oxygen, nutrients, plasma proteins, and waste. When a vessel is injured, a dynamic interplay between thrombogenic (activating) and antithrombotic (inhibiting) forces results in the local formation of a hemostatic plug that seals the vessel wall and prevents further blood loss (Figure 1).

A disruption of this delicate system of checks and balances may lead to inappropriate clot formation within the blood vessel that can obstruct blood flow or embolize to a distant vascular bed. Under normal circumstances, the endothelial cells that line the inside of blood vessels maintain blood flow by producing a number of substances that inhibit platelet adherence, prevent the activation of the coagulation cascade, and facilitate fibrinolysis ^[24,25] .

Vascular injury exposes the subendothelium. Platelets adhere to the subendothelium with their glycoprotein (GP) Ib surface receptors and facilitated by von Willebrand factor (vWF). This causes platelets to become activated, releasing a number of procoagulant substances that stimulate circulating platelets to expose GP IIb and IIIa surface receptors and subsequently allowing platelets to adhere to one another, resulting in platelet aggregation (Figure1). The damaged vascular tissue releases tissue factor that activates the extrinsic pathway of the coagulation cascade. The clotting cascade is a stepwise series of enzymatic reactions that results in the formation of a fibrin mesh ^[26] .

Clotting factors circulate in the blood in inactive forms. Once a precursor is activated by specific stimuli, it activates the next clotting factor in the sequence. The final steps in the cascade are the conversion of prothrombin (factor II) to thrombin (factor IIa) and fibrinogen to fibrin. Thrombin plays a key role in the coagulation cascade; it is responsible not only for the activation of fibrin but also for the activation of factors V and VIII, creating a positive feedback loop that greatly accelerates the entire cascade. Thrombin also enhances platelet aggregation.

Traditionally, the coagulation cascade has been divided into three distinct parts: the intrinsic, the extrinsic, and the common pathways. This artificial division is misleading because there are numerous interactions between the three pathways ^[27,28]. A number of tempering mechanisms modulate coagulation (Figure 1). Without effective self-regulation, the coagulation cascade would proceed unabated until all the clotting factors and platelets are consumed ^[29].



1.4. Clinical Presentation and Diagnosis:

Although a thrombus can form in any part of the venous circulation, most begin in the lower extremities. Once formed, a venous thrombus may (a) remain asymptomatic, (b) spontaneously lyse, (c) obstruct the venous circulation, (d) propagate into more proximal veins, (e) embolize, and/or (f) slowly incorporate into the endothelial layer of the vessel [31,32,33]. Most patients with VTE never develop symptoms [13,28]. However, even those who initially experience no symptoms may suffer long-term consequences, such as PTS and recurrent VTE. Given that VTE can be debilitating or fatal, it is important to treat it quickly and aggressively [34]. However, because major bleeding induced by antithrombotic drugs can be equally harmful, it is also important to avoid treatment when the diagnosis is not reasonably certain. Assessment should focus on patient-specific risk factors during the medical history [22,33]. Venous thrombosis is uncommon in the absence of risk factors, and the effects of these risk factors are additive. If a patient has multiple risk factors, VTE should be strongly suspected even when the symptoms are very subtle [34,35].

Generally most commonly develops in patients with identifiable risk factors during or following a hospitalization. Many patients have asymptomatic disease, and other patient may complain of persistent unilateral leg swelling, pain, warmth, and/or skin discoloration. Symptoms are nonspecific, and objective testing must be performed to establish the diagnosis, also these patients have many signs include superficial veins may be dilated and a “palpable cord” may be felt in the affected leg, unilateral leg edema with measurable difference in leg circumference compared to the unaffected leg, erythema, increase in warmth, and tenderness with palpation of calf muscles. May experience pain in the popliteal or calf region in the affected leg when the examiner dorsiflexes the foot while the knee is flexed/slightly bent (Homans sign) [36,37].

If the clinical probability of DVT is low, the initial laboratory evaluation should include complete blood count (CBC) with differential, coagulation studies (such as prothrombin time [PT]/international normalized ratio [INR], activated partial thromboplastin time [aPTT]), serum chemistries with renal and liver function, and urinalysis. Serum concentrations of D-dimer, a by-product of thrombin generation, will be elevated in an acute event. A negative D-dimer in a patient with low clinical probability of DVT can be used to rule out DVT. Patient may have an elevated erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count ^[38] .

Duplex ultrasonography is the most commonly used test to diagnose DVT. It is a noninvasive test that can measure the rate and direction of blood flow and visualize clot formation in proximal veins of the legs. It cannot reliably detect small blood clots in distal veins.

Coupled with a careful clinical assessment, it can confirm or rule out (exclude) the diagnosis in most cases. Repeat testing may be necessary if the first test is negative and the patient is still symptomatic. Venography (also known as phlebography) is the gold standard for the diagnosis of DVT. However, it is an invasive test that involves injection of radiopaque contrast dye into a foot vein. It is expensive and can cause anaphylaxis and nephrotoxicity ^[37,39] .

1.5. Risk Factor:

Risk factors for predicting venous thromboembolism (VTE) in general surgical patients (modified caprini risk assessment model for VTE in general surgical patients (Table 1) bleeding risk should also be assessed to help identify patients in whom the risk of bleeding may outweigh benefits of pharmacologic prophylaxis. lists general and procedure-specific risk factors for major bleeding complications.

patients with moderate to high risk of VTE should receive pharmacologic prophylaxis. if pharmacologic prophylaxis is contraindicated, such as in patients actively bleeding or at high risk of bleeding, non-pharmacologic prophylaxis should be used ^[40,41] .

Table 1 Risk Factors for Predicting Venous Thromboembolism (VTE) in General Surgical Patients (Modified Caprini Risk Assessment Model for VTE in General Surgical Patients)			
Risk Score			
1 Point	2 Points	3 Points	5 Points
Age 41–60 years Minor surgery BMI > 25 kg/m ² Swollen legs Varicose veins Pregnancy or postpartum History of unexplained or recurrent spontaneous abortion Oral contraceptives or hormone replacement Sepsis (< 1 month) Serious lung disease, including pneumonia (< 1 month) Abnormal pulmonary function Acute myocardial infarction Heart failure (< 1 month) History of inflammatory bowel disease Medical patient at bed rest	Age 61–74 years Arthroscopic surgery Major open surgery (> 45 minutes) Laparoscopic surgery (> 45 minutes) Malignancy Confined to bed (> 72 hours) Immobilizing plaster cast Central venous access	Age ≥ 75 years History of VTE Family history of VTE Factor V Leiden Prothrombin 20210A Lupus anticoagulant Anticardiolipin antibodies Elevated serum homocysteine Heparin-induced thrombocytopenia Other congenital or acquired thrombophilia	Stroke (< 1 month) Elective arthroplasty Acute spinal cord injury (< 1 month)
Risk Score Interpretation			
Total Risk Score		Risk of VTE	
0		Very low (< 0.5%)	
1–2		Low (1.5%)	
3–4		Moderate (3%)	
≥ 5		High (6%)	

1.6. Drugs Used:

1.6.1. Direct Oral Anticoagulants (DOACs):

Rivaroxaban, apixaban, edoxaban, and betrixaban are oral selective inhibitors of both free and clot-bound factor Xa and do not require antithrombin to exert their anticoagulant effect. Dabigatran is an oral selective, reversible, direct factor IIa inhibitor. Use DOACs with caution in patients with renal dysfunction. Single-drug oral therapy with rivaroxaban or apixaban produces similar rates of recurrent VTE compared to traditional therapy with warfarin overlapped with enoxaparin and perhaps less major bleeding. Both drugs are initiated with a higher dose and subsequently reduced to a maintenance dose. Until further data are available, these drugs should not be used in patients with creatinine clearance (CrCl) <25 mL/min (0.42 mL/s), active cancer, and patients requiring thrombolytic therapy. Neither drug requires routine anticoagulation monitoring, but the high acquisition cost may be a barrier for some patients ^[41,42].

Edoxaban and dabigatran must be given only after at least 5 days of subcutaneous (SC) anticoagulation with UFH, LMWH, or fondaparinux. These regimens were noninferior to warfarin in patients with acute VTE for the outcome of recurrent VTE. Compared to warfarin, dabigatran caused similar major bleeding and edoxaban caused significantly less bleeding. Until further data are available, these agents should not be given to patients with hemodynamically unstable PE or at high bleeding risk.

Bleeding is the most common adverse effect with DOAC therapy. Patients experiencing significant bleeding should receive routine supportive care and discontinuation of anticoagulant therapy. Idarucizumab (Praxbind) 5 g IV rapidly reverses the dabigatran anticoagulant effect when needed during emergency situations (eg, life-threatening bleeding) and when there is need for urgent surgical intervention.

Recombinant coagulation factor Xa (also known as andexanet alfa Andexxa) can reverse life-threatening bleeding in patients taking rivaroxaban or apixaban. Adding aspirin to DOAC therapy nearly doubles bleeding rates and should be avoided in most patients with VTE. All DOACs are P-gp substrates and subject to changes in anticoagulant effect when coadministered with P-gp inhibitors or inducers. Rivaroxaban and apixaban are subject to interactions involving inhibitors or inducers of CYP 3A4 ^[43]

1.6.2. Low-Molecular-Weight Heparin:

LMWH fragments produced by either chemical or enzymatic depolymerization of UFH are heterogeneous mixtures of sulfated glycosaminoglycans with approximately one-third the mean UFH molecular weight. LMWH prevents thrombus propagation by accelerating the activity of antithrombin similar to UFH. It given SC in fixed, weight-based doses is at least as effective as UFH given IV for VTE treatment. LMWH has largely replaced UFH for initial VTE treatment due to improved pharmacokinetic and pharmacodynamic profiles and ease of use.

Advantages of LMWH over UFH include: (1) predictable anticoagulation dose response; (2) improved SC bioavailability; (3) dose-independent clearance; (4) longer biologic half-life; (5) lower incidence of thrombocytopenia; and (6) less need for routine laboratory monitoring ^[43,44] . Recommended doses (based on actual body weight) include:

- ✓ Enoxaparin (Lovenox): For acute DVT treatment with or without PE, 1 mg/kg SC every 12 hours or 1.5 mg/kg every 24 hours.
- ✓ Dalteparin (Fragmin): For acute DVT treatment, 200 units/kg SC once daily or 100 units/kg SC twice daily (not FDA approved in the United States for this indication). For VTE in patients with cancer, 200 units/kg SC every 24 hours for 30 days, followed by 150 units SC every 24 hours. The maximum total daily dose is 18,000 units.

In patients without cancer, acute LMWH treatment is generally transitioned to long term warfarin therapy after 5–10 days. Routine laboratory monitoring is unnecessary because LMWH anticoagulant response is predictable when given SC. Prior to initiating therapy, obtain a baseline complete blood cell count (CBC) with platelet count and serum creatinine. Check the CBC every 5–10 days during the first 2 weeks of LMWH therapy and every 2–4 weeks thereafter to monitor for occult bleeding. Measuring anti-factor Xa activity is the most widely used method to monitor LMWH; routine measurement is unnecessary in stable, uncomplicated patients. Monitoring may be considered in patients who have significant renal impairment, are morbidly obese, or are pregnant ^[43].

As with other anticoagulants, bleeding is the most common adverse effect of LMWH therapy, but major bleeding may be less common than with UFH. If major bleeding occurs, IV protamine sulfate can be administered, but it cannot neutralize the anticoagulant effect completely. The recommended protamine sulfate dose is 1 mg per 1 mg of enoxaparin or 1 mg per 100 anti-factor Xa units of dalteparin administered in the previous 8 hours. A second dose of 0.5 mg per 1 mg or 100 anti-factor Xa units can be given if bleeding continues. Smaller protamine doses can be used if the LMWH dose was given in the previous 8–12 hours. Protamine sulfate is not recommended if the LMWH was given more than 12 hours earlier.

Thrombocytopenia can occur with LMWHs, but the incidence of heparin-induced thrombocytopenia (HIT) is one-third that of UFH. LMWH has been associated with osteopenia, but the risk of osteoporosis appears to be lower with LMWH than with UFH ^[44,45].

1.6.3. Fondaparinux:

Fondaparinux (Arixtra) prevents thrombus generation and clot formation by indirectly inhibiting factor Xa activity through its interaction with antithrombin. Unlike UFH or LMWH, fondaparinux inhibits only factor Xa activity. It is a safe and effective alternative to LMWH for acute VTE treatment and is likewise followed by long-term warfarin therapy. It is dosed once daily via weight-based SC injection: 5 mg if <50 kg, 7.5 mg if 50–100 kg, and 10 mg if >100 kg. Patients receiving fondaparinux do not require routine coagulation testing. Determine baseline kidney function before starting therapy because fondaparinux is contraindicated if CrCl is <30 mL/min (0.5 mL/s).

Bleeding is the primary adverse effect associated with fondaparinux therapy. Measure CBC at baseline and periodically thereafter to detect occult bleeding. Monitor for signs and symptoms of bleeding daily. There is no specific antidote to reverse the antithrombotic activity of fondaparinux ^[44,45]

1.6.4. Unfractionated heparin:

UFH has traditionally been the drug of choice for indications requiring a rapid anticoagulation including the acute treatment of VTE. Unlike thrombolytics, UFH and other anticoagulants will not dissolve a formed clot but prevent its propagation and growth. Heparin exerts its anticoagulant effect by augmenting the natural anticoagulant, AT. See (Figure 2).

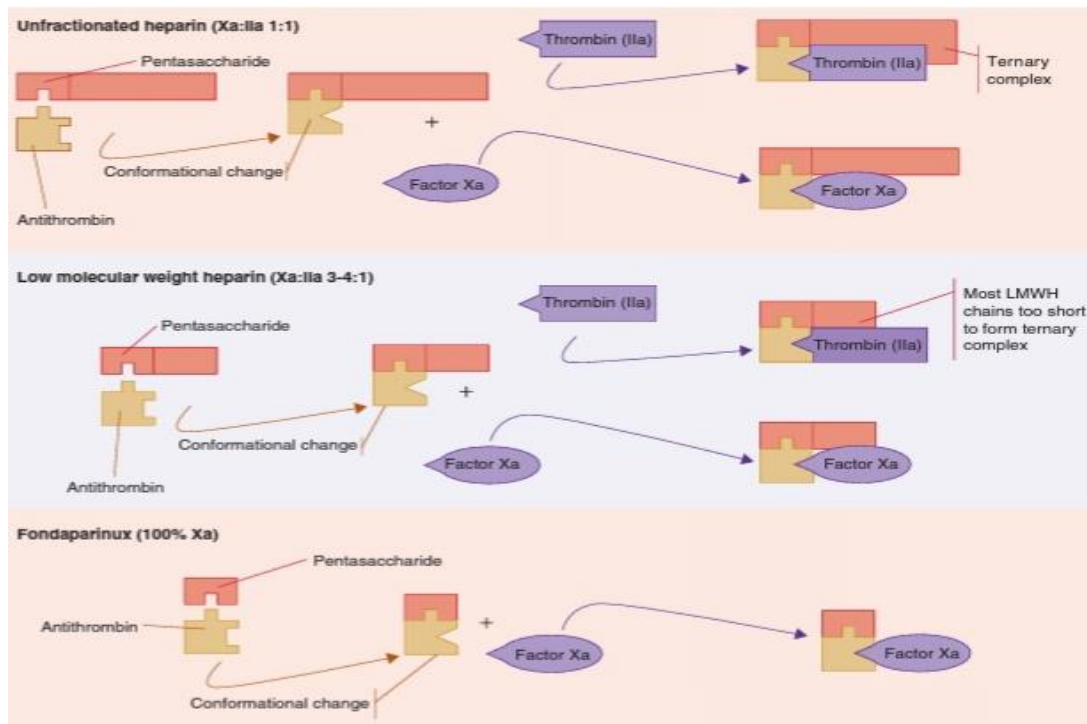


Figure 2: Mechanism of action of unfractionated heparin, LMWH, and fondaparinux ^[46].

UFH can be administered via the intravenous (IV) or subcutaneous (SC) route. When rapid anticoagulation is required, UFH should be administered IV and an initial bolus dose should be given. For the treatment of VTE, UFH is generally given as a continuous IV infusion. The half-life of UFH is dose dependent and ranges from 30 to 90 minutes but may be significantly longer, up to 150 minutes, with high doses.

UFH is eliminated by two mechanisms: (a) enzymatic degradation via a saturable zero-order process, and (b) renally via a first-order process. Lower UFH doses are primarily cleared via enzymatic processes, whereas higher doses are primarily renally eliminated. Clearance of UFH can be impaired in patients with renal and hepatic dysfunction. Patients with active thrombosis may require higher UFH doses due to a more rapid elimination or variations in the plasma concentrations of heparin-binding proteins ^[46, 47].

Certain patient-specific situations may require UFH higher doses to achieve a therapeutic anticoagulant effect. AT deficiency and elevated factor VIII levels are common in pregnant patients. AT deficiency has been linked to higher UFH dose requirements. The requirement of these higher UFH doses is termed heparin resistance. Factor VIII elevations can result in altered activated partial thromboplastin time (aPTT) response to UFH, and monitoring with antifactor Xa levels is recommended ^[44,47].

The dose of UFH required to achieve a therapeutic anticoagulant response is correlated to the patient's weight ^[47]. Weight-based dosing regimens should be used to exceed the therapeutic threshold in the first 24 hours after initiating treatment. Achieving a therapeutic aPTT in the first 24 hours after initiating UFH is critical because it has been shown to lower the risk of recurrent VTE. For nonobese patients, the actual body weight should be used to calculate the initial UFH dose. For obese patients, using the actual body weight to calculate the initial dose is also generally recommended; however, data are limited in morbidly obese patients, that is, weight more than 150 kg (330 lb). Some experts recommend using an adjusted body weight (ABW) in these patients instead. The infusion rate is then adjusted based on laboratory monitoring of the patient's response ^[46,48].

Due to significant interpatient variability and changes in patient response over time, UFH requires close monitoring and periodic dose adjustment. The response to UFH can be monitored using a variety of laboratory tests including the aPTT, the whole blood clotting time, activated clotting time (ACT), antifactor Xa activity, and the plasma heparin concentration. Although it has several limitations, the aPTT is the most widely used test in clinical practice to monitor UFH. Traditionally, therapeutic aPTT range is defined as 1.5 to 2.5 times the control aPTT value ^[48]. However, due to variations in reagents and instruments used to measure the aPTT in different laboratories, each institution should establish a therapeutic range for UFH.

The institution-specific therapy range should correlate with a plasma heparin concentration of 0.2 to 0.4 units/mL (kU/L) by protamine titration or 0.3 to 0.7 units/mL (kU/L) by an amidolytic antifactor Xa assay.^{4,27} An aPTT should be obtained at baseline, 6 hours after initiating the heparin infusion, and hours after each dose change because this is the time required to reach steady state. UFH dose is then adjusted based on the aPTT measurement and institutional-specific therapeutic range. In patients with heparin resistance, antifactor Xa concentrations may be a more accurate method of monitoring the patient's response ^[49].

Side effects associated with UFH include bleeding, thrombocytopenia, hypersensitivity reactions, and with prolonged use, alopecia, hyperkalemia, and osteoporosis. Bleeding is the most common adverse effect associated with antithrombotic drugs including UFH therapy. A patient's risk of major hemorrhage is related to the intensity and stability of therapy, age, concurrent drug use, history of gastrointestinal bleeding, risk of falls or trauma, and recent surgery. Several risk factors can increase the risk of UFH-induced bleeding.

The risk of bleeding is related to intensity of anticoagulation. Higher aPTT values are associated with an increased risk of bleeding. The risk of major bleeding is 1% to 5% during the first few days of treatment. In addition to the aPTT, hemoglobin, hematocrit, and blood pressure should be monitored. Concurrent use of UFH with other antithrombotic agents, such as thrombolytics and antiplatelet agents, also increases bleeding risk. Patients receiving UFH therapy should be closely monitored for signs and symptoms of bleeding, including epistaxis, hemoptysis, hematuria, hematemesis, hematochezia, melena, severe headache, and joint pain. If major bleeding occurs,

UFH should be stopped immediately and the source of bleeding treated. If necessary, use protamine sulfate as an antidote to reverse the effects of UFH. The usual dose is 1 mg protamine sulfate per 100 units of UFH, up to a maximum of 50 mg, given as a slow IV infusion over 10 minutes. The effects of UFH are neutralized in 5 minutes, and the effects of protamine persist for 2 hours. If bleeding is not controlled or the anticoagulant effect rebounds, repeated doses of protamine may be administered ^[48,49] .

Heparin-induced thrombocytopenia (HIT) is a very serious adverse effect associated with UFH use. Platelet counts should be monitored every 2 to 3 days throughout the course of UFH therapy. HIT should be suspected if the platelet count drops by more than 50% from baseline or to below $150 \times 10^3/\text{mm}^3$ ($150 \times 10^9/\text{L}$). HIT should also be suspected if thrombosis occurs despite UFH use. Immediate discontinuation of all heparin-containing products including the use of LMWHs and heparin-based flushes is required. Alternative anticoagulation with parenteral DTIs should be initiated. In patients with contraindications to anticoagulation therapy, UFH should not be administered ^[48].

UFH may be used to treat VTE during pregnancy. UFH should be used with caution in the peripartum period due to risk of maternal hemorrhage. UFH is not secreted into breast milk and is safe for use by women who wish to breastfeed.[45][49] For treatment of VTE in children, the UFH dose is 50 units /kg bolus followed by an infusion of 20,000 units/m² per 24 hours. Alternatively, a loading dose of 75 units/kg followed by an infusion of 28 units/ kg/hour if younger than 12 months old and 20 units/kg/hour if older than 1 year may be considered ^[50] .

1.6.5. Warfarin:

Warfarin inhibits enzymes responsible for cyclic interconversion of vitamin K in the liver. Reduced vitamin K is a cofactor required for carboxylation of the vitamin K-dependent coagulation factors II (prothrombin), VII, IX, and X and the endogenous anticoagulant proteins C and S. By inhibiting the reduced vitamin K supply needed for production of these proteins, warfarin therapy produces coagulation proteins with less activity. By suppressing clotting factor production, warfarin prevents initial thrombus formation and propagation.

The time required to achieve its anticoagulant effect depends on the elimination half-lives of the coagulation proteins (6 hours for factor VII and 72 hours for prothrombin). Full antithrombotic effect is not achieved for at least 6 days after warfarin therapy initiation. Because of its slow onset of effect, warfarin must be started concurrently with rapid-acting injectable anticoagulant therapy with an overlap of at least 5 days and until an international normalized ratio (INR) of 2 or greater has been achieved for at least 24 hours ^[50,51].

The initial dose should be 5–10 mg for most patients. Lower starting doses may be acceptable in patients with advanced age, malnutrition, liver disease, or heart failure. Starting doses more than 10 mg should be avoided. Monitor warfarin therapy by the INR; the recommended target INR for VTE treatment is 2.5, with an acceptable range of 2–3. After an acute thromboembolic event, obtain a baseline INR and CBC prior to initiating warfarin and every 1–3 days until stabilized. Once the patient's dose response is established, obtain an INR every 7–14 days until it stabilizes, then ideally every 4–12 weeks thereafter. In general, maintenance dose changes should not be made more frequently than every 3 days. Adjust maintenance doses by calculating the weekly dose and reducing or increasing it by 5%–25%. The full effect of a dose change may not become evident for 5–7 days ^[52].

Warfarin's primary adverse effect is bleeding that can range from mild to life threatening. It does not cause bleeding per se, but it exacerbates bleeding from existing lesions and enables massive bleeding from ordinarily minor sources. The likelihood of bleeding rises with increasing INR values; therefore, maintaining the INR within the target range is important to reduce bleeding risk:

- ✓ When the INR is >4.5 without evidence of bleeding, the INR can be lowered by withholding warfarin, adjusting the warfarin dose, and/or providing a small dose of vitamin K to shorten the time to return to normal INR. Although vitamin K can be given parenterally or orally, the oral route is preferred in the absence of serious bleeding.
- ✓ If the INR is between 5 and 10 and no bleeding is present, routine vitamin K use is not recommended because it has not been shown to affect the risk of developing subsequent bleeding or thromboembolism compared to simply withholding warfarin alone. For INR >10 without evidence of bleeding, oral vitamin K (phytonadione 2.5 mg) is suggested. Use vitamin K with caution in patients at high risk of recurrent thromboembolism because of the possibility of INR overcorrection.

Patients with warfarin-associated major bleeding require supportive care. Rapid reversal of anticoagulation with a four-factor prothrombin complex concentrate and 5–10 mg of vitamin K given by slow IV injection are also recommended. Non-hemorrhagic adverse effects of warfarin include the rare “purple toe” syndrome and skin necrosis. Because of the large number of food–drug and drug–drug interactions with warfarin, close monitoring and additional INR determinations may be indicated when other medications are initiated or discontinued or a change in consumption of vitamin K–containing foods occurs ^[52,53].

1.7. Management Of VTE:

Desired Therapeutic Outcomes

The goal of VTE treatment is to prevent short- and long-term complications of the disease. The aim of initial therapy is to prevent propagation or local extension of the clot, embolization, hemodynamic collapse, and death. The goal of long-term and extended therapy is to prevent complications such as PTS, pulmonary hypertension, and recurrent VTE ^[54,59] .

General Treatment Principles

Anticoagulant drugs are considered the mainstay of therapy for patients with VTE, and the therapeutic strategies for DVT and PE are similar. Management decisions are guided by balancing the risks and benefits of various treatment options. The treatment of VTE can be divided into three phases: acute (first 5–10 days), long term (first 3 months), and extended (beyond 3 months). The acute treatment phase of VTE is typically accomplished by administering a fast-acting parenteral or a DOAC.

The long-term and extended phase treatments of VTE are usually accomplished using oral anticoagulant agents such as warfarin, or one of the DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban). In certain populations, such as patients with cancer and women who are pregnant, the LMWHs are the preferred agents during long-term and extended treatment phases due to better safety or efficacy.

The etiology of VTE will guide the duration of therapy. VTE can be provoked (by transient risk factors), unprovoked (or idiopathic), and cancer associated. Patients with unprovoked or cancer-associated VTE have a significantly higher risk of recurrence compared to patients with provoked VTE. In the absence of contraindications, the treatment of VTE should initially include a rapid-acting injectable anticoagulant (eg, UFH, LMWH, fondaparinux) or a rapidly acting DOAC (eg, apixaban, rivaroxaban).

If warfarin is used for oral anticoagulation, it should be initiated on the same day as the parenteral anticoagulant, and the parenteral agent should be overlapped for a minimum of 5 days and until the INR is greater than or equal to 2 for at least 24 hours. If dabigatran or edoxaban are used for oral anticoagulation, they should be initiated after 5 to 10 days of initial treatment with a parenteral anticoagulant. Anticoagulation therapy should be continued for a minimum of 3 months. However, the duration of anticoagulation therapy should be based on the patient's risk of VTE recurrence and major bleeding ^[54,57] .

1.7.1. Prophylaxis of venous Thromboembolism:

Risk of Developing VTE consists of a DVT, a pulmonary embolism (PE), or both. Risk factors for developing VTE are listed in Table-1. Not all risk factors carry equal risk, patients with certain risk factors such as orthopedic surgery, trauma, cancer, certain hypercoagulable states, and a previous VTE have the highest risk of developing VTE. The risk of VTE on the basis of different patient groups are listed in (Table 2).

These event rates have typically been determined by venography in clinical trials and do not reflect the rates of symptomatic DVT or PE. The minor surgery in patients younger than 40 with no additional risk factors and medically ill patients who are fully mobile are in low risk for DVT. Most general, patients undergoing open gynecologic or urologic surgery and Medically ill patients, bed rest or sick are Moderate risk ^[55,56] .

The mechanical prophylaxis help patients with high risk bleeding and spinal cord injury in combination with pharmacologic prophylaxis Subcutaneous enoxaparin or dalteparin UFH- Subcutaneously twice daily or three times daily, Fondaparinux subcutaneously 2.5 mg daily, Iv Adjusted-dose warfarin – Only in orthopedic surgery. Dabigatran, rivaroxaban, and apixaban in orthopedic surgery; betrixaban and rivaroxaban for extended prophylaxis in the medically ill patient. Aspirin is questionable data, but is listed as a possible agent in orthopedic surgery ^[55,58] .

Table 2 VTE Risk in Different Hospitalized Patient Groups	
Patient Group	DVT Prevalence Without Prophylaxis
Medically ill patients Heart failure Chronic obstructive pulmonary disease Infection	10%–20%
General surgery	15%–40%
Major gynecologic surgery	15%–40%
Major urologic surgery	15%–40%
Neurosurgery	15%–20%
Stroke	20%–50%
Major orthopedic surgery	40%–60%
Total hip replacement surgery	57%
Hip fracture surgery	60%
Total knee replacement surgery	84%
Major trauma	40%–80%
Patients with spinal cord injury	60%–80%
Critical care patients	10%–80%

A. Orthopedic Surgery

The Orthopedic Surgery considered one of the highest-risk settings for developing VTE. More than 50% of patients have a VTE event without prophylaxis. DVT rates are higher in knee surgery, and PE rates are higher in hip surgery. Prophylactic regimens are listed in (Table 3). UFH has consistently shown insufficient protection against VTE in patients undergoing orthopedic surgery and should therefore not be considered an acceptable alternative. Although aspirin has a recommendation from ACCP and the American Association of Orthopaedic Surgeons guidelines, the recommendation is based on limited data with several limitations. Patients placed on mechanical prophylaxis after surgery because of a high risk of bleeding should have their risk of bleeding consistently reassessed, with pharmacologic prophylaxis started as soon as the bleeding risk is decreased. Patients undergoing knee arthroscopy typically do not need VTE prophylaxis beyond early mobilization unless they have additional VTE risk factors or have a complicated procedure. In those cases, patients should receive VTE prophylaxis with an LMWH. Dalteparin has not been evaluated in a published prospective trial for VTE prophylaxis in knee replacement surgery. Dabigatran is available in the United States for VTE prevention in patients undergoing hip replacement surgery, but not knee replacement surgery. Dabigatran was inferior to enoxaparin 30 mg twice daily in patients undergoing knee replacement surgery. Rivaroxaban has shown a superior reduction in VTE events compared with enoxaparin 40 mg once daily in hip replacement surgery and enoxaparin 40 mg once daily and enoxaparin 30 mg twice daily in knee replacement surgery. Although major bleeding was not significantly increased in these studies, the definition of major bleeding did not include surgical site bleeding (considered nonmajor bleeding) ^[50].

Apixaban has shown a superior reduction in VTE events compared with enoxaparin 40 mg once daily in hip and knee replacementsurgery, with no significant increase in major bleeding. Apixaban was not noninferior to enoxaparin 30 mg twice daily in knee replacement surgery, though the event rates were similar (9.0% apixaban vs. 8.8% enoxaparin). Although there was no difference in major bleeding, the combination of major and CRNM was significantly reduced with apixaban. Timing of initiation of VTE prophylaxis after surgery is an important and complicated issue. The risk of thromboembolic events begins immediately after surgery; therefore, VTE prophylaxis is generally more effective when started earlier rather than later. The challenge lies in that early VTE prophylaxis is also associated with increased bleeding compared with VTE prophylaxis started later. VTE prophylaxis after elective spinal surgery can typically be initiated 12–24 hours postoperatively. Prophylaxis may need to be delayed if the surgical site remains open ^[58,59,60] .

Table 3: VTE Prophylaxis in Orthopedic Surgery							
Orthopedic Indication	Enoxaparin	Dalteparin	Fondaparinux	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Knee replacement surgery	30 mg SC q12hr initiated 12–24 hr after surgery	2500 IU SC given 6–8 hr after surgery; then 5000 IU SC q24hra	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 - 0.5	Insufficient evidence	10 mg once daily initiated 6–10 hr after surgery	2.5 mg twice daily, initiated 12–24 hr after surgery
Hip replacement surgery	30 mg SC q12hr initiated 12–24 hr after surgery OR 40 mg SC q24hr initiated 10–12 hr before surgery	2500 IU SC given 6–8 hr after surgery; then 5000 IU SC q24hr OR 5000 IU SC q24hr initiated the evening before surgery	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5 -0.5	110 mg initiated 1–4 hr after surgery; then 220 mg once daily	10 mg once daily initiated 6–10 hr after surgery	2.5 mg twice daily, initiated 12–24 hr after surgery
Hip fracture surgery	30 mg SC q12hr initiated 12–24 hr after surgerya	Insufficient evidence	2.5 mg SC q24hr initiated 6–8 hr after surgery	Initiated preoperatively or the evening of the surgical day with adjusted dosing to achieve a target INR of 2.5-0.5	Insufficient evidence	Insufficient evidence	Insufficient evidence
Spine surgery	Pharmacologic prophylaxis is generally not recommended unless patients have additional risk factors of advanced age, malignancy, neurologic deficit, previous VTE, or an anterior surgical approach. Because of the lack of clinical trials, pharmacologic prophylaxis recommendations are general and include SC UFH or LMWH						

B. Non-orthopedic Surgery :

Contains a very heterogeneous group of patients and surgical procedures with varying risk, Prophylactic regimens are listed in (Table 4). Meta-analysis comparisons between UFH and LMWHs in general surgery show comparative efficacy in preventing DVT, but a greater reduction in the incidence of PE when an LMWH is used. Mechanical prophylaxis is sometimes inappropriately selected over pharmacologic prophylaxis because of concerns for bleeding in surgical patients. A meta-analysis of almost 34,000 surgical patients showed that the most common bleeding complications are injection-site bruising (6.9%) and wound hematomas (5.7%). Major bleeding complications occur in less than 1% of patients. In neurosurgery pharmacologic prophylaxis is typically given with mechanical prophylaxis, and the combination is as safe as, and more effective than, mechanical prophylaxis alone. The pharmacologic prophylaxis is typically started 18–24 hours after neurosurgery ^[59] .

In vascular surgery, Routine prophylaxis is recommended for patients with additional risk factors such as advanced age, limb ischemia, long duration of surgery, and intraoperative local trauma. Because of the limited number of trials of patients undergoing vascular surgery, dosing recommendations are based on evidence for pharmacologic agents in general surgery. UFH or an LMWH should be received for undergoing major gynecologic surgery without malignancy where Gynecologic cancer surgery is using UFH three times daily instead of twice daily. UFH three times daily and an LMWH seem to have similar efficacy and safety.

In a subgroup analysis of a general surgery trial, fondaparinux was more effective than dalteparin in patients undergoing surgery for cancer ^[60]. Patients undergoing a transurethral or laparoscopic urologic procedure do not require prophylaxis beyond early ambulation. Because of the limited number of trials of patients undergoing urologic surgery, dosing recommendations are based on the evidence for pharmacologic agents in general surgery. Because of the limited number of trials in patients undergoing thoracic surgery and Coronary bypass surgery, dosing recommendations are based on the evidence for pharmacologic agents in general surgery. Because of concerns about the higher incidence of heparin-induced thrombocytopenia in patients undergoing cardiac surgery, an LMWH may be preferred to UFH for prophylaxis ^[61,62].

Table 4 VTE Prophylaxis in Non-orthopedic Surgery				
Surgical Indication	Unfractionated Heparin	Enoxaparin	Dalteparin	Fondaparinux
General surgery	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr
Neurosurgery	5000 units SC q8hr	40 mg SC q24hr	Insufficient evidence	Insufficient evidence
Vascular surgery	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr
Gynecologic	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr
Urologic	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr
Laparoscopic	Patients undergoing laparoscopic procedures without additional VTE risk factors do not require prophylaxis beyond early ambulation			
Bariatric	5000 units SC q8hr	40 mg SC q12hr	7500 IU SC q24hr	5 mg SC q24hr
Thoracic	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hr
Coronary bypass surgery	5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	Not current discussed guidelines

C. Medically Ill Patients :

Clinical trials typically include patients with heart failure, acute infection, respiratory failure, inflammatory bowel disease, and rheumatoid arthritis and sometimes patients with cancer. The risk of VTE is typically lower than in surgical patients, but medically ill patients make up around 60% of all VTE cases because of the higher number of medically ill patients. The prophylactic regimens are listed in (Table 5).

Many clinical trials have not shown efficacy with UFH 5000 units every 12 hours; therefore, UFH 5000 units every 8 hours may be the preferred UFH regimen. Although not evidence based, UFH 5000 units every 12 hours or enoxaparin 30 mg every 24 hours may be considered in individuals of advanced age and low weight (i.e., total body weight less than 50 kg) or with elevated baseline activated partial thromboplastin time [aPTT] (greater than 1.3–1.4 times baseline).

In head-to-head trials of UFH 5000 units every 8 hours and enoxaparin 40 mg daily, the regimens have had similar efficacy, except for in higher-risk medically ill patients (heart failure and ischemic stroke), in which enoxaparin seems to confer greater protection against VTE. In the same trials, enoxaparin has caused significantly less hematoma (greater than 5 cm) than UFH. Although some data suggest a lower bleeding rate with LMWH in medically ill patients, these findings are not consistent across trials^[63].

Table 5 VTE Prophylaxis in Medically Ill Patients				
UFH	Enoxaparin	Dalteparin	Fondaparinux	Rivaroxaban
5000 units SC q8hr or 5000 units SC q12hr	40 mg SC q24hr	5000 IU SC q24hr	2.5 mg SC q24hra	10 mg orally q24hr

Risk of VTE is known to extend beyond discharge, with almost two-thirds of all events occurring within 30 days after hospitalization. Extended prophylaxis (35–42 days) with enoxaparin has shown a significant reduction in developing VTE, but with significantly more major bleeding than with enoxaparin for 10 days. Whereas extended prophylaxis with apixaban 2.5 mg twice daily did not improve efficacy compared with enoxaparin for 10 days but did significantly increase major bleeding. This may be because of the lower-risk patients in this study, but further study is needed before apixaban is used in medically ill patients.

Rivaroxaban is approved for extended VTE prophylaxis (35 +/- 4 days) in medically ill patients with moderate to severe restricted morbidity. Use 10 mg once daily significantly reduced VTE events without significantly increasing major bleeding compared to enoxaparin for 10 days in a subpopulation trial. Five groups found to have the highest risk of bleeding were removed from the data. These groups were as follows: treatment of active cancer during admission, use of dual antiplatelet therapy, history of bronchiectasis/pulmonary cavitation, active GI bleeding, or any bleeding in the previous 3 months. These patients comprised about 20% of the initial study population ^[63,64].

D. Critically Ill Patients :

A group of patients at very high risk of developing VTE, typically includes patients in general critical care environments, including patients with trauma, acute spinal cord injury, and burns . The prophylactic regimens are listed in (Table 6).

a. Trauma:

Patients with severe trauma (injury severity score greater than 23) may present with antithrombin deficiency; therefore, subcutaneous prophylaxis may be insufficient. Although not prospectively evaluated, an option may be to use an UFH infusion while the patient is in the intensive care unit early in the course of therapy.

Only a slight increase in the aPTT (35–45 seconds) would be targeted because VTE prevention is the goal. Enoxaparin 30 mg twice daily has better efficacy than UFH 5000 units twice daily. Pharmacologic prophylaxis can safely be started within 24–36 hours. Pharmacologic prophylaxis for patients with acute spinal cord injury may need to be delayed for 48–72 hours ^[64] .

b. Acute spinal cord injury:

UFH three times daily had DVT and bleeding rates similar to enoxaparin twice daily, but PE was significantly reduced with enoxaparin. Although enoxaparin 30 mg twice daily should be used during the acute injury period (about 2–3 weeks), either regimen can be used during the rehabilitation period. In a retrospective case-control study, dalteparin 5000 units daily failed to show noninferiority to enoxaparin 30 mg twice daily in preventing VTE (9.7% vs. 1.6%). Further investigations of dalteparin are warranted ^[64] .

c. Burns:

The current evidence in burn patients comes from only observational studies with UFH, enoxaparin, and dalteparin. The most commonly used regimen is UFH 5000 units subcutaneously every 12 hours ^[65] .

d. Critical care:

In medically ill or postoperative general surgery patients, UFH or LMWH can be used. In orthopedic surgery or trauma, an LMWH is preferred. If mechanical prophylaxis is selected because of a patient's high risk of bleeding, the patient should be reevaluated often and changed to pharmacologic prophylaxis when the bleeding risk decreases. Some pharmacodynamic studies suggest that critical care patients with significant edema or critical care patients receiving vasopressors will not achieve detectable anti-Xa concentrations with LMWH.

In the largest trial of VTE prevention in critical care patients, dalteparin 5000 units subcutaneously once daily provided similar protection against proximal DVT and better protection against PE, similar bleeding, and less heparin-induced thrombocytopenia than UFH 5000 units twice daily. Dalteparin does not have significant accumulation in critical care patients with renal insufficiency ^[66] .

Table 6. VTE Prophylaxis in Critically Ill Patients			
Critical Care Setting	UFH	LMWH	Fondaparinux
Trauma	Insufficient evidence	Dalteparin 5000 IU SC q24hr Enoxaparin 30 mg SC q12hr	Insufficient evidence
Acute spinal cord injury	5000 units SC q8hr	Enoxaparin 3040mg mgSC SCq12hr q24hr or	Insufficient evidence
Burns	5000 units SC q8hr or 5000 units SC q12hr	Dalteparin 5000 IU SC q24hr Enoxaparin 40 mg SC q24hr	Insufficient evidence
Critical care	5000 units SC q8hr or 5000 units SC q12hr	Dalteparin 5000 IU SC q24hr Enoxaparin 30 mg SC q12hr or Enoxaparin 40 mg SC q24hr	Insufficient evidence 2.5 mg SC daily may be an option in suspected HIT

E. Duration of VTE Prophylaxis:

Varies depending on patient risk and group (Table 7).

Table 7. Duration of VTE Prophylaxis	
Indication	Duration
General medically ill patients	6–14 days or as long as immobile during acute illness. Rivaroxaban for patients with moderate to severe immobility for a total of 31–39 days (inpatient and outpatient)
Major general surgery	Until hospital discharge
Major general surgery in patients with previous VTE	Beyond hospital discharge for up to 28 days
Surgery for gastrointestinal, GU, or gynecologic cancer	Beyond hospital discharge for up to 28 days
Total knee replacement surgery	At least 10 days
Total hip replacement surgery	4–6 wk
Hip fracture surgery	4–6 wk
Critical care patients	For the duration of the intensive care unit stay with reevaluation when the patient is transferred to the general medical ward
Major trauma	Until hospital discharge and continued prophylaxis in patients with impaired mobility who undergo inpatient rehabilitation (up to 8 wk)
Patients with spinal cord injury	Until hospital discharge in patients with incomplete injuries For 8 wk in patients with uncomplicated complete motor injury.

F. Special Populations :

Patients with renal insufficiency are at higher risk of bleeding, regardless of the anticoagulant used. Patients with $\text{SCr} > 2.5 \text{ mg/dL}$ have been excluded from most clinical trials. Enoxaparin should be dosed at 30 mg SC once daily, regardless of the indication for $\text{CrCl} < 30 \text{ mL/min/1.73 m}^2$. Dalteparin does not seem to significantly accumulate in patients with severe renal insufficiency until the CrCl is $< 20 \text{ mL/min/1.73 m}^2$ when prophylactic doses are used. Fondaparinux, rivaroxaban, and dabigatran are contraindicated in patients with a $\text{CrCl} < 30 \text{ mL/min/1.73 m}^2$ and apixaban in patients with a $\text{CrCl} < 25 \text{ mL/min/1.73 m}^2$. Patients on hemodialysis (renal failure) should receive SC UFH ^[62,66].

ACCP guidelines recommend possible weight-adjusted dosing in patients with obesity but provide no insight regarding at what weight this should be considered or what the “adjusted” dosing should be. Patients with obesity are at considerable risk of PE, but data from clinical trials on drug dosing are limited. Several studies suggest that the typical LMWH dose has to be higher in patients with a $\text{BMI} \geq 40 \text{ kg/m}^2$. Enoxaparin 40 mg SC twice daily has been more efficacious than 30 mg SC twice daily in patients undergoing bariatric surgery. It is reasonable to use enoxaparin 40 mg twice daily or UFH 7500 units three times daily in patients with a $\text{BMI} > 40 \text{ kg/m}^2$ or weight $> 120 \text{ kg}$. Injections of enoxaparin into the thigh in patients with obesity have a lower bioavailability than injections into the abdomen ^[67].

For pregnancy warfarin has been associated with congenital abnormalities when used during the first trimester and is therefore contraindicated. Although warfarin could be used during the second trimester, it is typically avoided throughout pregnancy. A LMWH or UFH can be used throughout pregnancy.

LMWHs (or fondaparinux) are not contraindicated in the third trimester of pregnancy and can be used in the early third trimester. During the peripartum period, many prefer to use UFH because of its shorter half-life and risk of bleeding during delivery. DOACs currently have no role in pregnancy ^[67,68] .

1.7.2. Treatment Of Venous Thromboembolism:

Three different approaches to acute treatment of VTE (Table 8). ACCP guidelines prefer DOACs to warfarin for patients with VTE without cancer because of less bleeding and greater convenience for patients and health care providers. Initiate therapy until the VTE is ruled out ^[66,69] .

Table 8 Approaches to VTE Treatment	
Treatment Strategy	Anticoagulant Choices
Bridging therapy	Injectable anticoagulant (UFH, LMWH, or fondaparinux) initiated with warfarin and overlapped for at least 5 days and until a therapeutic INR is achieved. Then discontinue injectable anticoagulant and continue warfarin for the appropriate duration
Changing therapy	Injectable anticoagulant (UFH, LMWH, or fondaparinux) for at least 5 days; then stop injectable anticoagulant therapy and initiate dabigatran or edoxaban for the appropriate duration
Monotherapy	Initiate rivaroxaban or apixaban at higher initial dose and then convert patient to lower maintenance dose for the appropriate duration

Bridging therapy approach to VTE treatment because of the delay in achieving systemic anticoagulation with warfarin therapy and the significant thrombus burden in patients with VTE, an injectable anticoagulant is initiated on the suggestion of a VTE and bridged to warfarin if the diagnosis is confirmed. Dosing of injectable anticoagulants for VTE treatment can be found in (Table 9). Achieving therapeutic anticoagulation within the first 24 hours has been associated with reduced rates of recurrent VTE events.

ACCP guidelines recommend initial injectable anticoagulant therapy with an LMWH or fondaparinux over intravenous or subcutaneous UFH. Warfarin dosing in the stable outpatient setting is similar to that discussed in the AF section. In the acute situation, dosing may depend on cofactors that drive initial dosing approaches. Goal INR is 2.0–3.0. Lower INR goals or 1.5–2.0 have not been proven as effective at preventing recurrent VTE and have not shown a meaningful safety benefit. Bridging to warfarin would likely be the preferred approach when patients have renal dysfunction because patients in the DOAC trials were excluded if their CrCl was less than 30 mL/minute/1.73 m² (less than 25 mL/minute/1.73 m² for apixaban), and when transition to outpatient therapy makes acquiring a DOAC difficult. Pharmacists play a crucial role in assisting with confirming insurance coverage and other transition issues in these patients ^[69].

Table 9 Dosing of Injectable Anticoagulants for VTE	
Agent and Route	Dosing
Unfractionated Heparin	
IV UFHa	Weight adjusted with an initial bolus of 80 units/kg, followed by an initial infusion of 18 units/kg/hr. Subsequent doses should be adjusted to maintain the institution's goal Aptt
SC UFH	17,500 units (250 units/kg) given q12hr.b Subsequent doses should be adjusted to maintain the institution's goal Aptt
SC UFH	333 units/kg, followed by 250 units/kg given q12hr without aPTT monitoring
Low-Molecular-Weight Heparin (SC)	
Enoxaparin	1 mg/kg q12hr or 1.5 mg/kg q24hrd; if CrCl < 30 mL/min/1.73 m ² , give 1 mg/kg q24hr
Dalteparine	100 units/kg q12hr or 200 units/kg q24hr
Pentasaccharide (SC)	
Fondaparinux	Weight < 50 kg – Give 5 mg q24hr Weight 50–100 kg – Give 7.5 mg q24hr Weight > 100 kg – Give 10 mg q24hrCrCl < 30 mL/min/1.73 m ² Contraindicated

All patients received a median of 9 days of injectable anticoagulation. Patients randomized to dabigatran started the drug after discontinuing the injectable. Patients randomized to warfarin started the drug at the same time as the injectable anticoagulant and were bridged to an INR of 2.0–3.0 for at least 5 days. Patients were treated for 6 months. All patients received a median of 7 days of injectable anticoagulant. Patients randomized to edoxaban started the drug after discontinuing the injectable. Patients randomized to warfarin started the drug at the same time as the injectable anticoagulant and were bridged to an INR of 2.0–3.0 for at least 5 days. Patients were followed for 12 months. The reduced edoxaban dose was used in 18% of patients with maintained efficacy and safety.⁷ Around 80% of patients with a DVT can be treated on an outpatient basis. Most patients with a low-risk PE can also be treated at home.

Use of outpatient treatment for PE may vary depending on geographic practices. Increased education is needed to promote this practice. The ability to use a DOAC without injectable anticoagulation offers an attractive option and easier transition of care^[68,69].

All patients with secondary prevention of VTE should be treated for at least 3 months (Table 10). Patients without a transient or reversible cause should be considered for long-term, potentially indefinite, oral anticoagulant therapy. Data analyses consistently show significant reductions in VTE with continued therapy for 12–24 additional months. Once therapy is discontinued, VTE rates catch up with those who did not receive extended therapy. ACCP guidelines state that the oral anticoagulant need not be changed if therapy is continued beyond 3 months^[71]. Adjusted-dose warfarin to an INR of 2.0–3.0. Dabigatran 150 mg twice daily has been non-inferior to warfarin for efficacy, with similar major bleeding but less major and CRNM bleeding (RE-MEDY trial).

Dabigatran was superior to placebo for efficacy, with similar major bleeding but more major and CRNM bleeding (RE-SONATE trial). Rivaroxaban 20 mg daily was superior to placebo for efficacy, with similar major bleeding and more major and CRNM bleeding (EINSTEIN-Extension trial). Both rivaroxaban 20 mg and rivaroxaban 10 mg once daily were superior to aspirin, with similar safety in patients who had already completed 6 months of therapy. Apixaban 5 mg and 2.5 mg twice daily were superior to placebo for efficacy, with similar safety in patients who had already completed 6 months of therapy. Edoxaban has not completed a long-term trial. Aspirin (100 mg daily) has shown a 32% relative reduction in recurrent VTE events compared with placebo in two trials after patients completed at least 6 months of oral anticoagulant therapy. Relative reductions in patients receiving a DOAC compared with placebo are typically 70%–80%. In which both rivaroxaban doses were superior to aspirin for efficacy, with similar low rates of bleeding^[70,72,73].

Table 10 Duration of Anticoagulation Therapy in Patients with VTE		
Indication	Therapy Duration	Comments
First episode of VTE secondary to a transient or reversible risk factor	3 month	Recommendation applies to both proximal DVT and PE
First episode of unprovoked VTE	At least 3 month	Continue oral anticoagulant therapy if patient is not at high risk of bleeding and is adherent to therapy Risk-benefit of indefinite therapy should be reassessed at periodic intervals
First episode of VTE with inherited or acquire thrombophilia	At least 3 month	Continue oral anticoagulant therapy if patient is not at high risk of bleeding and is adherent to therapy Several abnormalities or homozygous traits have a least additive risk Risk-benefit of indefinite therapy should be reassessed at periodic intervals
First episode of cancer associated VTE	At least 3–6 month and consider extended duration until cancer resolves and cancer treatment is completed	LMWH, rivaroxaban, or edoxaban are recommended over other anticoagulants
Second VTE (provoked or unprovoked)	Indefinite	Applies to patient not at high risk of bleeding

Chapter-2

2. MATERIALS AND METHODS:

2.1.Study area, setting, sample size and inclusion criteria

The study was conducted in the internal section of a private hospital in Sana'a Yemen, during a period of one month (Oct 2021). The sample size was 80 inpatients medical chart. All patients were ≥ 17 years old of both sexes.

2.2. Study design

The study design is a prospective cross-sectional study review that evaluates of Heparin dosing for thromboembolism prophylaxis. The patient's medical charts were reviewed to obtain their medication lists. The screening tool was based on Guideline.

2.3.Data collection

The study reviewed patients' medical charts extracted from the files health record (EHR) database to obtain the required data. Collected demographic data include:

(a) Age and gender, (b) the diagnosis (c) creatinine clearance, (d) BMI Meaning,(e) Platelets,(d) PT,(e) aPTT (f) INR (g) the list of discharged medications and each medication generic name, dose, frequency, dosage form, duration of medications and route of administration. The selection of these variables is based on previous similar studies.

2.4.Statistical analysis

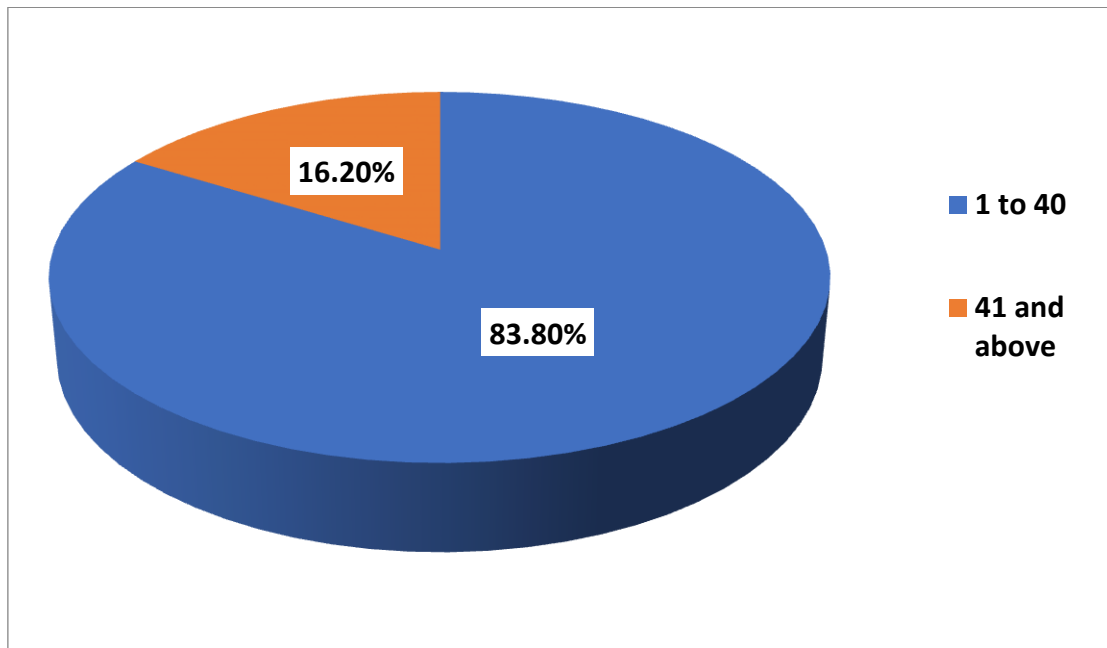
Following data collection, data was analyzed using statistical package for social science (SPSS) version 21. Continuous variables were presented as mean and standard deviation. Categorical variables were presented as frequencies and percentages.

Chapter-3

3.1.Age Distribution

It was found that age of the patients involved varied from 17 to 80 years. The age groups were categorized into two: 1-40 years, and 41 years and above. [Table 11].

[Table 11] Age Distribution		
	Frequency	Percent(%)
1 _40	67	83.8
41 and above	13	16.3
Total	80	100

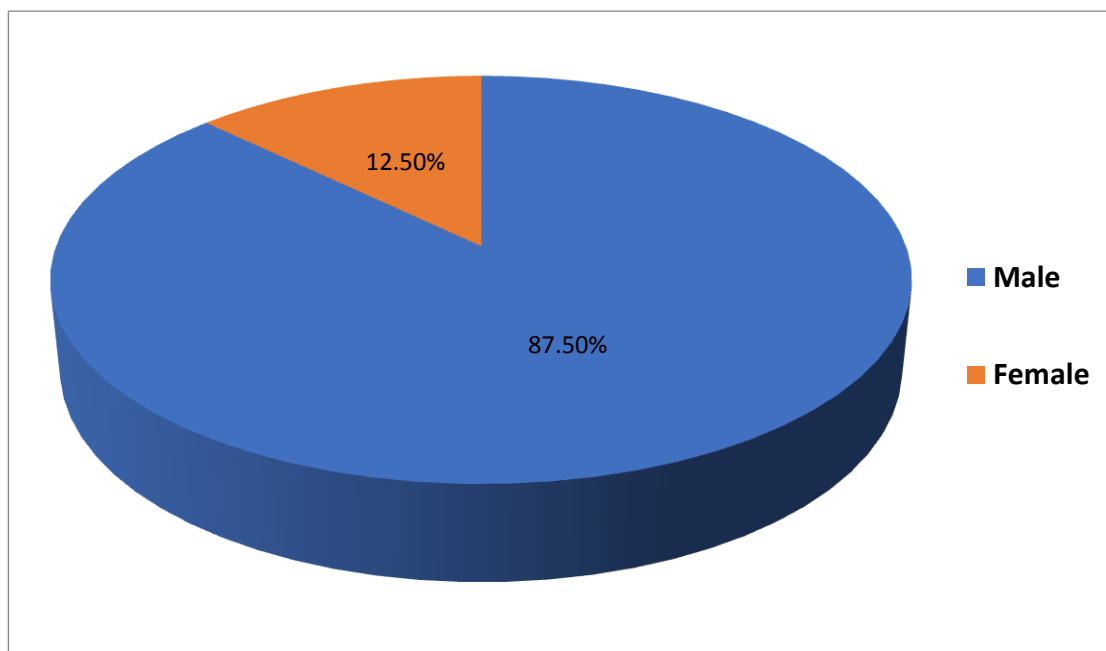


[Figure 3] Age Distribution

3.2. Gender Distribution

During the period of this study a total of 80 in-patients records were reviewed, among which majority were males and the remaining were female [Table 12]

[Table 12] Gender Distribution		
	Frequency	Percent(%)
Male	70	87.5
Female	10	12.5
Total	80	100

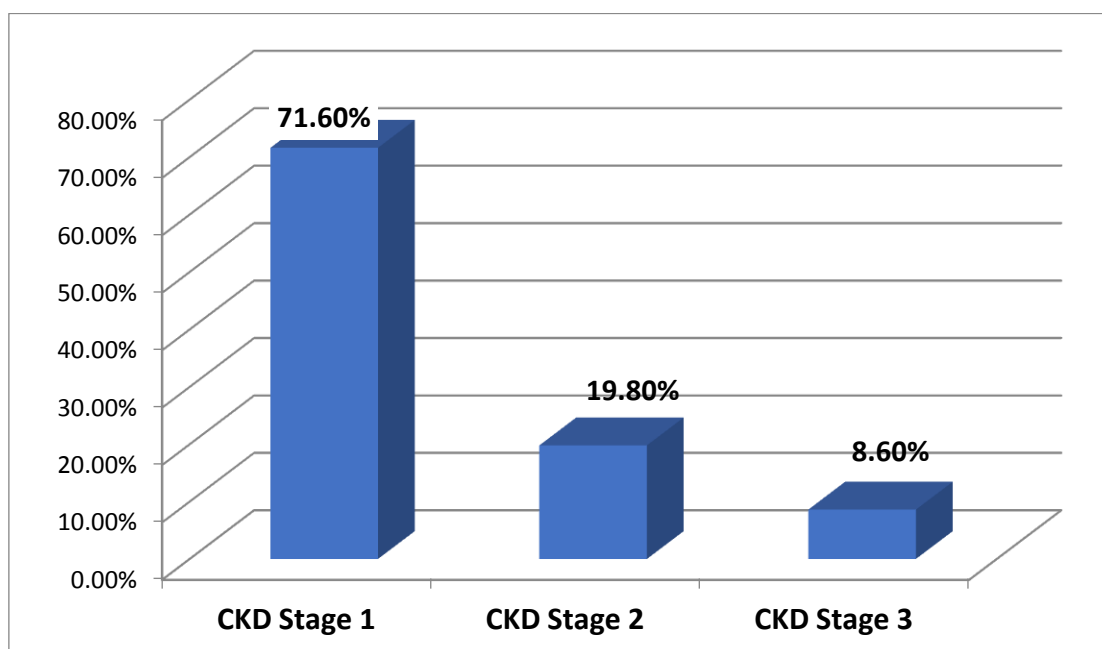


[Figure 4] Gender Distribution

3.3.Chronic Kidney Disease Stages According to GFR.

Based on GFR category 80 inpatients were screened for chronic kidney disease stages and the results were as followed: [Table 13].

[Table 13] Chronic Kidney Disease Stages According to GFR		
	Frequency	Percent (%)
CKD Stage 1	61	71.60
CKD Stage 2	15	19.80
CKD Stage 3	7	8.60
CKD Stage 4	0	00.0
CKD Stage 5	0	00.0
Total	80	100

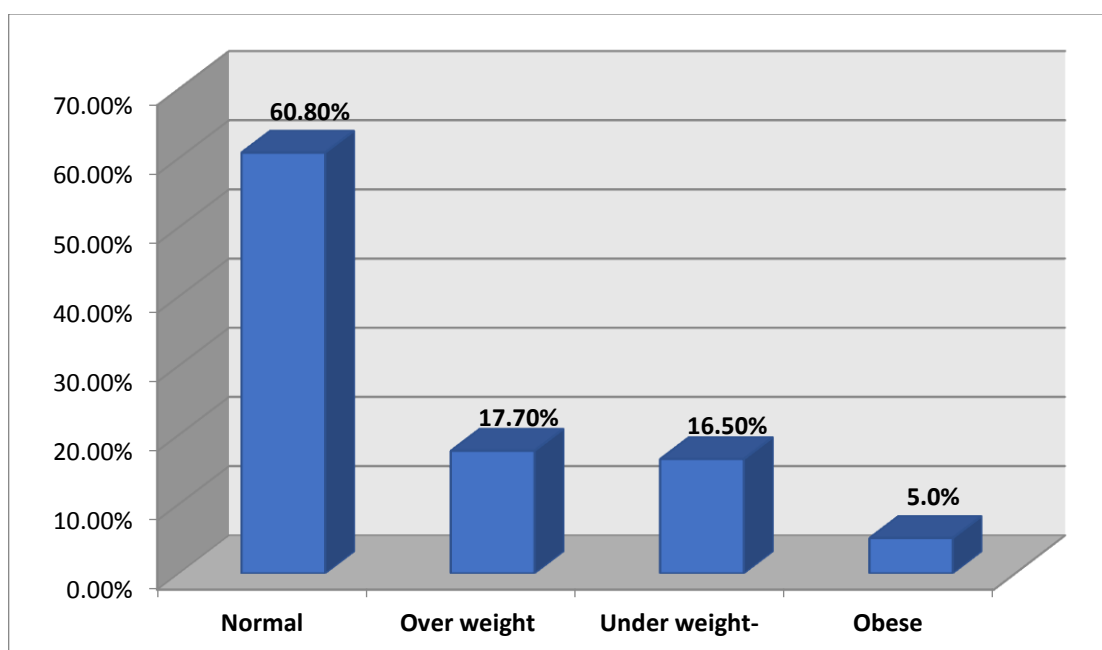


[Figure 5] Chronic Kidney Disease Stages According to GFR

3.4.BMI Meaning Distribution

Among patient in this study most of them at normal BMI and almost over weight equal under-weight [Table 14].

[Table 14] BMI Meaning distribution		
	Frequency	(%) Percent
Normal	48	60.80
Over weight	14	17.70
Under-weight	13	16.50
Obese	4	5.0
Total	80	100

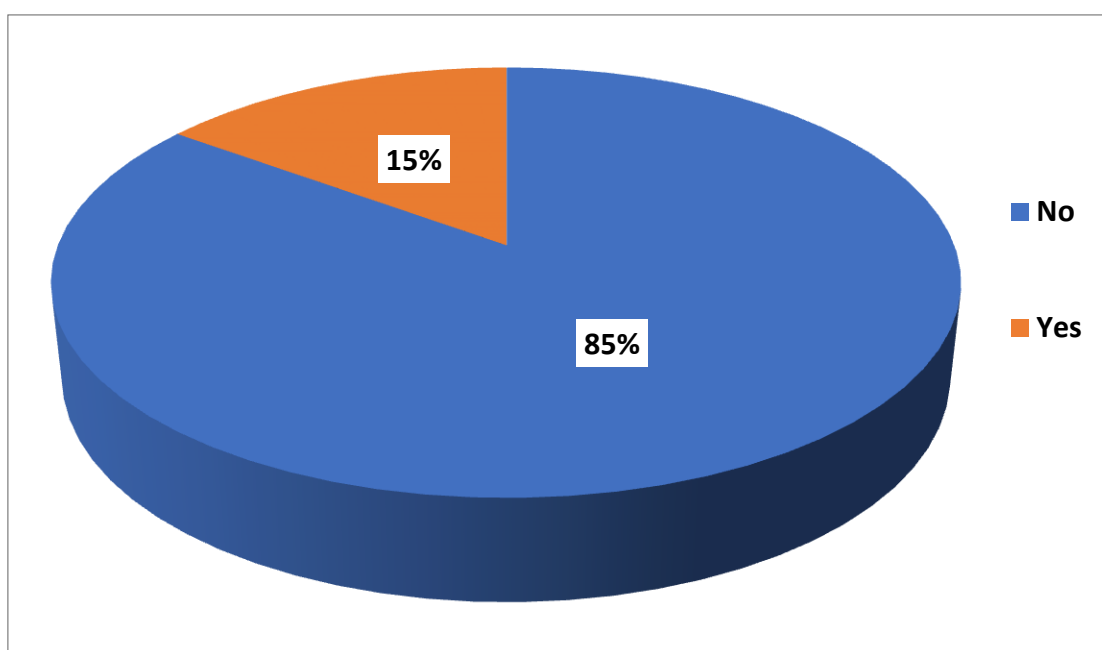


[Figure 6] BMI Meaning Distribution

3.5.Risk of HIT Distribution

During the period of this study a total of 80 in-patients records were reviewed, among which majority were without risk (No) and the remaining were with risk (Yes) of HIT. [Table 15].

[Table 15] Risk of HIT Distribution		
	Frequency	Percent(%)
No	68	85.0
Yes	12	15.0
Total	80	100

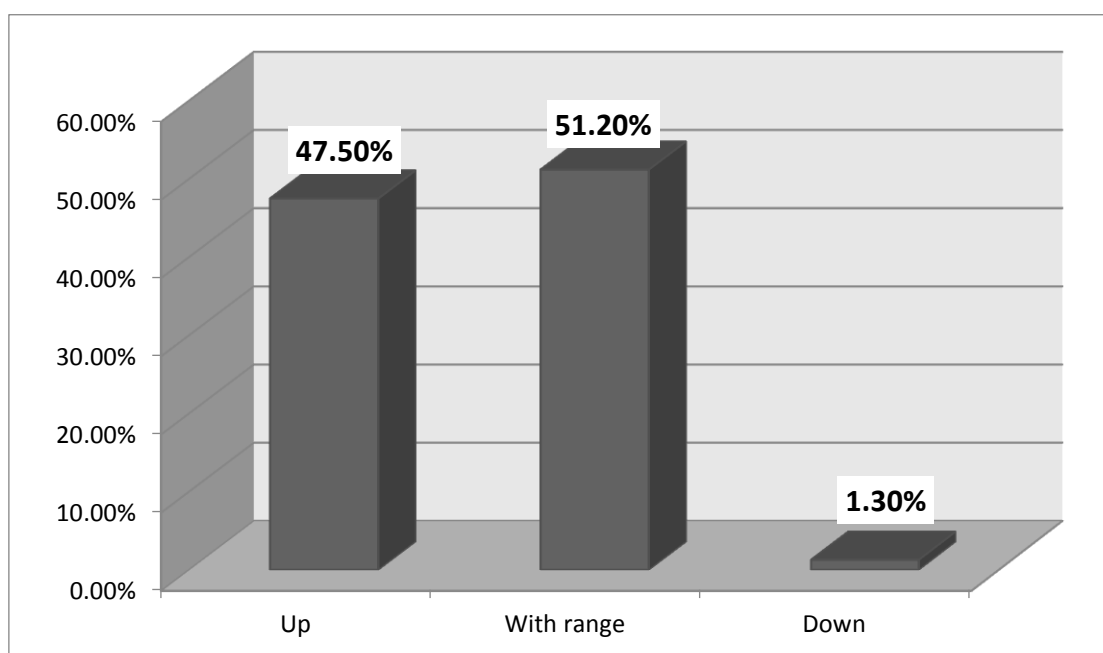


[Figure 7] Risk of HIT distribution

3.6. Range of aPTT Distribution

During the period of this study a total of 80 in-patients records were reviewed, among which majority were with range and the remaining were up range and one case was down the range. [Table 16].

[Table 16] Range of aPTT Distribution		
	Frequency	Percent(%)
UP	38	47.5
With Range	41	51.2
Down	1	1.3
Total	80	100

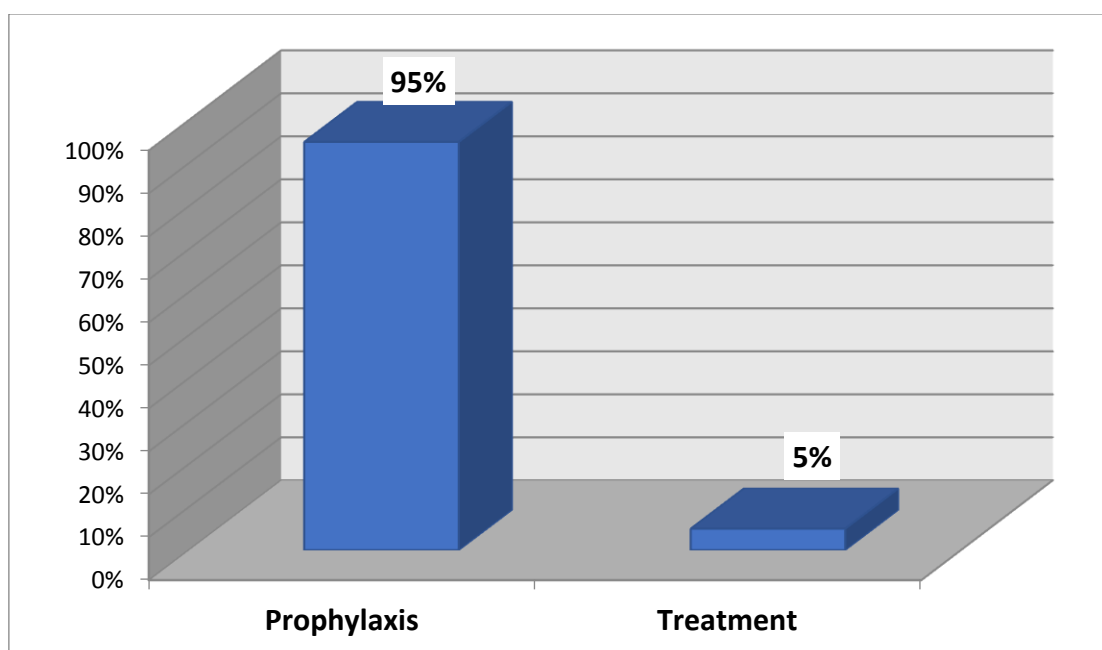


[Figure 8] Range of aPTT Distribution

3.7.Strategy of Intervention Distribution

During the period of this study a total of 80 in-patients records were reviewed, among which majority were prophylaxis and little patient with treatment according to heparin doses. [Table 17].

[Table 17] Strategy of Intervention Distribution		
	Frequency	Percent(%)
Prophylaxis	76	95.0
Treatment	4	5.0
Total	8	100

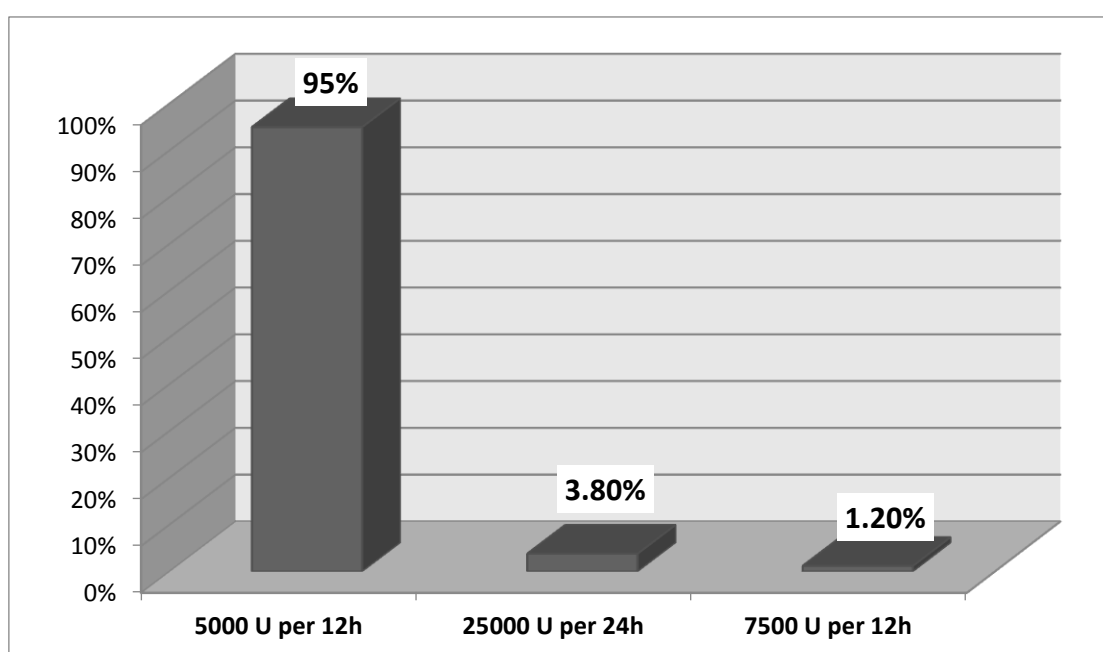


[Figure 9] Strategy of Intervention Distribution

3.8.Heparin Dose Distribution

During the period of this study a total of 80 in-patients records were reviewed, among which majority were 5000 U per 12h and the remaining were 25000 U per 24h and 7500 U per 12h from Heparin dose. [Table 18].

[Table 18] Heparin dose Distribution		
	Frequency	Percent(%)
5000 U per 12h	76	95
25000 U per 24h	3	3.8
7500 U per 12h	1	1.3
Total	80	100

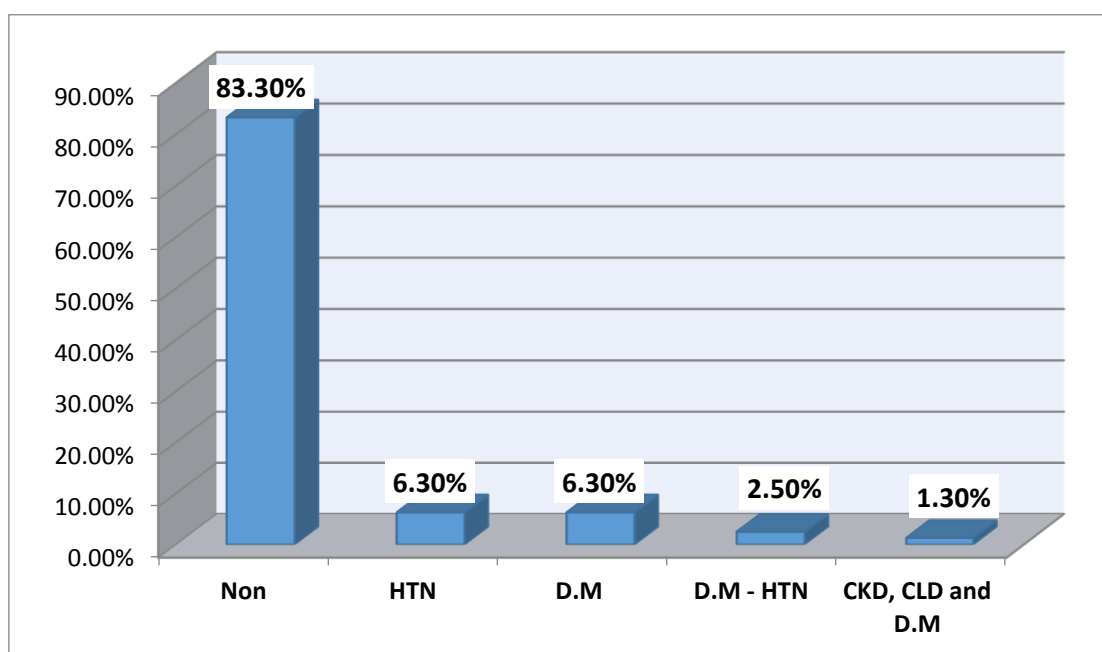


[Figure 10] Heparin Dose Distribution

3.9.Chronic Disease Distribution

Chronic disease distribution in 80 patients were screened for using heparin in surgery ward in 48 typical hospital [Table 19]

[Table 19] CD Distribution		
	Frequency	Percent(%)
Non	67	83.8
HTN	5	6.3
D.M	5	6.3
D.M – HTN	2	2.5
CKD, CLD and D.M	1	1.3
Total	80	100

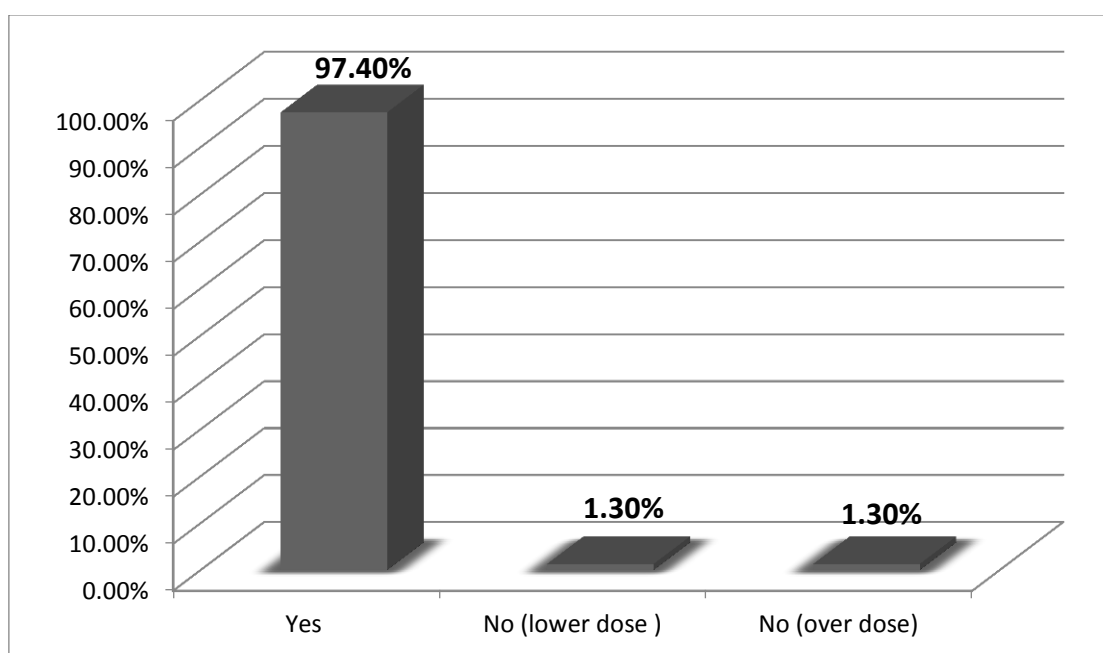


[Figure 11] Chronic Disease Distribution

3.10.Heparin Use According to Guideline

The data describe heparin use according to guideline and patients that use lower and over dose. [Table 20]

[Table 20] Heparin Use According to Guideline		
	Frequency	Percent %
Yes	78	97.4
No (lower dose)	1	1.3
No (over dose)	1	1.3
Total	80	100

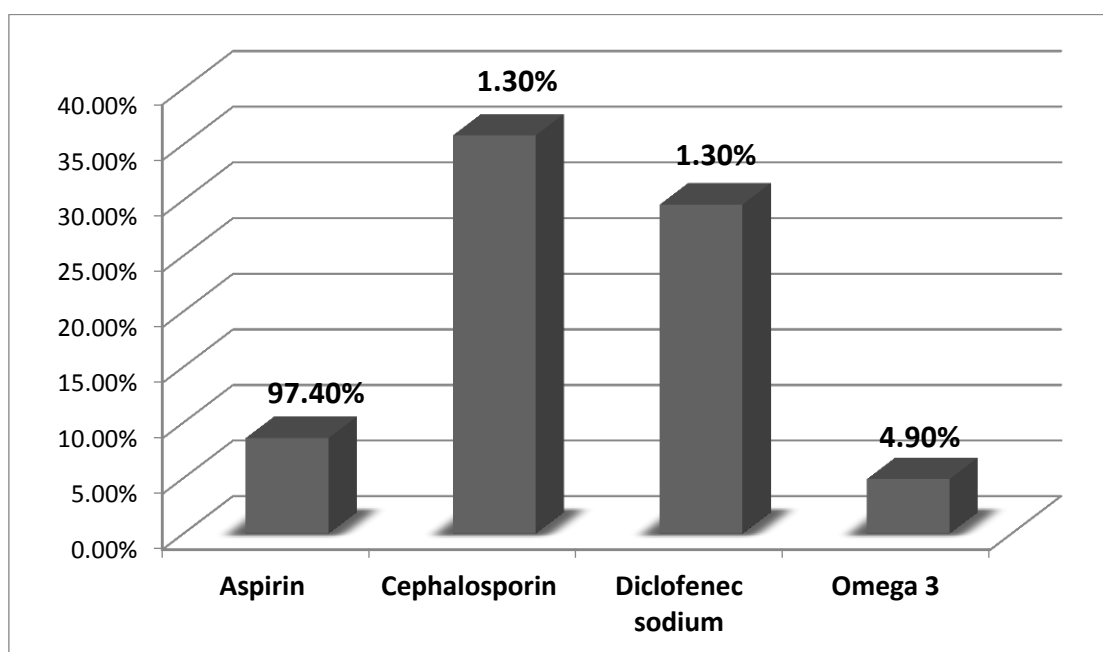


[Figure 12] Heparin Use According to Guideline

3.11.Heparin-Drug Interaction

The data describe interaction between heparin and drug that can interact with it. [Table 21]

[Table 21] Heparin-Drug interaction		
	Frequency	Percent(%)
Aspirin	7	8.6 %
Cephalosporin	29	35.8%
Diclofenec sodium	24	29.6%
Omega 3	4	4.9 %



[Figure 13] Heparin-Drug Interaction

Chapter-4

4.1. Discussion

This is the first Yemeni study and one of the few international studies that evaluates of Heparin using for thromboembolism prophylaxis in hospitalized patients based on the latest version of Guideline. Multiple studies have demonstrated a significant association prevention of venous thromboembolism disease in adult orthopedic and nonorthopedic surgical patients. When you take BMI meaning were normal weight 48 patients (60.80%). In this study 95% of patient use heparin as prophylaxis as 5000 unit BID except a patient. Used heparin as prophylaxis as 75000 BID (spinal cord injury), and 5% used heparin as treatment (table 8). The percent of patient used correct dose were 78 (96.3%), 1(1.2%) were used lower dose and 1 (1.2 %) used over dose (treatment), percent of aPTT score minimum rang is 23 second and the maximum rang is 92 second and the percent of patient need dose adjustment is 47.5% and percent of patient need increase dose is 1.3 % (table 6). The percent of patients have shown risk of HIT is 15% and need dose adjustment. In this study the majority percent of patients use heparin had non chronic disease 67 patients (83.8%),5 (6.3%) of patients have HTN ,5 (6.3 %) of patients have DM ,2 (2.5 %) have HTN with DM together. and 1 (1.3 %) of patients have CKD,CLD and DM together (table 9).

During the period of this study a total of 80 in-patients records were reviewed, among which majority were 5000 U per 12h and the remaining were 25000 U per 24h and 7500 U per 12h from Heparin dose. For patient in this study many heparin drug interaction mentioned in Table 21 the most Heparin-drug interaction found was with cephalosporin (ceftriaxone, cefuroxime) because they increase the level or effect of heparin by anticoagulation and my increase prothrombin activity, heparin and declofinac sodium may increase anticoagulation. and heparin and omega 3 patients taking omega3 and anticoagulant should be monitored.

4.2.Limitations of the study

The study is subjected to some limitations. One of the study limitations is that not all medications of beers criteria are available in the hospital formulary. Also, this study is done over one hospital only, one department and the study duration was short so, the results may be not representative of all patients in Yemen.

Chapter-5

4.3.Conclusion & Recommendations:

According to the results obtained in this work, the following recommendations are proposed:

- ✓ Further studies should be done on all departments of Yemen's hospitals.
- ✓ Physicians should be aware and given more attention during prescribing of drugs.
- ✓ Clinical pharmacists should be present in all branches of the hospitals in order to correct such errors.
- ✓ Upgrade the clinic to cover all anticoagulation medication is needed.

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الخلاصة

مقدمة: النظر في معدل انتشار وخطر تجلط الأوردة العميقة DVT في المرضى في المستشفيات، ووجود طرق وقائية مختلفة في هؤلاء المرضى ، وضرورة تقييم الإدارة العقلانية للهيبارين و الوقاية الميكانيكية هي واحدة من الأولويات الهامة .تهدف الدراسة الحالية إلى تقييم اتساق إدارة الهيبارين بالمقارنة مع المبادئ التوجيهية في المرضى في مستشفى النموذجي.

الطريقة: في هذه الدراسة المرتقبة تقييم تعاطي الادوية في 80 مريضاً في المستشفى تم تسجيل تلقي العلاج الوقائي من الجلطة الوريدية ، والتي تم اختيار المرضى منها من اقسام الجراحة. تم جمع البيانات الديموغرافية والسريية للمرضى باستخدام المرضى والسجلات السريية لهم استخدمنا قوائم المراجعة بناءً على حسب المعايير العالمية، و استبيانات المرضى في أجنحة الجراحة لتقييم ما إذا كان المرضى قد استقبلوا الوقاية من الهيبارين والوقاية الميكانيكية من الإصابة بجلطات الأوردة العميقة وفقاً للإرشادات، وقد تم تحليل البيانات التي تم الحصول عليها باستخدام الإحصاء الوصفي الإصدار 21 من SPSS.

الهدف من الدراسة: مراقبة جرعة الهيبارين في مستشفى ٤٨ في قسم الجراحة ، تقييم جرعة الهيبارين للأشخاص المصابين بأمراض مزمنة ، تقييم جرعة الهيبارين كما العلاج الوقائي أو العلاج وفقاً للمبادئ التوجيهية ، الكشف عن التفاعل بين الهيبارين وغيرها من الأدوية وتقليل التأثير الضار أثناء استخدام الهيبارين.

النتيجة: في قسم الجراحة تم إدخال 80 مريض إلى أجنحة الجراحة ، 70 مريض 87.5% كانوا من الذكور، 10 مرضى 12.5% كانوا من الإناث ، 67 مريض 83.8% كانوا دون 40 سنة، 76 (95%) كانوا معظم المرضى يستخدمون الهيبارين 5000 وحدة لكل 12 ساعة كجرعة وقائية، وقد تم إعطاء الجرعة الوقائية في أجنحة الجراحة لعدد 78 مريض حسب التوصيات العالمية (Guideline).



كلية الصيدلة السريرية



الجمهورية اليمنية
وزارة التعليم العالي والبحث العلمي
جامعة ٢١ سبتمبر للعلوم الطبية
والتطبيقية
كلية الصيدلة السريرية

تقييم استخدام الهيبارين للمرضى المتواجدين بقسم الجراحة في مستشفى ٤٨ النموذجي

قدمت هذه الدراسة

استكمالاً لمتطلبات الحصول على درجة البكالوريوس

في تخصص الصيدلة السريرية في جامعة ٢١ سبتمبر للعلوم الطبية والتطبيقية.

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