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Evaluation of Median Time for Complete Discontinuation of Uf Heparin and Lmwh in Venous Thromboembolism Patients at Tertiary Care Hospitals

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Abstract

Venous Thromboembolism (VTE) presents a significant clinical challenge in tertiary care, requiring prompt and effective anticoagulation therapy. Unfractionated Heparin (UFH) and Low Molecular Weight Heparin (LMWH) are common therapeutic options, but their relative efficacy in this context remains debated. We conducted a retrospective study of patients diagnosed with VTE in our tertiary care facility over a six- month period. Patients were stratified into two groups based on their initial anticoagulation therapy: UFH or LMWH. The main outcome assessed was median time taken for complete stoppage of both the anticoagulants. Among the included patients (n=96), 53 were females and 43 were males. Out of which 36.46% received UFH and 63.54% received LMWH as initial therapy.

The median time taken for complete stoppage of overall treatment with UF heparin was 26 weeks (6.5 months) and LMWH was 22 weeks (5.5 months). The study reinforces the finding that UFH treatment might require a longer duration (almost a month) compared to LMWH for complete stoppage. Thus, considering certain factors like cost, treatment duration and de-escalation protocols, UFH emerges to be a more advisable option in clinical practice especially in low- resource setting where cost is the main concern

Keywords: Venous Thromboembolism, Unfractionated Heparin, low molecular weight heparin.

INTRODUCTION

Venous Thromboembolism (VTE) is a condition that occurs when a blood clot forms in the vein.

VTE include Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) and Cerebral Venous Sinus Thrombosis (CVST). A blood clot in the deep vein, generally in the lower leg, thigh, or pelvis, causes DVT. Additionally, DVTs can develop in the arms, particularly if the vein has a sizable intravenous central line. When a clot breaks free and enters the bloodstream and goes to the lungs, it can cause a pulmonary embolism. Pain, redness, and swelling are the few of the signs of DVT. Breathlessness and acute chest discomfort are symptoms of a pulmonary embolism. Blood clot in the veins is medically known as venous thromboembolism (VTE), a dangerous and often misdiagnosed disorder that can be prevented and results

in disability or even death.[1]

There are three types of VTE:

1. DEEP VEIN THROMBOSIS (DVT)-

DVT is a condition in which a blood clot develop in a deep vein, typically in the lower leg or pelvis. Sometimes it affects veins of the arm. Usually, DVT starts in the leg's calf region. Most distal DVT originate below the popliteal trifurcation and are most likely to resolve on their own without causing any symptoms. DVT develops in 60–70% of patients with symptomatic VTE. When distal DVT spreads to the femoral, popliteal, and other proximal veins, the majority of patients begin to exhibit symptoms. Complications from DVT might include postphlebitic syndrome, PE, and even death. Patients with untreated symptomatic proximal DVT have a 50% likelihood of developing symptomatic PE in three months. Post thrombotic syndrome is a significant DVT consequence that affects 20–50% of patients and can cause lifetime limb discomfort, swelling, heaviness, edema, and leg pain. Common symptoms of DVT include pain in lower limbs, swelling, redness, tenderness and difficulty in walking.

2. PULMONARY EMBOLISM (PE)-

PE is a condition in which a blood clot that escapes from the wall of a vein, travels to the lungs, and obstructs and prevents blood flow to a lung artery. Blood clots that start in the thigh have a higher chance of breaking off and moving to the lungs than blood clots that start in the lower leg or other body areas. The blood clot usually begins in a deep vein in the leg and proceeds to the lung. In rare instances, the clot develops in a vein in a different body area. Pulmonary embolism symptoms can vary greatly, depending on how much of your lung is involved, the size of the clots, and whether you have underlying lung or heart disease. Common symptoms of PE include shortness of breath, chest pain, cough and tachycardia.

3. CEREBRAL VENOUS SINUS THROMBOSIS (CVST)-

CVST or CVT is a condition in which a blood clot forms in the venous sinuses of the brain. This reduces blood supply to the brain. Sometimes a hemorrhage may occur as a result of blood cells breaking and leaking blood into the brain's tissues. Depending on where the thrombus is located, different cerebral venous sinus thrombosis symptoms may occur. Recovering from these symptoms is more likely if prompt action is taken. Common symptoms of CVST include headache, seizure, blurred vision, fainting and loss of control.[2]

EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) occurs as often as stroke and recurs often, with around 30% of individuals with VTE experiencing recurrence within ten years. The occurrence of VTE, particularly pulmonary embolism (PE), is related with decreased survival, and PE is an independent predictor of lower survival for up to three months.

VTE is a rather prevalent condition, especially in the elderly, and it is associated with lower survival rates, significant health-care expenses, and a high likelihood of recurrence. VTE is a complicated (multifactorial) condition characterized by interactions between acquired or inherited thrombotic predispositions and numerous risk factors. Individuals with European ancestry is expected to have an average yearly incidence rate of between 104 and 183 cases per 100,000 person-years; this incidence is comparable to that of stroke. The overall incidence of VTE may vary among African-Americans by US area and be higher in African-Americans and lower in Asians, Asian-, and Native-Americans. PE + DVT and leg DVT alone have reported incidence rates ranging from 29 to 78 and 45 to 117 per 100,000 person-years, respectively. VTE is infrequent before late adolescence and is primarily a condition of older adults. Age-related increases in

incidence are seen in both DVT and PE cases for both men and women. Men had a greater overall age-adjusted prevalence.[3]

ETIOLOGY OF VENOUS THROMBOEMBOLISM

The two primary etiologies of VTE are acquired and hereditary, however there aren't enough studies to determine the occurrence of either category. Factor V Leiden and the G20210A mutation in the prothrombin gene are frequent in white healthy people and highly rare in Asian and African populations, respectively. The incidence of the so-called hereditary thrombophilia differs within the investigated groups. Patients with DVT have a higher incidence and a higher likelihood of coinheritance with other thrombophilia. The risk of DVT increases significantly when hyperhomocysteinemia, which can also be brought on by a hereditary illness that affects the homocysteine metabolism, folic acid insufficiency, vitamin B6 or B12 deficiency, renal failure, hypothyroidism, etc., is added to one of these conditions. When Factor V Leiden was the sole factor present, the prevalence of DVT in families with protein C, protein S, or antithrombin deficits was 13-25%. About 5% of people have heterozygous factor V Leiden, which is more common in those with North European ancestry and in some Middle Easterners; homozygous form is less than 1% of the population. It is extremely uncommon in Asian, African, Native American, and Hispanic populations. Although heterozygous individuals with factor V Leiden have a five- to seven-fold greater risk for developing DVT initially, they frequently have other risk factors that also play a role in the development of DVT. There can be a 25–50-fold increase in the risk of DVT with homozygous factor V Leiden. Studies that address the many anatomical locations of DVT, such as the hip area, upper extremities, mesenteric, calf, cerebral, etc., are not widely published enough.

Although cerebral venous thrombosis (CVT) seems to be uncommon, more people are becoming aware of it because to improved diagnostic techniques like nuclear magnetic resonance. Less than 10% of patients die, and 80% of them fully recover. A combination of prothrombotic risk factors (factor V Leiden, protein C or S deficiency, and elevated lipoprotein (a)) and/or underlying clinical condition (vascular trauma, infections, immobilization, malignancies, autoimmune diseases, etc.) can cause CVT in children, which is a multifactorial disease. 80% of symptomatic occurrences of isolated calf DVT involve proximal veins, and clinically significant PE is infrequently caused by this condition. Most cases of DVT begin in the veins of the calf and go away on their own. The degree and location of the thrombosis are related to the existence of symptoms. At the time of presentation, the majority of symptomatic patients had occlusive proximal thrombosis. Travel as a risk factor for DVT. The thrombophilic condition known as primary anti-phospholipid syndrome (APS) is typified by recurrent arterial thrombosis, cerebral ischemia, transient ischemic crises, lower limb DVT with or without PE, repeated miscarriages, and fetal mortality. An estimated 35,000 additional instances of DVT in younger people than those usually affected by thrombosis are reported to occur each year in the USA. Fifteen to fifty-five percent of these patients have ophthalmologic characteristics. In general, approximately 30% of people with APS have thrombosis. Obstetric problems occur in 15–20% of cases. The odds ratios for current miscarriages and fetal death and anticardiolipin antibodies range from 0.86 to 20 in the case of lupus anticoagulants and fetal death, respectively. After eight years of follow-up, there is a cumulative incidence of 17–29% for post-thrombotic syndrome, which is characterized by leg pain, heaviness, and swelling that worsens when walking or standing. With a cumulative incidence of 25% after five years, the severe form is marked by skin and subcutaneous alterations ranging from varicose eczema to ulceration. [4]

PATHOPHYSIOLOGY OF VENOUS THROMBOEMBOLISM

A thrombus is a solid mass that forms inside a blood vessel and is made up of platelets, fibrin, and a few red and white blood cells that have become trapped. The deep veins in the arms, legs, or pelvis might thrombus because to hypercoagulability or blockage.

Proximal extension happens as the clot spreads, and this could cause it to dislodge or break apart and embolize the pulmonary arteries. This results in pulmonary artery blockage, and platelets' production of vasoactive substances, such as serotonin, raises pulmonary vascular resistance. Because the artery is blocked, there is an increase in alveolar dead space and blood flow redistribution, which compromises gas exchange by creating low ventilation-perfusion zones in the lung. Alveolar hyperventilation is a result of irritant receptor stimulation. Airway augmenting reflex bronchoconstriction takes place.

Venous stasis, or abnormal blood flow, usually results from extended bed rest or immobilization. Venous blockage can result from intravascular compression from prior thromboses, exterior compression from enlarged lymph nodes, or bulky tumors. An increased risk of venous thromboembolism in the tiny initial risk has been linked to pharmacologically boosted estrogens, as shown in postmenopausal women on hormone replacement treatment and using oral contraceptives. Increased venous thromboembolism is also linked to cancer, especially adenocarcinomas and metastatic malignancies. In fact, upon follow-up, certain idiopathic venous thromboembolisms have shown concealed malignancies at the time of presentation. The clotting system can also be activated by malignancy and pharmaceutical estrogens.[5,6]

COMPLICATION OF VENOUS THROMBOEMBOLISM

When a portion of the clot breaks off and enters the bloodstream and the lungs, it can cause a blockage known as a pulmonary embolism (PE), which is the most catastrophic consequence of DVT. People with PE can recover with the right care if the clot is tiny. Nonetheless, there can be some lung injury. Large clots can be lethal because they obstruct blood flow to the lungs. Furthermore, a long-term consequence known as post-thrombotic syndrome (PTS) affects one-third to half of DVT patients due to the harm the clot causes to the vein's valves. PTS patients experience symptoms include discomfort, swelling, discoloration, and, in extreme situations, ulcers or scaling in the afflicted area of the body.[7]

DIAGNOSIS OF VENOUS THROMBOEMBOLISM

The diagnosis of venous thromboembolism can be confirmed by doing certain blood test, imaging studies and other lab test. Some test could also be organ specific-

Certain blood test include:

1. D Dimer test - used to detect a substance released when a clot breaks up. Normal values <500 mg/dl.
2. Platelet count-counts the number of platelets in the blood, as they are the cells that help the blood to clot, they are an important diagnostic tool. Normal values 1.5lac-4lac/cells.
3. Activated partial thromboplastic time[aPTT]-measures how long it takes for the blood to form a clot. Normal values-21-35 seconds.
4. International normalized ratio [INR]-measures as to how quickly the blood clots also called as the prothrombin time. Normal values-<1.1.
5. Factor VIII blood test- used to detect a protein essential to blood clotting.

Some of the imaging test include:

1. Duplex ultrasound- A non-invasive imaging test able to detect blockages in deep veins using sound waves.

2. Contrast venography-An X-ray procedure that involves the injection of contrast dye into a vein.
3. Magnetic resonance imaging [MRI]- An imaging study that uses powerful magnetic fields and radio waves to create highly detailed images of soft tissues.
4. Pulmonary angiography- A specialized X-ray that delivers a contrast dye to the vessel of the lungs.
5. Computed tomographic pulmonary angiography- An imaging test that involves the injection of a contrast dye to locate a blockage in the lungs.
6. Ventilation-perfusion[V/Q] scan: A specialized procedure that uses a radioactive substance to highlight parts of the lungs that are and are not getting oxygen.[8]

TREATMENT OF VENOUS THROMBOEMBOLISM

There are mainly 2 types of treatment for Venous Thromboembolism, these include pharmacological treatment and non- pharmacological treatment.

1. NON-PHARMACOLOGICAL TREATMENT:

Interventions include graduated compression, stockings, intermittent pneumatic compression devices, inferior vena cava filters and dietary modifications have advantage for the treatment of venous thromboembolism with no risk of further bleeding.

- Graduated Compression Stockings:
  These are the devices that apply greater pressure at the ankle thus reducing pooling of blood in the deep veins which can also enhance the velocity of blood flow to the heart. These are also known to help reduce pain and swelling specially in DVT cases, studies have also shown that use of graduated compression stockings with pressure of 30-40mmHg at the ankle for 2 years continuously can also reduce post thrombotic syndrome.
- Intermitted Pneumatic Compression Devices
  This device functions by cyclic inflation and deflation that promote venous return, they have shown excellent efficacy in several venographic studies, these devices are of different types and include single chamber, multiple chambers, calf length, thigh length, that are intermittently inflated with air to a 35-55mmHg in a uniform fashion for 10-35 seconds.
  This is then followed by 1min deflation period to allow the leg to refill with blood. They are also known to have advantageous uses even prior to surgery.
- Inferior Vena Cava Filters
  They are inserted through the infrarenal jugular, femoral or antecubital veins to reduce pulmonary vascular obstruction in patients with DVT. However, they must be combined with pharmacological intervention to reduce risk of further development of thrombosis.[9]

DIETARY AND LIFESTYLE MODIFICATIONS:

- Low fat and high fiber diet is recommended.
- Daily exercise is also to be strictly followed.
- Increase intake of fruits and vegetables and reduce meat.
- Drink plenty of water.
- Weight control should also be focused to avoid obesity. [10]

SURGICAL TREATMENT

- Thrombectomy/Embolectomy:

In certain cases, a surgical procedure is carried out to remove the clot. Thus, thrombectomy involves removal of clot in patients with DVT. Embolectomy involves removal of the blockage in the lungs caused by the clot in a patient with PE. [11]

PHARMACOLOGICAL TREATMENT:

1. UNFRACTIONATED HEPARIN [UFH]

Unfractionated heparin (UFH) is a naturally occurring anticoagulant medication that is commonly used to prevent and treat blood clots. It is derived from the mucosal lining of animal intestines, typically porcine (pig) or bovine (cow). It is a heterogenous mixture of glycosaminoglycans with molecular weight ranging from 3,000 to 30,000 daltons. A typical initial bolus dose of UFH ranges from 5,000 to 10,000 units, administered intravenously. This bolus dose is often followed by a continuous infusion of UFH, typically started at a rate of 18 units/kg/hour.

- The activated partial prothrombin time is generally recommended for monitoring UFH, measurements should be done prior to initiation of therapy and also 6 hours after start of therapy, thus needed adjustments must be carried out based on patient response and APTT values.
- Monitor closely also for bleeding signs, if bleeding continues stop UFH find out the bleeding source and provide protamine sulfate by slow IV infusion over 10 minutes.
- Possible ADR is heparin induced thrombocytopenia [HIT] which is an immunologic reaction requiring quick intervention as it also may be fatal.
- **Mechanism of action:**

They bind to antithrombin, provoking a confirmation change that makes it much more potent in inhibiting the activity of factors IXa, Xa, XIIa, and IIa. This prevents thrombus growth allowing endogenous thrombolytic systems to lyse the clot.

2. LOW MOLECULAR WEIGHT HEPARIN [LMWH]

LMWH are a class of anticoagulant medications derived from unfractionated heparin through chemical or enzymatic depolymerization, resulting in smaller, more uniform molecules with molecular weights ranging from 1,000 to 10,000 daltons. It has predictable anticoagulant response and longer half-life than UF heparin. Lower risk of heparin induced thrombocytopenia (HIT). It is more convenient for outpatient treatment due to less frequent dosing and no need for routine monitoring. The drugs include-

- Enoxaparin-for acute DVT treatment with or without PE, 1mg/kg SC every 12 hours.
- Dalteparin-for acute DVT treatment, 200units/kg SC every 24 hours.
- **Mechanism of action:**

They prevent thrombus propagation by accelerating the activity of anti thrombin similar to UFH.

3. NOVAL ORAL ANTICOAGULANTS [NOACs]

It includes direct thrombin inhibitors (Dabigatran) and factor Xa inhibitors (Rivaroxaban, Apixaban, Edoxaban). It is given as fixed dose with no routine monitoring required. It is increasingly preferred for both initial and long-term treatment due to ease of use. Drugs include:

- Dabigatran-150mg PO twice daily [with or without food]
- Rivaroxaban-15mg PO twice daily [with food]
- Apixaban-10mg PO twice daily [with or without food]
- Edoxaban-60mg PO once daily [with or without food]

Rivaroxaban, Apixaban, Edoxaban are oral selective inhibitors of both free and clot bound factor Xa and dabigatran is an oral selective, reversible direct factor IIa inhibitor.

- **Mechanism of action:**

They intervene directly in the coagulation cascade and inhibit directly specific clotting factors, thus prolonging formation of blood clots.

D. VITAMIN K ANTAGONISTS [VKAs]

Warfarin is the most common VKA. It requires regular monitoring of the INR. Dose-5-10mg

- **Mechanism of action:**

Inhibits enzyme responsible for cyclic interconversion of vitamin K in the liver. Thus, warfarin produces coagulation proteins with less activity. Warfarin also inhibits thrombus propagation and formation. Due to slow onset effect warfarin must be started with injectable anticoagulants with an overlap of at least 5days.Mointor INR values which should be near to 2.5, also measure CBC values prior to therapy and at least 3 times a week. The major adverse effect is bleeding which can be mild to life threatening thus require supportive care. Non hemorrhagic adverse effects include rare purple toe syndrome and skin necrosis.[12]

OBJECTIVE

The main aim of the study is to estimate the median time taken to completely stop the unfractionated heparin and low molecular weight heparin in patients having venous thromboembolism and those who are admitted for treatment in tertiary care hospitals. Standardized treatment can be provided only after knowing the time difference between stopping both the drugs, which may help enhance the efficacy of the treatment provided.

MATERIAL AND METHODOLOGY

This retrospective cohort study aims to evaluate the time difference for complete stoppage between both Unfractionated Heparin and Low Molecular Weight Heparin for the underlying disease condition in tertiary care setting hospitals in Kerala, India. The study was conducted from November 2023 to April 2024 with 96 participants, the study received approval from Institutional Review Board in Kerala India. All patients with a confirmed diagnosis of VTE were included. The excluded patients include ages below 18 years, patients discharged against medical advice and patients those who are on both drugs were excluded.

In order to assess the participant's information and detail data in accordance with established goals, all information was obtained from the medical records and patient drug charts. The data was thus analyzed from the standard criteria given in accordance with relevant guidelines.

The statistical formula used for calculating the sample size was-

$[Z^2 \text{ x } p \text{ x } (1\text{-}p)/e^2] / [1 + (Z^2 \text{ X } p \text{ x } (1\text{-}p)/e^2 \text{ N}]$

Where,

P= Standard deviation

N= Population size

e= margin of error

Z= 95% confidence of Z

Mean and SD for quantitative variables and proportions for qualitative factors were used to define the research population profile. Kaplan Meier Curves were used to determine the median time. The statistical log rank test was used to determine the likelihood of an event at a given time. All analysis was carried out in the SAS software.

RESULTS

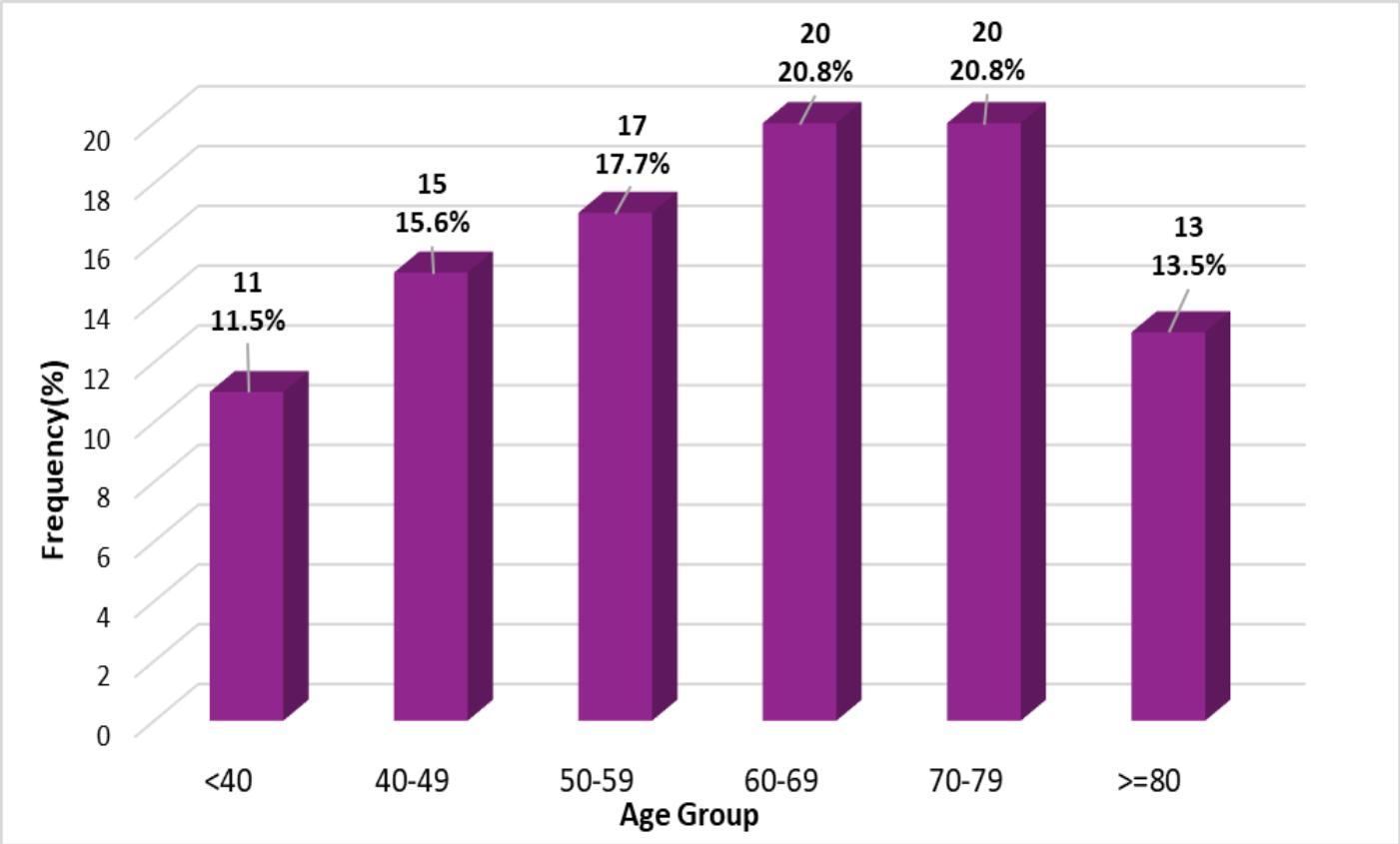

FIGURE 1: DISTRIBUTION OF AGE GROUP

It was observed from our study conducted on 96 VTE patients that VTE was most frequently found to occur in the age groups of 60-69, 70-79 (about 20 peoples accounting for 20.8%) followed by the respective age groups 50-59 (15 people accounting for 17.7%), age group of 40-49 (15 people accounting for 15.6%), age group of >80 (13 people accounting for 13.5%), age group of < 40 (11 people accounting for 11.5%).

TABLE 1: DISTRIBUTION OF TYPES OF VTE

SL NO	TYPES OF VTE	FREQUENCY	PERCENTAGE
1.	DVT	54	56.25%
2.	DVT & PE	15	15.63%
3.	PE	25	26.04%
4.	CVT	1	1.04%
5.	DVT + PE + CVT	1	1.04%

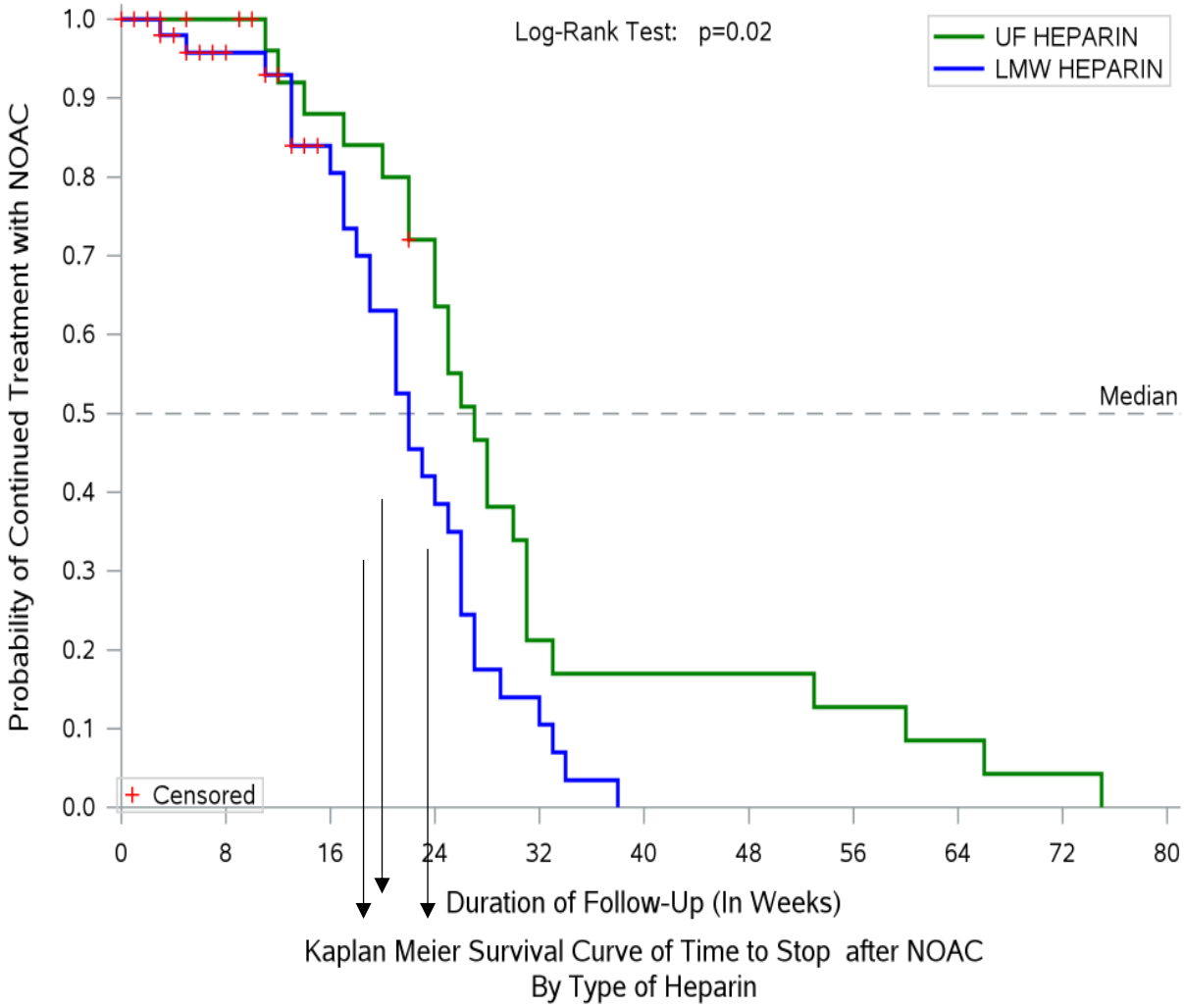

FIGURE 2: TIME TAKEN TO COMPLETE STOPPAGE BASED ON TYPE OF HEPARIN

As the graph progresses from left to right (more weeks of follow-up), the lines slope downward. This indicates that over time, more and more people discontinue taking NOAC, regardless of the type of heparin they received initially. Patients who got UF Heparin had a larger median time to quitting NOAC than patients who received LMW Heparin, indicating that those who received UF Heparin were more likely to remain on NOAC for a longer amount of time. Here, "Log-Rank Test: p=0.02". This suggest that there is a significant difference between the two groups on LMWH is likely to stop the treatment faster than those patients received UF heparin.

DISCUSSION

1. DISTRIBUTION OF AGE

Our study results showed that age groups of 60-80 years were more prone to have VTE. Therefore, these results are similar to the published study conducted by **Kotaro Takahashi (2023) on age and long-term outcomes of patients with venous thromboembolism.**[13]

2. DISTRIBUTION ON TYPE OF VTE

The study confirmed that the most common type of VTE was DVT in the clinical setting, these results were similar to the study conducted by **Clive Kearon (2001) on epidemiology of venous thromboembolism.**[14]

3. TIME TAKEN TO COMPLETE STOPPAGE BASED ON TYPE OF HEPARIN

According to our study it was found that LMWH took 22 weeks and UF Heparin took 26 weeks, for the complete stoppage of the treatment. This suggests that there is a significant difference between the two groups. Patients on LMWH is likely to stop the treatment faster than those patients received UF heparin. The results were similar to the study conducted by **Lisa R Dolovich et al., (2000) on "A Meta-analysis Comparing Low-Molecular-Weight Heparins with Unfractionated Heparin in the Treatment of Venous Thromboembolism".**[15]

CONCLUSION

Venous Thromboembolism is a condition requiring major concern as they can develop in the leg, thighs, pelvis or arms and can be a cause of serious illness, disability and death. In our study there were 96 hospitalized patients, out of which 53 patients were elderly (over 60) with various co-morbidities like diabetes (39.6%), hypertension (53.1%), and dyslipidemia (13.5%), and stroke (2.1%). Existing literatures suggests that LMWH is effective. Our study results showed that in terms of drug stoppage UF heparin took more time that LMWH as UF heparin took 26 weeks (6.5 months) and LMWH took 22 weeks (5.5 months) for complete stoppage of the overall treatment. Even though our study results establish the fact that LMWH is better, in clinical practice UF Heparin is more preferred as cost being a major factor in the treatment of VTE. The study conducted focuses on the South Indian population which include people of different financial backgrounds hence it is recommended that the decision on whether to use LMWH or UFH should depend on not only a single factor but on various patient factors. The decision of prioritizing the drug should be done on a case-by-case basis which may help in enhancing patient adherence and efficacy of the treatment.

FUTURE PERSPECTIVES

1. Patient counselling may play an important role in reducing Venous Thromboembolism and also might prevent the possibility and problems related to reoccurrence of VTE.
2. The result of our study can be put to use for further evaluation of VTE treatment with UFH or LMWH and will help in choosing the most appropriate and best cost-effective treatment with minimum side effects.
3. Study of the Pharmacokinetic parameters of both drugs may also be considered.

LIST OF ABBREVIATIONS

VTE- Venous Thromboembolism
DVT- Deep Vein Thrombosis
PE- Pulmonary Embolism
CVT- Cerebral Venous Thrombosis
UFH- Unfractionated Heparin

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