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Comparative Clinical Study of Warfarin and Rivaroxaban (Newer Anti-Coagulant) with Respect to Efficacy and Side Effects in the Treatment of Peripheral Venous Thromboembolism

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Abstract: ***New oral anticoagulants (NOAC; rivaroxaban, dabigatran, apixaban) have become available as an alternative to warfarin anticoagulation in peripheral venous thromboembolism. We assessed the effectiveness and safety along with side effects of rivaroxaban vs warfarin in patients experiencing venous thromboembolism (both deep vein thrombosis and pulmonary embolism).***

Keywords: Venous thromboembolism, Warfarin, Rivaroxaban, Bleeding

1. Introduction

A venous thrombus is a blood clot (thrombus) that forms within a vein. Thrombosis is a term for a blood clot occurring inside a blood vessel. A common type of venous thrombosis is a deep vein thrombosis (DVT), which is a blood clot in the deep veins of the leg. If the thrombus breaks off (embolizes) and flows towards the lungs, it can become a pulmonary embolism (PE), a blood clot in the lungs.

An inflammatory reaction is usually present, mainly in the superficial veins and, for this reason this pathology is called most of the time thrombophlebitis. The inflammatory reaction and the white blood cells play a role in the resolution of venous clots.[1] It includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Although the exact incidence of VTE is unknown, an estimated 1 million people in the United States are affected each year, with about a third experiencing a recurrence within 10 years.[2] VTE affects hospitalized and non -hospitalized patients, is often overlooked, and results in long-term complications including post thrombotic syndrome (PTS) for DVT, post pulmonary embolism syndrome and chronic thromboembolic pulmonary hypertension for PE, and death.[3]Venous thromboembolism (VTE) is a common complication during and after hospitalisation for acute medical illness or surgery. Pulmonary embolism accounts for 5–10% of deaths in hospitalised patients, making VTE the most common preventable cause of in-hospital death.[4]

1.1 Deep Vein Thrombosis (DVT)

DVT occurs most commonly in the lower extremities or pelvis (see Figure: Deep veins of the legs.). It can also develop in deep veins of the upper extremities (4 to 13% of DVT cases). Lower extremity DVT is much more likely to cause pulmonary embolism (PE), possibly because of the higher clot burden. The superficial femoral and popliteal veins in the thighs and the posterior tibial and peroneal veins in the calves are most commonly affected. Calf vein DVT is less likely to be a source of large emboli but can propagate to the proximal thigh veins and from there cause PE. About 50% of patients with DVT have occult PE, and at least 30% of patients with PE have demonstrable DVT.

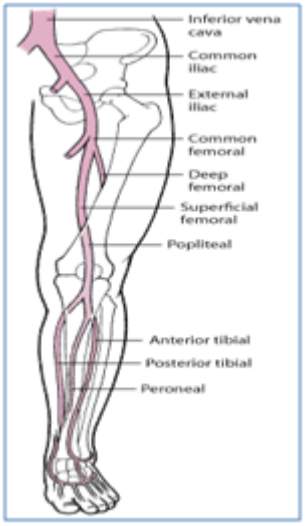

Figure 1: Deep veins of legs

1.2 Symptoms and Signs

DVT may occur in ambulatory patients or a complication of surgery or major medical illness.Among high-risk hospitalized patients, most deep vein thrombi occur in small calf veins, are asymptomatic, and may not be detected.[5]

Common symptoms include-

1) Swelling in your foot, ankle, or leg, usually on one side
2) Cramping pain in your affected leg that usually begins in your calf.
3) Severe, unexplained pain in your foot and ankle
4) An area of skin that feels warmer than the skin on the surrounding areas
5) Skin over the affected area turning pale or a reddish or bluish color

People with an upper extremity DVT, or a blood clot in the arm, may also not experience symptoms. If they do, common symptoms include:

1) Neck Pain
2) Shoulder Pain
3) Swelling in the Harm or Hand
4) Blue-Tinted Skin Color
5) Pain that moves from the arm to the Forearm
6) Weakness in the Hand.

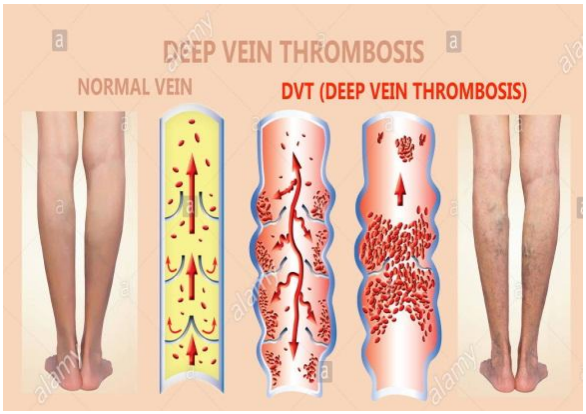

Figure 2: Normal vein Vs Deep vein thrombosis

1.3 Diagnosis

Ultrasonography,Sometimes d-dimer testing.[6]

1.4 Pulmonary Embolism

A pulmonary embolism **(**PE) is a blood clot that blocks the blood vessels supplying the lungs. The clot (embolus) most often comes from the leg veins and travels through the heart to the lungs. When the blood clot lodges in the blood vessels of the lung, it may limit the heart's ability to deliver blood to the lungs, causing shortness of breath and chest pain, and, in serious cases, death.[7] PE is a serious condition that can cause-

- Permanent damage to the lungs
- Low oxygen levels in your blood
- Damage to other organs in your body from not getting enough oxygen

PE can be life-threatening, especially if a clot is large, or if there are many clots. The cause is usually a blood clot in the leg called a deep vein thrombosis that breaks loose and travels through the bloodstream to the lung.[8]

1.5 Symptoms and Signs

Many pulmonary emboli are small, physiologically insignificant, and asymptomatic. Even when present, symptoms are nonspecific and vary in frequency and intensity, depending on the extent of pulmonary vascular occlusion and preexisting cardiopulmonary function. Emboli often cause-

- Acute dyspnea
- Pleuritic chest pain (when there is pulmonary infarction)

Dyspnea may be minimal at rest and can worsen during activity. Less common symptoms include cough (usually caused by comorbid disorders), Hemoptysis (occasionally occurs when there is pulmonary infarction)

In elderly patients, the first symptom may be altered mental status. Massive PE may manifest with hypotension, tachycardia, light-headedness/pre-syncope, syncope, or cardiac arrest. The most common signs of PE are tachycardia, tachypnea. Less commonly, patients have hypotension. A loud 2nd heart sound (S2) due to a loud pulmonic component (P2) is possible but uncommon in acute PE because increases in pulmonary artery pressures are only modest. Crackles or wheezing may occur but are usually due to comorbid disease. In the presence of right ventricular failure, distended internal jugular veins and a RV heave may be evident, and a RV gallop (3rd heart sound [S3]), with or without tricuspid regurgitation, may be audible. Fever, when present, is usually low-grade unless caused by an underlying condition. Pulmonary infarction is typically characterized by chest pain (mainly pleuritic) and, occasionally, hemoptysis. The chest wall may be tender.Chronicthromboembolic pulmonary hypertension causes symptoms and signs of right heart failure, including exertional dyspnea, easy fatigue, and peripheral edema that develops over months to years.

1.6 Diagnosis

D-Dimer testing, CT angiography,V/Q scanning, Duplex ultrasonography.[11]

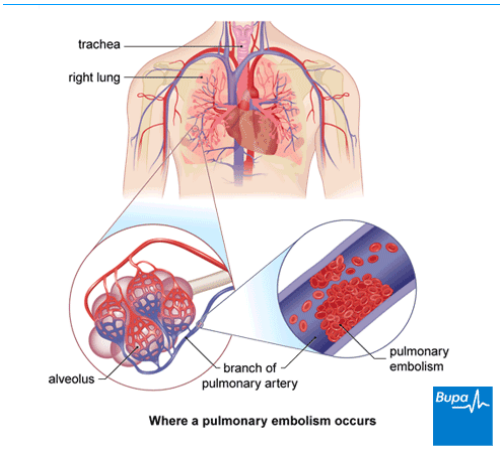

Figure 3: Pulmonary embolism

1.7 Treatment

Treatment for VTE should be initiated in the following cases:

- Proximal DVT of the lower extremity
- Symptomatic distal (calf vein) DVT
- Symptomatic upper extremity DVT (axillary-subclavian veins)
- PE
- Subsegmental PE in a patient at risk for recurrence
- Surveillance for subsegmental PE in a patient with no proximal DVT and a low risk of recurrence.

Once VTE is suspected, anticoagulation should be started immediately unless there is a contraindication such as a risk of bleeding. A risk assessment should be performed in all

patients before and during anticoagulation therapy (Table 1).In addition to anticoagulants, other more aggressive therapies for VTE may be appropriate, such as systemic thrombolysis in the case of PE or catheter-directed thrombolytic or pharmaco mechanical therapies for DVT or PE, surgical intervention (acute pulmonary embolectomy), or placement of an inferior vena cava (IVC) filter.[12]

1.8 Anticoagulants

Anticoagulants are used in the acute (first 0 to 7 days), long-term (7 days to 3 months), and extended (3 months to indefinite) treatment phases of VTE.[13] Anticoagulation therapy options include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux, vitamin K antagonists (VKAs) (ie, warfarin), and direct oral anticoagulants (DOACs).

Deciding on which anticoagulant to use depends on the indication, the patient's underlying condition, the patient's preference, and the patient's risk of bleeding. Heparin, the LMWHs, fondaparinux and the DOACs (rivaroxaban and apixaban) are the only agents approved by the US Food and Drug Administration (FDA) recommended for the acute treatment phase, while the DOACs and warfarin are anticoagulation options for the long-term and extended treatment phases. The LMWHs should be used for the patient with cancer and during pregnancy.[13]

1.9 Direct Oral Anti-Coagulants:

The DOACs, which include the factor Xa inhibitors rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) and the direct thrombin inhibitor dabigatran (Pradaxa), been studied extensively and shown to be non-inferior to VKAs for treatment of VTE. DOACs are currently recommended by the ACCP for long-term treatment of VTE, and several have extended treatment recommendations for VTE over the VKAs.[12]

The advantages of DOACs include no need for PT/INR monitoring, a fixed dosage, shorter half-life, rapid onset of action (for monotherapy), and in most cases, no need for bridging for interventional or surgical procedures. Additional advantages may include a decreased burden of care for the physician and improved quality of life for the patient. DOACs are also the agents of choice for patients who prefer oral therapy (avoiding parenteral therapy), have limited access to an anticoagulation clinic (home bound or geographic inaccessibility for PT/INR monitoring), or have food or drug-drug interactions. Patients at risk of gastrointestinal bleeding or dyspepsia should avoid dabigatran, while apixaban may be preferred if there is a history of gastrointestinal bleeding.[14]

1.11 WARFARIN

Warfarin, a VKA, was the mainstay of therapy for long-term and extended treatment of VTE until the advent of the DOACs. Warfarin must be coadministered with heparin, LMWH, or fondaparinux initially and continued as overlap therapy for a minimum of 5 days until the international normalized ratio [INR] is at least 2.0 for 24 hours.[13] Early initiation of a VKA on the first day of parenteral therapy is advised.

Warfarin remains the best option for patients on long-term or extended anticoagulation with liver dysfunction (elevated serum transaminases exceeding twice the upper limits of normal or active liver disease) or renal disease (CrCL< 30 mL/min), as well as patients unable to afford DOACs. Additionally, select patient populations may still be best served by warfarin as these groups were underrepresented or not included in DOAC trials, including pediatric patients, individuals with body weight less than 50 kg or greater than 150 kg, and patients with select types of thrombophilia (eg, antiphospholipid syndrome).

Warfarin is also advised for patients with poor compliance, as international normalized ratio of prothrombin time (PT/INR) monitoring is required using a point-of-care testing device or during a visit to an anticoagulation clinic. DOACs do not require monitoring, and noncompliance will not be readily apparent.[12]

Pharmacology:

1) **Indication:** For the treatment of retinal vascular occlusion, pulmonary embolism, cardiomyopathy, atrial fibrillation and flutter, cerebral embolism, transient cerebral ischaemia, arterial embolism and thrombosis.
2) **Pharmacodynamics:** Warfarin, a coumarin anticoagulant, is a racemic mixture of two active isomers. It is used in the prevention and treatment of thromboembolic disease including venous thrombosis, thromboembolism, and pulmonary embolism as well as for the prevention of ischemic stroke in patients with atrial fibrillation (AF).
3) **Mechanism of action:** Warfarin inhibits vitamin K reductase, resulting in depletion of the reduced form of vitamin K (vitamin KH2). As vitamin K is a cofactor for the carboxylation of glutamate residues on the N-terminal regions of vitamin K-dependent proteins, this limits the gamma-carboxylation and subsequent activation of the vitamin K-dependent coagulant proteins. The synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S is inhibited. Depression of three of the four vitamin K-dependent coagulation factors (factors II, VII, and X) results in decreased prothrombin levels and a decrease in the amount of thrombin generated and bound to fibrin. This reduces the thrombogenicity of clots.
4) **Absorption:** Rapidly absorbed following oral administration with considerable interindividual variations. Also absorbed percutaneously.
5) **Volume of distribution:** 0.14 L/kg
6) **Protein binding:** 99% bound primarily to albumin
7) **Metabolism:** Metabolized stereo- and regio-selectively by hepatic microsomal enzymes. S-warfarin is predominantly metabolized by cytochrome P450 (CYP) 2C9 to yield the 6- and 7-hydroxylated metabolites. R-warfarin is metabolized by CYP1A1, 1A2, and 3A4 to yield 6-, 8-, and 10-hydroxylated metabolites. Hydroxylated metabolites may be further conjugated prior to excretion into bile and urine. UGT1A1 appears to be responsible for producing the 6-O-glucuronide of warfarin, with a possibly contribution from UGT1A10.

Five UGT1As may be involved in the formation of 7-O-glucuronide warfarin. S-warfarin has higher potency than R-warfarin and genetic polymorphisms in CYP2C9 may dramatically decrease clearance of and increase toxicity of the medication.

8) **Route of elimination:** The elimination of warfarin is almost entirely by metabolism. Very little warfarin is excreted unchanged in urine. The metabolites are principally excreted into the urine; and to a lesser extent into the bile.
9) **Half-life:** R-warfarin $t_{1/2}$=37-89 hours; S-warfarin $t_{1/2}$=21-43 hours.[18]

1.12 Rivaroxaban

Rivaroxaban or apixabancan be used as monotherapy for the initial treatment of VTE, while a 5-day course of heparin, LMWH, or fondaparinux is necessary with dabigatran or edoxaban. Rivaroxaban has been approved by the FDA for use in the prevention and treatment of VTE.[15,16] For VTE prophylaxis, rivaroxaban is given orally at 10 mg once daily for 35 days for patients undergoing total hip replacement surgery and for 12 days for patients undergoing knee replacement surgery. For the treatment of VTE, rivaroxaban is given orally at 15 mg twice a day for the initial 21 days of treatment, followed by once daily at 20 mg per day for long-term treatment. It is also approved for extended-duration therapy in both 10-mg and 20-mg doses. In a recently published randomized double-blind trial of rivaroxaban compared with aspirin, the risk of a recurrent event was lower with either dose of rivaroxaban compared with aspirin without an increase in bleeding.[17]Rivaroxaban is contraindicated in patients with renal insufficiency (CrCL< 30 mL/min). Both the 15-mg and 20-mg tablets must be taken with food.

Pharmacology:

1) **Indication:** Rivaroxaban is indicated for the prevention of venous thromboembolic events (VTE) in patients who have undergone total hips replacements and total knee replacement surgery; prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation; treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); to reduce risk of recurrent DVT and/or PE. Rivaroxaban is also indicated, in combination with aspirin, for reducing the risk of major cardiovascular events in patients with chronic coronary artery disease or peripheral artery disease. Due to a lack of safety studies, it is not recommended for use in those under 18 years old. Its use is also not recommended in those with severe renal impairment (<30mL/min).
2) **Pharmacodynamics:** Rivaroxaban is an anticoagulant which binds directly to factor Xa. Thereafter, it effectively blocks the amplification of the coagulation cascade, preventing the formation of thrombus. Rivaroxaban is aunqiue anticoagulant for two reasons. First of all, it is does not involve antithrombin III (ATIII) to exert its anticoagulant effects. Secondly, it is an oral agent whereas the widely used unfractionated heparin and low molecular weight heparins are for parenteral use only. Although the activated partial thromboplastin time (aPTT) and HepTest (a test developed to assay low molecular weight heparins) are prolonged in a dose-dependant manner, neither test is recommended for the assessment of the pharmacodynamic effects of rivaroxaban. Anti-Xa activity and inhibition of anti-Xa activity monitoring is also not recommended despite being influenced by rivaroxaban
3) **Mechanism of action:** Rivaroxaban competitively inhibits free and clot bound factor Xa. Factor Xa is needed to activate prothrombin (factor II) to thrombin (factor IIa). Thrombin is a serine protease that is required to activate fibrinogen to fibrin, which is the loose meshwork that completes the clotting process. Since one molecule of factor Xa can generate more than 1000 molecules of thrombin, selective inhibitors of factor Xa are profoundly useful in terminating the amplification of thrombin generation. The action of rivaroxaban is irreversible.
4) **Absorption:** Following oral administration, rivaroxaban is rapidly absorbed and reaches peak plasma concentration in 2-4 hours. Bioavailability of the 10 mg dose is >80%. However, the 15-20 mg dose have a lower bioavailability if taken in the fasted state and consequently should be taken with food.
5) **Volume of distribution:** The steady state Vd is 50 L
6) **Protein binding:** Plasma protein binding is about 92% to 95%
7) **Metabolism:** Approximately two-thirds of the dose is metabolized. It is metabolized by CYP3A4, CYP3A5, CYP2J2 and CYP-independant mechanisms
8) **Route of elimination:** Approximately two-thirds of rivaroxaban is excreted into urine (via active tubular secretion in which approximately 36% as unchanged drug and 30% as inactive metabolism). The remaining third of the administered dose is excreted via feces in which 7% is in the form of unchanged drug and 21% as inactive metabolites.
9) **Half-life:** The terminal half-life is 5-9 hours in adults and 11-13 hours in the elderly[19].

1.13. Duration of Treatment

The duration of treatment following the diagnosis of VTE depends on the individual patient's risk of recurrence. Patients with unprovoked VTE have a risk of recurrence reported to be between 25% and 30% at 5 to 10 years after their event.[18,19] Risk factors for recurrence include unprovoked or proximal DVT or PE, certain underlying hyper-coagulable conditions such as the anti-phospholipid syndrome, and underlying active malignancy. Additional risk factors that may predispose the patient to recurrent VTE include placement of an IVC filter, elevated D-dimer levels following discontinuation of anticoagulation, advanced age, male sex, increased body mass index, the presence of the PTS, and residual vein thrombosis .Although the risk of recurrence decreases with longer durations of anticoagulation, clinicians must weigh the risk of bleeding against the risk of new thrombosis. The duration of treatment for unprovoked VTE remains controversial. In the most recent ACCP guidelines, indefinite or extended anticoagulation is indicated for patients with a low or moderate risk of bleeding for a first (and second) unprovoked VTE.[13] Patients with a high risk of bleeding with a first (or second) unprovoked VTE that is a proximal DVT of the leg or PE be treated for 3 months.[12,13] Three

DOACs (rivaroxaban, apixaban, and dabigatran) have extended-duration indications.

2 Objectives

2.1 General Objectives

- To determine and compare the role of warfarin and rivaroxaban in the treatment of peripheral venous thromboembolism.
- Includes efficacy, dosage and side effects of the drugs and compared therapeutically to get appropriate results and outcome.

2.2 Specific Objectives

The specific objectives are to assess:

1) Demographic data
   a) Age
   b) Gender
   c) Socioeconomic status
   d) Domicile
   e) First aid given
   f) Chief complaints
   g) Risk factor
   h) Severity of disease
2) Social history
   a) Smoker
   b) Alcoholic
   c) Food habbits- V/NV
   d) Marital status
   e) Allergies
3) Physical examination
4) Provisional diagnosis
5) investigations
6) Final diagnosis
7) Drugs prescribed
8) Drug interactions
9) Adverse effects
10) Prothrombin time (with INR monitoring)
11) Bleeding risk
12) Drug compliance
13) Duration of hospital stay
14) Therapeutic outcome

The study was carried out to

- Determine the clinical efficacy of warfarin and rivaroxaban (newer anti-coagulant) in patients with peripheral venous thromboembolism.
- Determine the possible adverse/side effects of warfarin and rivaroxaban in management.
- To compare the dosage between the two drugs given to the patients.
- To determine the frequency of both the drugs.
- To compare warfarin with rivaroxaban (newer anti-coagulant).
- To provide standard treatment for the patients with VTE.

3 Methodology

3.1 Data

a) Primary parameters/end point:

For peripheral VTE:

1) Platelet count.
2) Chest x-ray.

For pulmonary embolism (PE):

1) CTA (computed tomography angiography).

For DVT (deep vein thrombosis):

1) D- dimer test.
2) Doppler test.

b) Secondary paramters/end point:

Prothrombin time

The primary endpoint was to evaluate the patterns of use for oral anticoagulation. Secondary endpoints included determining the indication for anticoagulation, LOS from initiation of anticoagulation, and major bleeding events. Major bleeding events were defined by a drop in hemoglobin >2 grams/dL, or overt signs of a gastrointestinal bleed.

Data will be collected from:

1) Case sheets of peripheral Venous thromboembolism (VTE) patients.
2) Lab reports of VTE patients.
3) Other relevant sources.

3.2 Method and collection of Data

a) Study site: This study is conducted in department of general medicine, Krishna institute of medical sciences (KIMS) hospital.
b) Study design: “A prospective observational study”.
c) Study period: This study is conducted for 6 months.
d) Sample size: 50
e) Study criteria:

Inclusion criteria

- Adults (≥18 years of age) whose condition is venous thromboembolism (VTE).
- Patient cases of either sex.
- Both outpatients and inpatients case sheets.

Exclusion criteria

- Pregnant and lactating women.
- Pediatrics.

3.3 Source of data

All the relevant and necessary data will be collected from out patient records, case sheets (in patients), lab reports, prescription.Communicating with health care professionals.

4 Results and Discussion

During the study period of six months, a total of 30 VTE patient cases were enrolled into the study and data was collected and analysed.

Age Distribution of VTE Cases

A total number of 30 cases were enrolled in study. Out of which **03(10%)** were in the group of 20-30yrs, followed by **07(23.3%)** were in age group of 30-40 years, **08(26.7%)** were in the age group of 40-50 years, **08(26.7%)** were in the age group of 50-60 years, **04(13.3%)** were in age group of above 60 years old. (Table-4, Figure-4).

Table 4: Details of age distributions of VTE case

Age	No. of patients	Percentage (%)
20-30	3	10
30-40	7	23.3
40-50	8	26.7
50-60	8	26.7
>60	4	13.3

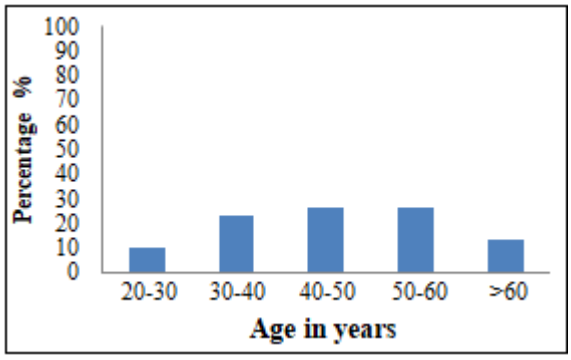

Figure 4: Details of age distribution of VTE cases

Details of Gender Distribution:

Out of 30 patient cases, it is found that there are 21 male patients and 09 female patients in the collected data. (Table-5, Figure-5)

Table 5: Details of gender distribution

Gender	No. of cases	Percentage (%)
Male	21	70
Female	9	30

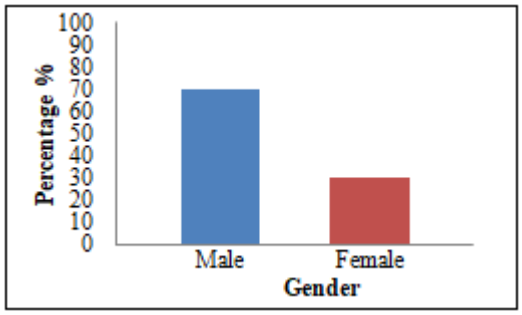

Figure 5: Details of gender distribution

First Aid / Primary Treatment:

Primary treatment is given based upon the patient condition. Among 30 patient cases, **25(83.3%)** patients were provided first aid care or primary treatment and **05(16.6%)** were not provided with first aid care. (Table-6, Figure-6)

Table 6: Details of patients given with first aid care

First aid	No. of patients	Percentage (%)
Given	25	83.4
Not given	05	16.6
Total	30	100

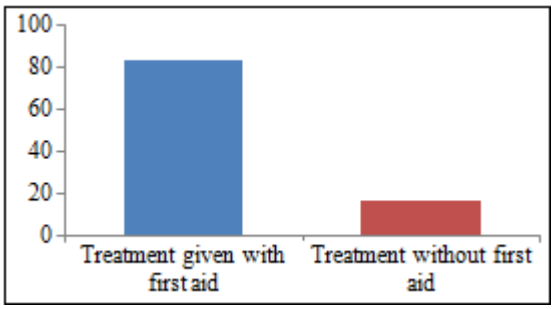

Figure 6: Details of patients given with first aid care

Among 30 patient cases first aid treatment , **2(8%)** are given only antibiotics, **2(8%)** are given only with anticoagulants, **2(8%)** are given with combination of Antibiotics+ Anti-hypertensives+ PPI, **1(4%)** are given with Antibiotic+ Anticoagulant+ Analgesics+ PPI, **1(4%)** patient cases are given with Antibiotics+ Anti-tussives+ PPI+ Analgesics+ Vitamins and minerals, **1(4%)** are given with Antibiotic + Anticoagulant+ PPI+ Anti-hypertensives+Bronchodilators, **1(4%)** are given with Antibiotics +PPI + Vitamins and minerals, **1(4%)** are given with Antibiotics+ LMWH+ Bronchodilator+ PPI, **1(4%)** are given with Antibiotics+ Antidepressants+ PPI+ Anti-tussives, **1(4%)** are given with Anticoagulants+ Antiplatelet+ PPI +Benzodiazepines, **1(4%)** are given with Anticoagulants+ Anti-Hypertensives, **2(8%)** are given with Anti-neoplastics+ Anti-inflammatory+ Anticoagulant, **1(4%)** are given with Anticoagulants+ LMWH+ Vitamins and minerals, **1(4%)** are given with Antiplatelets+ PPI+ LMWH, **1(4%)** are given with Anticoagulants+ PPI+ LMWH, **1(4%)** are given with Anti-platelets+ Anti-hypertensives, **2(8%)** are given with LMWH+ PPI, **1(4%)** are given with LMWH+ Antihypertensives, **1(4%)** are given with PPI, **1(4%)** are given with Thrombolytics agents.

Drugs with combination are given in the first aid treatment of VTE are clearly mentioned in the figure-7 below.

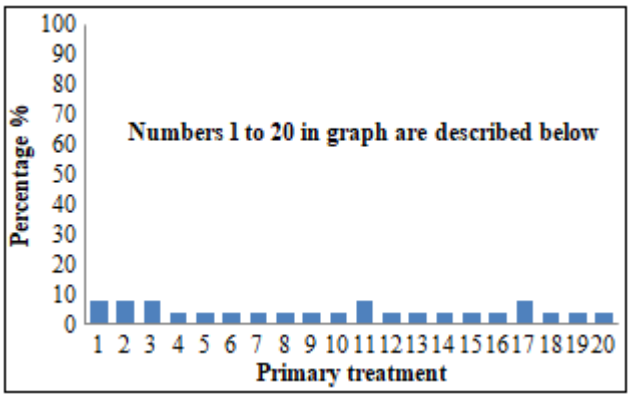

Figure 7: Details of type of therapy provided to VTE patients

1) Antibiotics
2) Anticoagulants
3) Antibiotics+Antihypertensives+PPI
4) Antibiotic+Anticoagulant+Analgesics+PPI
5) Antibiotics+Antitussives+PPI+Analgesics+Vitamins and minerals
6) Antibiotic + Anticoagulant + PPI+Anti-hypertensives+ Bronchodilators
7) Antibiotics+PPI+Vitamins and minerals

8) Antibiotics+LMWH+Bronchodilator+PPI
9) Antibiotics+Antidepressants+PPI+Anti-tussives
10) Anticoagulants+Antiplatelet+PPI+Benzodiazepines
11) Anticoagulants+Anti-hypertensives
12) Anti-neoplastics+Anti-inflammatory+ Anticoagulant
13) Anticoagulants+LMWH+Vitamins and minerals
14) Antiplatelets+PPI+LMWH
15) Anticoagulants+PPI+LMWH
16) Anti-platelets+Anti-hypertensives
17) LMWH+PPI
18) LMWH+Antihypertensives
19) PPI
20) Thrombolytic agents

Among 30 cases, **5(16.7%)** cases are given with warfarin in first aid treatment in which **2(6.7%)** are females whereas **3(10%)** cases are males(M). **2(6.7%)** cases are given with rivaroxaban as first aid treatment in which **1(3.35%)** are females(F) whereas **1(3.35%)** are males as shown in Figure-8

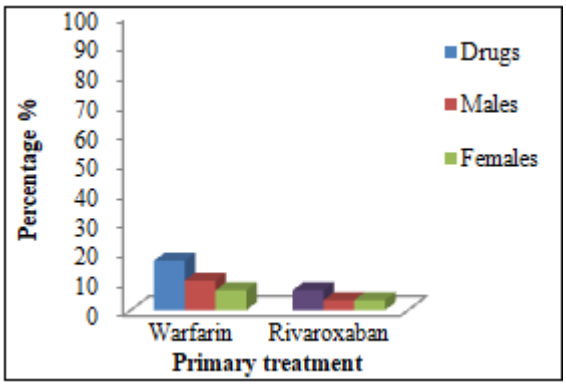

Figure 8: Details of warfarin and rivaroxaban in primary treatment

Adverse Effects:
Among 30 patient cases, **12(40%)** are found to have adverse drug reaction in which **8(26.7%)** cases are given with warfarin, **4(13.3%)** cases are given with rivaroxaban and **18(60%)** were found to have no adverse reactions in which **4(13.3%)** cases are given with warfarin, **14(46.7%)** cases are given with rivaroxaban. (Table-9, Figure-9)

ADRS seen:
Snoring, fatigue, obesity,Dyspnea reduced sedimentation, Shortness of breath, Chestpain, Anemia, Menstrual bleeding, Epigastricpain, Joint pains, Hemolysis, Hypokalemia and Hypoxemia. The above conditions are found in combination in the collected patient data forms.

ADRS	Drugs	
	W(a)	R(b)
Patients with ADRS	8	4
Patients without ADRS	4	14

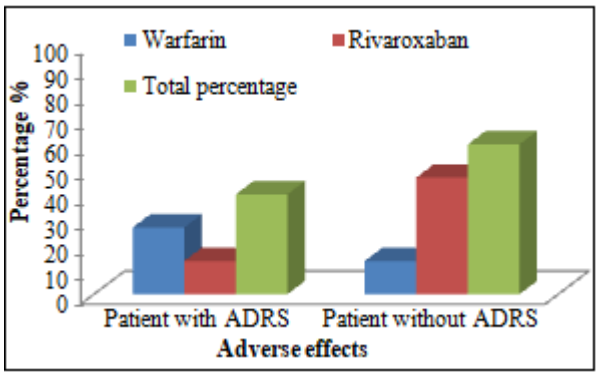

Figure 9: Number of patients seen with adverse effects

Duration of Hospital Stay:
Among 30 patient cases, **21(70%)** patients were in the hospital 1-5days, **05(16.6%)** patients were found to be in hospital in between 5-10 days, **02(6.7%)** patients were found to be in hospital between 10-15 days, **00(0%)** patients were found to be in hospital between 15-20 days, **02(6.7%)** patients were found to be in hospital >20 days. The average duration of hospital stay was found to be 5 days. (Table-10, Figure-10)

Table 10: Duration of hospital stay

Duration of stay (in days)	No. of patients	Percentage (%)
1-5	21	70
5-10	5	16.6
10-15	2	6.7
15-20	0	0
>20	2	6.7

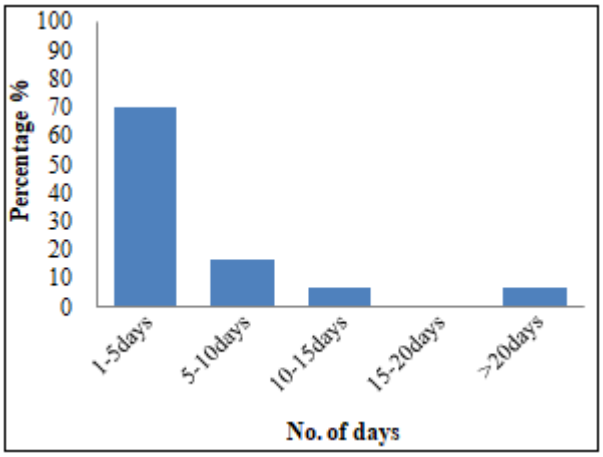

Figure 10: Duration of hospital stay

Risk Factor:
Among 30 cases, **2(6.7%)** with warfarin drug given and **1(3.35%)** with rivaroxaban drug given in therapy are the cases that are only found to have risk factor i.e., bleeding risk when compared with other **27(90%)** patient cases given with drug therapy. This risk is seen more in patients because of the treatment of warfarin only when compared with rivaroxaban. The risk seen is shown in (Table-11, figure-11).

Table 11: Details of risk factor in warfarin and rivaroxaban

Drugs	Risk factor	No. of cases	Percentage (%)
Warfarin	Bleeding	2	6.7
Rivaroxaban	Bleeding	1	3.35

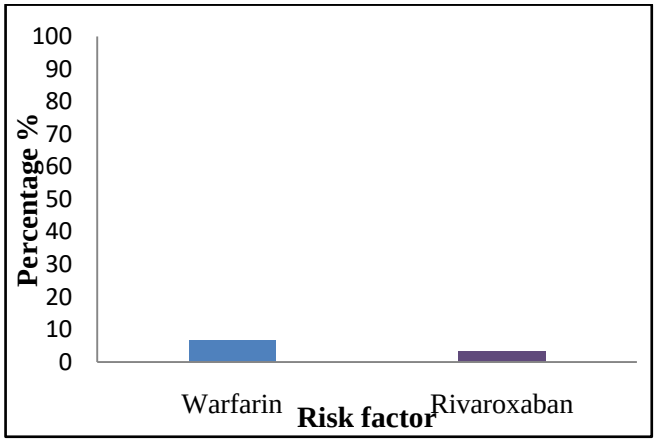

Figure 11: Patient cases seen with risk factor-Bleeding risk

Drug Compliance:

Among 30 patient cases, warfarin is given as a discharge medication in **7(23.3%)** cases, rivaroxaban is given as a discharge medication in **14(46.7%)** cases. Discharge medication without warfarin and rivaroxaban are given in **9(30%)** cases as shown in Table-12, figure-12

Table 12: Drug compliance

Discharge medication	No. of cases	Percentage (%)
Warfarin	7	23.3
Rivaroxaban	14	46.7
Not given with warfarin or rivaroxaban	9	30
Total	30	100

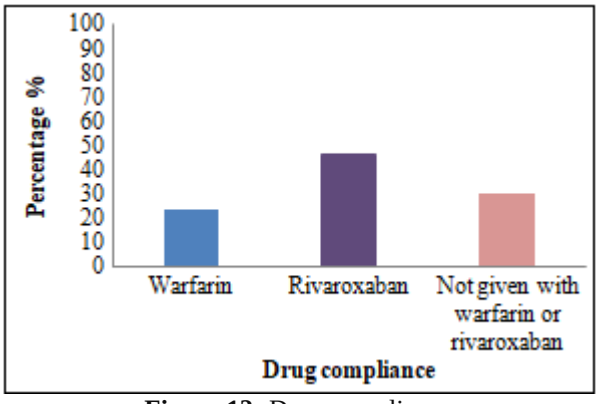

Figure 12: Drug compliance

Severity of VTE

Out of 30 venous thromboembolism cases, **13(43.4%)** were mild, **16(53.3%)** were moderate and **01(3.3%)** were severe patient cases.Table-13, Figure-13

Table 13: Details of severity of venous thromboembolism

Severity	No. of patients	Percentage (%)
Mild	13	43.4
Moderate	16	53.3
Severe	1	3.3
Total	30	100

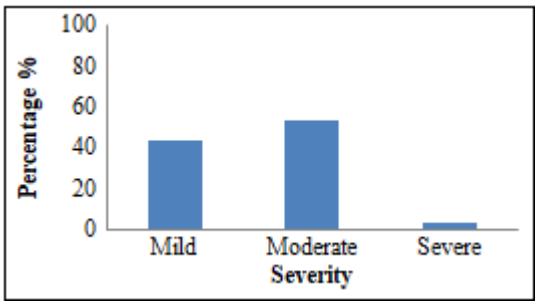

Figure 13: Details of severity of venous thromboembolism

Treatment

Among 30 cases, the number of cases given with warfarin are **14(46.7%)** cases in which most of the treatment with warfarin drug is done in male patients **12(32%)** cases when compared with female patients **2(14.2%)** cases the number of cases given with newer anticoagulant that is rivaroxaban are **16(53.3%)** cases in which most of the treatment with rivaroxaban drug is done in male patients **9(30%)** cases when compared with female patients **7(23.3%)** cases as shown in figure-14

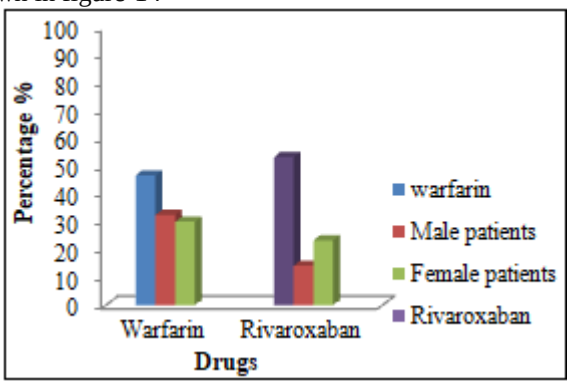

Figure 14: Treatment with warfarin and rivaroxaban

Therapeutic Outcome

Out of 30 venous thromboembolism cases, **17(56.6%)** were discharged with medications and without any review in which **8(26.7%)** were discharged without any drug either warfarin or rivaroxaban, **7(23.3%)** were discharged with rivaroxaban, **2(6.6%)** were discharged with warfarin, **8(26.7%)** were advised to review in a week to 15 days in which **5(16.7%)** are prescribed with warfarin and **3(10%)** are prescribed with rivaroxaban, **5(16.7%)** were advised to get review between 3-6 months in which **2(6.7%)** are prescribed with warfarin and **3(10%)** are prescribed with rivaroxaban, **30(100%)** of total cases are found to be impprovedwith **0(0%)** were dead.

Table 15: Details of therapeutic outcome of VTE cases
W-Warfarin,R-Rivaroxaban

Therapeutic Outcome	No. of cases		Percentage (%)	
Drugs	W	R	W	R
Discharge medications with	2	7	6.6	23.3
Discharged without warfarin or rivaroxaban	88		26.7	
Total	17		56.6	
Review within a week or 15 days	5	3	16.7	10
Total	08		26.7	
Review in 3-6 months	2	3	6.7	10
Total	05		16.7	
Improved	30		100	
Death	0		0	

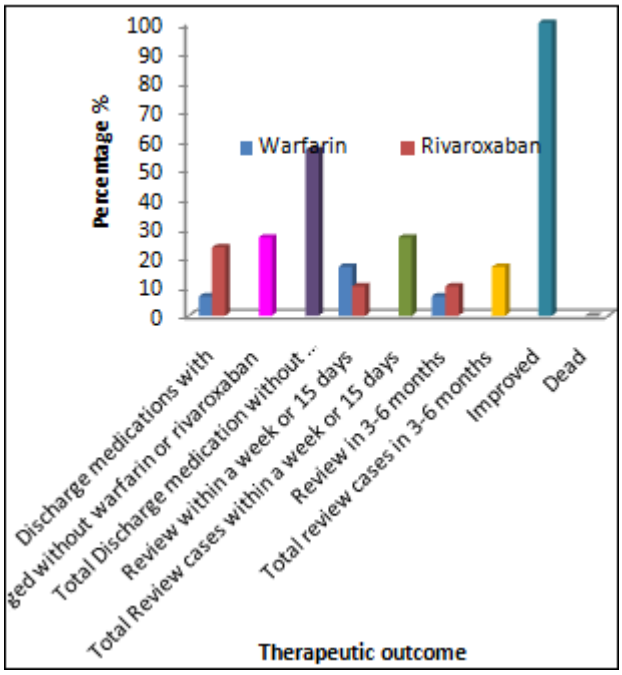

Figure 15: Details of therapeutic outcome of VTE cases

A total of 30 cases were enrolled in the study. The data from enrolled VTE cases were collected and analysed. The results revealed that out of total cases in the study, majority of the cases were in **40-50** and **50-60(26.7%)** followed by **30-40(23.3)**, **>60(13.3%)**, **20-30(10%)**. Our findings comply with the study conducted by Frederick A. Anderson Jr. and Frederick A. Spencer[31] in which it is stated that patients >40 years of age are at significantly increased risk compared with younger patients.

Overall, the incidence of VTE does not appear to vary significantly by sex, as evidenced by a lack of consistency in the magnitude and even direction of effect of sex in a variety of epidemiologic studies of varying design.[32] The gender distribution of VTE cases revealed that male patients cases are **21(70%)** and female patient cases are **09(30%).** The study findings are different from other studies since there are no gender differences in the rate of DVT or PE recurrences. The prevalence of VTE cases is more among males **(70%)** than in females. Among 30 patient cases enrolled primary treatment was given for **25(83.4%)** patients where **05(16.6%)** patients are not given with any first aid treatment. Patients with sudden onset of chest pain and shortness of breath are given with anti-coagulation medications along with pantoprazole in order to avoid gastric troubles. Whereas patients with chief complaints of abdominal distension/edema feet, right- thigh pain, dyspnea are given anti- coagulants along with antibiotics. The primary treatment was given in combination with other drugs. Most of the cases are treated with pantoprazole, antibiotics (clexane, magnex forte, monocef), anti-coagulants (enoxaparin, fragmin, warfarin, rivaroxaban).

The study findings identified that patient cases without ADRS are found to be more when compared with rest of the patient cases. Among 30 patient cases, **12(40%)** are found to have adverse drug reaction in which **8(26.7%)** cases are given with warfarin, **4(13.3%)** cases are given with rivaroxaban and **18(60%)** were found to have no adverse reactions in which **4(13.3%)** cases are given with warfarin, **14(46.7%)** cases are given with rivaroxaban. Adverse effects such as increased shortness of breath, snoring, fatigue, chest pain, anemia, obesity, menstrual bleeding, joint pains and epigastric pain are seen in the study.

The duration of hospital stay of venous thromboembolism cases shows that majority of cases **(70%)** stayed in the hospital for duration of 1-5 days followed by **(16.6%)** stayed in hospital for duration of 5-10 days, **(6.7%)** for 10-15 days and more than 20 days but patients who stayed in hospital for duration between 15-20 were not found in the study. The average duration of hospital stay was found to be 5 days.
Warfarin therapy is found to have more risk of bleeding compared with newer anti-coagulants that is rivaroxaban in our clinical study. Among 30 cases, **2(6.7%)** with warfarin drug given and **1(3.35%)** with rivaroxaban drug given in therapy are the cases that are only found to have risk factor i.e., bleeding risk when compared with other **27(90%)** patient cases given with drug therapy. This risk is seen more in patients only because of the treatment of warfarin when compared with rivaroxaban.

It is interesting that majority of patient cases were given with first aid treatment in our study. Primary treatment is given based upon the patient condition. Among 30 patient cases, **25(83.3%)** patients were provided first aid care or primary treatment and **05(16.6%)** were not provided with first aid care.

Out of total study subjects i.e., 30 patient cases, **2(8%)** are given only antibiotics, **2(8%)** are given only with anticoagulants, **2(8%)** are given with combination of Antibiotics+ Anti-hypertensives+ PPI, **1(4%)** are given with Antibiotic+ Anticoagulant+ Analgesics+ PPI, **1(4%)** patient cases are given with Antibiotics+ Anti-tussives+ PPI+ Analgesics+ Vitamins and minerals, **1(4%)** are given with Antibiotic + Anticoagulant+ PPI+ Anti-hypertensives+Bronchodilators,**1(4%)** are given with Antibiotics +PPI + Vitamins and minerals, **1(4%)** are given with Antibiotics+ LMWH+ Bronchodilator+ PPI, **1(4%)** are given with Antibiotics+ Antidepressants+ PPI+ Anti-tussives, **1(4%)** are given with Anticoagulants+ Antiplatelet+ PPI +Benzodiazepines, **1(4%)** are given with Anticoagulants+ Anti-Hypertensives, **2(8%)** are given with Anti-neoplastics+ Anti-inflammatory+ Anticoagulant, **1(4%)** are given with Anticoagulants+ LMWH+ Vitamins and minerals, **1(4%)** are given with Antiplatelets+ PPI+ LMWH, **1(4%)** are given with Anticoagulants+ PPI+ LMWH, **1(4%)** are given with Anti-platelets+ Anti-hypertensives, **2(8%)** are given with LMWH+ PPI, **1(4%)** are given with LMWH+ Antihypertensives, **1(4%)** are given with PPI, **1(4%)** are given with Thrombolytics agents.

Although NOACs are associated with shorter LOS, lower costs, and better patient outcomes vs VKAs, it appears in one study that only a small percentage of patients with stable VTE who are discharged to home may be receiving NOACs. As a part of objective, we took a closer look on compliance (also adherence, capacitance) that describes the degree to which a patient correctly follows medical advice. When drug compliance is studied, among 30 patient cases, warfarin is given as a discharge medication in **7(23.3%)**

cases, rivaroxaban is given as a discharge medication in **14(46.7%)** cases. Discharge medication without warfarin and rivaroxaban are given in **9(30%)** cases.

When severity of venous thromboembolism were studied, out of 30 venous thromboembolism cases, **13(43.4%)** were mild, **16(53.3%)** were moderate and **01(3.3%)** were severe patient cases.

Among 30 patient cases, **21(70%)** patients were in the hospital 1-5days, **05(16.6%)** patients were found to be in hospital in between 5-10 days, **02(6.7%)** patients were found to be in hospital between 10-15 days, **00(0%)** patients were found to be in hospital between 15-20 days, **02(6.7%)** patients were found to be in hospital >20 days. The average duration of hospital stay was found to be 6 days.

When therapy given is analysed, among 30 patient cases, the number of cases given with warfarin are **14(46.7%)** in which most of the treatment is done with warfarin drug in male patients **12(32%)** cases when compared it with female patients **2(14.2%)** cases, the number of cases given with newer anticoagulant that is rivaroxaban are **16(53.3%)** cases in which the treatment donewithrivaroxaban drug in male patients was found to be **9(30%)** cases when compared it with female patients **7(23.3%)** cases.

With respect to patient outcomes, therapeutic effect refers to the response(s) after a treatment of any kind, the results of which are judged to be useful or favorable. This is true whether the result was expected, unexpected, or even an unintended consequence. When outcome of VTE cases were analysed, out of 30 venous thromboembolism cases, **17(56.6%)** were discharged with medications and without any review in which **8(26.7%)** were discharged without any drug either warfarin or rivaroxaban, **7(23.3%)** were discharged with rivaroxaban, **2(6.6%)** were discharged with warfarin, **8(26.7%)** were advised to review in a week to 15 days in which **5(16.7%)** are prescribed with warfarin and **3(10%)** are prescribed with rivaroxaban, **5(16.7%)** were advised to get review between 3-6 months in which **2(6.7%)** are prescribed with warfarin and **3(10%)** are prescribed with rivaroxaban, **30(100%)** of total cases are found to be improvedwith **0(0%)** were dead.

Conclusion

A total of 30 peripheral venous thromboembolism cases were analysed during the study period. The study reveals that majority of patient cases were in the age group of 40-60 years. This shows that younger generation is the minor victim of VTE. In this study, it is found that majority of cases are male when compared with females cases in gender distribution and turns out to be common in male.

The study explains that the primary treatment given in these patients plays a major role since, 25 patient cases are given with primary treatment. The primary objectives for the treatment of deep venous thrombosis (DVT) are to prevent pulmonary embolism (PE), reduce morbidity, and prevent or minimize the risk of developing the post-thrombotic syndrome (PTS). Warfarin and rivaroxaban are also prescribed because of its effective and safety as standard therapy for the treatment of acute, symptomatic DVT inboth the primary treatment and secondary prevention of VTE.

Predominance is seen in patients without ADRS when compared with other patients who have complaints of ADRS. The patients given with warfarin in drug therapy were mostly found to be complained with ADRS in which the main risk factor found to be is bleeding. Whereas in patients given with rivaroxaban in the treatment have less complaints when compared to warfarin.

This study identifies that patients admitted to the hospital for treatment of VTE had a significantly shorter mean LOS by 5 days, with fewer days from the first treatment dose to discharge, when initiating oral anticoagulation with warfarin compared with rivaroxaban. In case of severity, study states that mean LOS is about a month or may exceed it. This study's results are combined data from both primary DVT and primary PE patient hospitalizations.

Warfarin is an anticoagulant drug and oldest drug that is used till now but when compared with rivaroxaban which is an newer anticoagulant drug doesn't require any therapeutic monitoring and has lower ADRS than warfarin. Rivaroxaban was associated with the highest incidence of bleeding and in this study only 1 patient case was found to have bleeding risk when given with rivaroxaban.

Drug compliance of our study plays a crucial role in discharge medication and is useful for the patients in taking drugs even after discharge. The study analysis found that rivaroxaban is more convenient than warfarin. About 46.7% of patients cases are prescribed with rivaroxaban in discharge medication.

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