# INTRODUCTION

The complications of acute deep venous thrombosis, pulmonary embolism and post-thrombotic syndrome are one of the most common causes of hospital death. Approximately 300,000 die per year in United States from pulmonary embolism, the majority of which results from deep venous thrombosis ***(Silva, 2001)***.

Understanding underlying epidemiology, pathophysiology and natural history in deep venous thrombosis is essential in guiding appropriate prophylaxis, diagnosis and treatment. Deep venous thrombosis is usually silent in nature in most of hospitalized patients and usually presented by non-specific symptoms and signs ***(Haeger, 2000)***.

Components of triad described by Rudolf Virchow for risk factor of Deep venous thrombosis which includes abnormalities of thrombosis, abnormalities of blood flow and vascular injury remains applicable today ***(Sue et al., 2005)***.

There are many recognized risk factors for venous thrombo-embolism which include immobilization, surgery, malignancy, trauma, pregnancy history of previous attacks of venous thrombo-embolism and oral contraceptive drugs ***(Cogo et al., 2004)***.

Malignancy is considered one of the most important risk factors of the deep venous thrombosis and this is what we are going to focus in this research. Patients with cancer are at increased risk of venous thrombo-embolism. Approximately 15% of malignancies are complicated by venous thrombo-enbolims with higher prevalence in autopsy studies ***(Maxwell and Bennett, 2012)***.

Thrombogenic mechanisms associated with cancer may be heterogenous, but likely they involve substances that are directly or indirectly activate coagulation. About 90% of patients with cancer have abnormal coagulation parameters including increased coagulation factors, fibrinogen and thrombocytosis. Levels of coagulation inhibitors, antithrombin, protein C & S may be reduced in malignancy ***(Falanga et al., 2010)***.

The role of cancer treatment related factors including chemotherapy has been a focus of recent investigations because most cases of venous thrombo-embolism in the oncology settings occur in ambulatory patients ***(Kirwan et al., 2003)***.

Deep venous thrombosis may have a lot of complications which gives impact on short-term life especially in patients with cancer like pulmonary embolism and postthrombotic syndrome. Thus, we have aiming to prevention, early diagnosis and treatment of deep venous thrombosis ***(Amit, 2007)***.

Clinical trials have shown that thromboprophylaxis reduces the incidence of symptomatic venous thrombosis in cancer patients. An increase in major bleeding events was suggested but not confirmed in most recent trials. However, as the incidence of venous thrombosis is relatively not low in general cancer population, thromboprophylaxis should not be recommended for all cancer outpatients. Instead, to optimize the risk/benefit ratio ***(Crobash et al., 2014).***

# Aim of the Work

The aim of this study is to focus on the efficacy of preventive measures in reduction of deep venous thrombosis in malignancy as well as its lethal complications.

*Chapter One*

# EPIDEMIOLOGY AND RISK FACTORS OF DEEP VENOUS THROMBOSIS

## Epidemiology:

Venous thrombosis, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs with an incidence of approximately 1 per 1000 annually in adult populations ***(White, 2003).*** Rates are slightly higher in men than women. About two-thirds of episodes manifests as DVT and one-third as PE with or without DVT. The major outcomes of venous thrombosis are death, recurrence, post-thrombotic syndrome and major bleeding due to anticoagulation. Thrombosis is also associated with impaired quality of life, particularly when post-thrombotic syndrome develops ***(Kahn et al., 2005).***

Death occurs within one month of an episode in about 6% of those with DVT and 10% of those with PE. The mortality rate for PE has been estimated to be as high as 30% in studies that included autopsy-based PE diagnosis, pointing out the fact that many PE are not recognized clinically before death. Mortality rates are lower among patients with idiopathic venous thrombosis and highest among those whose thrombosis occurs in the setting of cancer ***(Cushman et al., 2004).***

There are also differences in incidence of diagnosed venous thrombosis among ethnic groups with rates lower, in the United States, in Asians, Pacific Islanders and Hispanics than in whites, and with some studies reporting an approximate 25% higher rate in African-Americans ***(Stein et al., 2004).***

There is little information on epidemiology of thrombosis in Africa. Two recent reports suggested that rates of hospital triggered DVT or postoperative DVT were similar in Asian and in Western countries. Although the population rate of DVT in China has been estimated at only 0.17 per 1000 annually ***(Leung et al., 2006).***

Comparing the incidences of VT in the young and older population shows clearly that aging is one of the strongest and most prevalent risk factor for venous thrombotic disease, resulting in a high incidence of VT in the elderly population ***(Naess et al., 2007).***

This study focuses on correlation between deep venous thrombosis and malignancy. Cancer patients are characterized by an acquired thrombophilic condition predisposing to increased risk of VTE ***(Walker et al., 2013).***

Next table shows rates of deep venous thrombosis and pulmonary embolism in different malignancies.

**Table (1):** Rates of DVT/PE in different malignancies

| Site | Rate of DVT/PE per 10000 patients |
|---|---|
| Head/neck | 16 |
| Bladder | 22 |
| Breast | 22 |
| Oesophagus | 43 |
| Uterus | 44 |
| Cervix | 49 |
| Prostate | 55 |
| Lung | 61 |
| Rectal | 62 |
| Liver | 69 |
| Colon | 76 |
| Leukaemia | 81 |
| Renal | 84 |
| Stomach | 85 |
| Lymphoma | 96 |
| Pancreas | 110 |
| Brain | 117 |
| Ovary | 120 |

An analysis of > 1.2 million US medicine (age≥ 65) patients admitted to the hospital with a malignancy ***(Levitan et al., 1999).***

It is well established that cancer patients are at an increased risk of VTE; the risk of VTE is four-fold to seven-fold higher in patients than in those without cancer ***(Stein et al., 2006).***

The incidence of VTE in hospitalized patients with cancer increased sharply between 1979 and 1999 (Figure 1) This increase has been substantially sharper than the rise in incidence observed among hospitalized patients who do not have cancer ***(Stein et al., 2006).***

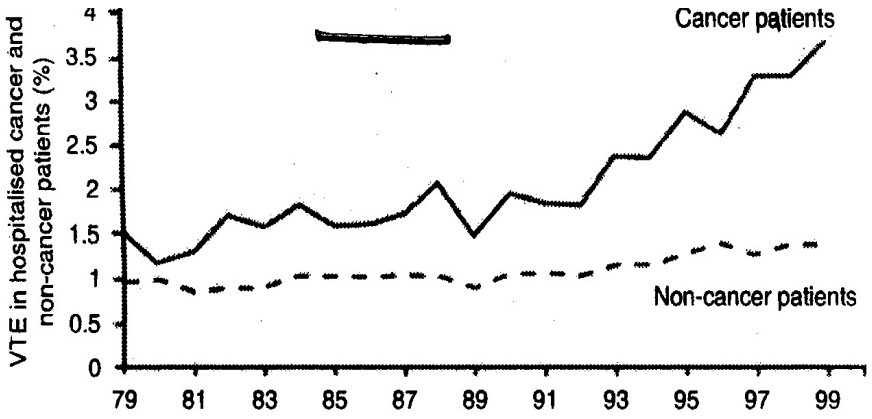


**Figure (1):** Increased VTE prevalence over time in patients with cancer, but not in those without cancer ***(Stein et al., 2006).***

The reported incidence varies widely between studies depending on patient population, start and duration of follow-up, and the method of detecting and reporting thrombotic events ***(Timp et al., 2013).***

The recent meta-analysis by Horsted et al described incidence rates of venous thrombosis in cancer patients, stratified by background risk of venous thrombosis; the incidence among cohorts with average-risk patients was estimated to be 13 per 1000 person-years. Among cohorts with high-risk patients, the overall incidence rate was 68 per 1000 person-years ***(Horsted et al., 2012).***

It is estimated that about 4–20% of patients with cancer experience venous thrombosis, with the annual incidence of 0.5% in them compared to 0.1% in the general population. Overall, cancer patients constitute 15–20% of the patients diagnosed with VTE ***(Lee, 2005).***

VTE and thrombotic complications are the second most frequent cause of mortality in patients with cancer. Several studies have showed that the incidence of VTE is associated with the duration of the underlying illness. The highest rate of VTE is seen in the initial period after diagnosis and mortality from VTE is highest in one year after diagnosis ***(Wun and White, 2009).***

A high incidence of VTE following chemotherapy was reported in cancers. Chemotherapy increased the risk of VTE and recurrent VTE six-fold and two-fold, respectively, in patients with cancer, and it is estimated that the annual incidence of VTE in cancer patients undergoing chemotherapy is about 10.9% ***(Haddad and Greeno, 2006).***

## Risk Factor of Acute Deep Venous Thrombosis:

Deep venous thrombosis (DVT) remains a common and serious medical condition, frequently complicating the postoperative recovery of surgical patients or manifesting de novo in patients with recognized (or unrecognized) risk factors. More than 1 million cases of DVT are diagnosed in the United States annually, resulting in approximately 50,000 to 200,000 deaths due to pulmonary emboli ***(Rutherford, 2010).***

### *Age:*

Comparing the incidences of VT in the young and older population shows clearly that aging is one of the strongest and most prevalent risk factor for venous thrombotic disease, resulting in a high incidence of VT in the elderly population ***(Naess et al., 2007).***

### *Immobility:*

Immobility increases the risk of thrombosis, presumably due to stasis of blood flow in the venous system. Relevant settings of immobility include bed rest, plaster casts on the legs and paresis of the legs due to neurological conditions. Research-based definitions of immobility due to bed rest differ, but a duration of 4 days seems reasonable. Minor forms of immobility, such as after minor surgery or injury, have also been linked to thrombosis risk ***(Eekhoff et al., 2000).***

### *Travel:*

Any type of travel has the potential to increase the risk of venous thromboembolism; duration of travel is a key factor. Travel by air, car, train or bus for 4 or more hours all increase the risk by about 2-fold for several weeks after travel .As before, the risk is higher when other thrombosis risk factors are present ***(Cannegieter et al., 2006).***

## *History of DVT:*

Venous thrombosis is often a chronic condition, with recurrence rates estimated at 5–7% annually after a first episode. The risk is highest among those whose initial episode was associated with cancer, and lowest among those whose initial episode was associated with a temporary risk factor such as surgery. In one study, older age and obesity were associated with higher recurrence risks ***(Cushman et al., 2004).***

Recent reports suggest an approximate 60% higher recurrence risk among men compared to women ***(McRae et al., 2006).***

One study suggested that this increase in risk could be explained by a lower recurrence risk among women who were using exogenous hormones at the time of their first event .The risk appears to be highest in the 6–12 months following cessation of anticoagulation, regardless of the initial duration of anticoagulation ***(Cushman et al., 2006).***

## *Obesity and height:*

Investigations that reported an increased risk for VTE caused by obesity have been criticized because they failed to control for hospital confinement or other risk factors. High proportions of patients with VTE have been found to be obese but the importance of the association is diminished because of the high proportion of obesity in the general population ***(Heit et al., 2001).***

Various abnormalities of hemostasis have been described in obesity, in particular increased plasminogen activator inhibitor-1 (PAI-1). Other abnormalities of coagulation have been reported as well, including increased platelet activation, increased levels of plasma fibrinogen, factor VII, factor VIII, and von Willebrand factor. Fibrinogen, factor VIIc, and PAI-1 correlated with BMI ***(De Pergola and Pannacciulli, 2002).***

Regarding height, in the study of Swedish men, those taller than 179 cm had a 1.5 times higher risk of VTE than men shorter than 172 cm. The Physicians' Health Study of male physicians also showed that taller men had a significantly increased risk of VTE ***(Glynn and Rosner, 2005).***

## *Congenital hypercoagulable disorders*

### 1. Antithrombin deficiency

Antithrombin is a serine protease inhibitor of thrombin and also inhibits factors IXa, Xa, XIa, and XIIa. Thrombin is irreversibly bound by antithrombin and prevents thrombin's action on fibrinogen, on factors V, VIII, and XIII, and on platelets.This anticoagulant is synthesized in the liver and endothelial cells, and has a half-life of 2.8 days ***(Johnson et al., 2005).***

Antithrombin deficiency is associated with lower extremity venous thrombosis as well as mesenteric venous thrombosis. The most common presentation in those with antithrombin deficiency is deep venous thrombosis with or without pulmonary embolism ***(Johnson et al., 2005).***

## 2. Protein C and protein S deficiency

Protein C is a vitamin K dependent anticoagulant protein that once activated by thrombin, will inactivate factors Va and VIIIa, thereby inhibiting the generation of thrombin. Additionally, activated protein C stimulates the release of t-PA. It is produced in the liver ***(Bick, 2003).***

Protein S is also a vitamin K dependent anticoagulant protein that is a cofactor to activated protein C. The actions of protein S are regulated by complement C4b binding protein and only the free form of protein S serves as an activated protein C cofactor ***(Nicolaes and Dahlback, 2003).***

Clinically, protein C and S deficiencies are essentially identical. With homozygous protein C and S deficiencies, infants typically will proceed to purpura fulminans, a state of unrestricted clotting and fibrinolysis. In heterozygotes, venous thrombosis may occur at an early age especially in the lower extremity. Thrombosis may also occur in mesenteric, renal, and cerebral veins ***(Nicolaes and Dahlback, 2003).***

## 3. Factor V Leiden mutation and activated protein C resistance

Factor V is a glycoprotein synthesized in the liver. With Factor V Leiden, a point mutation occurs when arginine is substituted by glutamine at position. This point mutation causes the activated Factor V to be resistant to inactivation by

activated protein C thus causing a procoagulant state. Clinically, patients may present with deep venous thrombosis in the lower extremities, or less commonly in the portal vein, cerebral vein, or superfi cial venous system ***(Nicolaes and Dahlback, 2003).***

**4. Hyperhomocysteinemia**

Homocysteine is an amino acid formed during the metabolism of methionine and may be elevated secondary to inherited defects in two enzymes that are part of the conversion of homocysteine to cysteine. Elevated homocysteine has been consistently reported as a risk factor for venous thrombosis and levels can be reduced with B vitamin supplementation ***(Cattaneo, 2006).***

## *Co morbidity*

**1. Heart failure**

Congestive heart failure (CHF) is considered a major risk factor for VTE. Among patients with established CHF, those with lower ejection fractions had a higher risk of thromboembolic event ***(Beemath et al., 2006).***

Heart failure is the second most common risk factor for VTE in hospitalized patients ***(Cohen et al., 2008).***

**2. Stroke**

Patients with stroke are at particular risk of developing DVT and PE because of limb paralysis, prolonged bed rest, and increased prothrombotic activity. Among 14,109,000 patients with ischemic stroke hospitalized in short-stay hospitals from 1979 to 2003, VTE was diagnosed in 165,000 (1.17%). Among 1,606,000 patients with hemorrhagic stroke, the incidence of VTE was higher (1.93%) ***(Skaf et al., 2006).***

**3. COPD**

COPD is a risk factor for PE and DVT. In individuals aged 60 years or more, the presence of COPD was associated with a 1.2 to 1.4 increased risk of PE. In a younger population (aged 40–59 years) the relative risk was found to be higher, i.e. 2–5 ***(Stein et al., 2007).***

**4. Diabetes mellitus**

In a meta-analysis it was shown that individuals with diabetes mellitus have an almost 50% increased risk of VT compared with individuals without diabetes ***(Ageno et al., 2008).***

## *Surgery*

Surgery constitutes a spectrum of risk that is influenced by patient age thrombotic risk factors, type of procedure, extent of surgical trauma, length of procedure and duration of postoperative immobilization. All components of Virchow's