OVERVIEW OF VENOUS THROMBOEMBOLISM

Venous Thromboembolism consists of deep vein thrombosis (DVT) and pulmonary embolism (PE). The true incidence of VTE is hard to estimate because of the often silent nature of the condition. In the western world, the incidence is one case of DVT and 0.5 cases of PE per 1000 population/year. Hospitalized patients are especially at risk for VTE as most have multiple risk factors. Autopsy studies have shown that the incidence of VTE in hospitalized patients to be as high as 34.7% with fatal pulmonary embolism in 9.4% of cases. VTE contributes substantially to patient morbidity, mortality and cost of management. PE accounts for 5-10% of death in hospitalized patients, making VTE the most common preventable cause of in-hospital death. It has been estimated that between 5 Lakh and 2 million VTE cases including PE occur annually in the USA.

DVT and PE are distinct but related aspects of VTE. Approximately one third of patients with symptomatic VTE manifest PE, whereas two thirds manifest DVT alone. VTE is often silent and difficult to diagnose because approximately 80% of all DVTs are asymptomatic and even symptoms do occur they may be nonspecific. Silent VTE may develop into PE which may be unrecognized. PE is often asymptomatic and even when symptoms do appear they may be difficult to recognize. Consequently less than half of all cases of fatal PE are detected prior to death.

It is perceived by many that thromboses in the deep veins proximal to the knee (proximal DVT) are associated with an increased risk for PE and thromboses of calf vein (calf DVT) are associated with post-thrombotic syndrome. Studies show that 15 – 25% of calf DVT propagate and converts into proximal DVT. Such “proximal conversion” renders a calf DVT just as dangerous as any proximal DVT and this occurs within initial 2 weeks after diagnosis.

The risk of early death among patients with symptomatic PE is 18 fold higher compared to patients with DVT alone. PE is an independent predictor of reduced survival for up to 3 months after onset. For almost 25% of PE patients the initial clinical presentation is sudden death. In untreated patients death from PE occurs most frequently within 24 – 48 hours of initial presentation. All cause mortality in treated patients with PE is 11% at 2 weeks and 17% at 3 months. VTE is a chronic disease with episodic recurrence. About 30% of patients develop recurrence within next 10 years and is highest within first 6 to 12 months of presentation.

VTE predominantly a disease of old age. The overall age adjusted incidence rate is higher for men (114 per 100,000) than women (105 per 100,000). Male to female sex ratio is 1.2 : 1.

PATHOPHYSIOLOGY AND RISK FACTORS

The factors that predispose to venous thrombosis have been originally described by Virchow in 1859. These include (i) circulatory Stasis (ii) Hypercoagulability (iii) Vascular wall injury. Venous thrombi are intravascular deposits composed of cellular material (RBC, WBC, Platelets) enmeshed with fibrin strands. Typically, these thrombi are belived to start in areas of slow or turbulent venous flow such as large venous sinuses or venous valve cusps or in areas of direct venous trauma. Hypercoagulability or activation of blood coagulation can be initiated by many factors such as tissue or vascular injury and inflammation. Vascular wall injury occurs as a result of mechanical or chemical trauma, which subsequently stimulates an inflammatory response known as “Phlebitis”. Circulatory stasis may be due to a reduced or altered blood flow through the deep veins of the lower limb which impairs clearing of clotting factors allowing them to concentrate locally, further favouring activation of blood coagulation.

Endothelial injury can expose collagen causing platelet aggregation and tissue thromboplastin release. Tissue thromboplastin forms thrombin and fibrin that traps RBCs and propagates proximally as a red or fibrin thrombus. More than 95% of pulmonary emboli originate as thrombi from deep veins of lower extremeties.

Important risk factors are shown in Table 1. Other risk factors include air travel (more than 8 hours), varicose vein, heavy smoking etc. Most hospitalized patients have one or more risk factor for VTE. These risk factors are generally cumulative. Recent family-based studies indicate that VTE is highly heritable and follows a complex mode of inheritance involving environmental interaction. Inherited reduction in plasma natural anticoagulants (e.g. antithrombin, protein C or S) are uncommon but potent risk factors for VTE. Recent discoveries of impaired down regulation of the procoagulant system (e.g. activated protein – C resistance, factor – V – Leiden), increased plasma concentrations...
**Table 1 : Risk factors for VTE**

| Surgery                                    | Trauma (major trauma or lower – extremity injury) | Immobility, lower – extremity paresis | Cancer (active or occult) | Cancer therapy (hormonal, chemotherapy, angiogenesis inhibitors, radiotherapy) | Venous compression (tumor; hematoma, arterial abnormality) | Previous VTE | Increasing age | Pregnancy and the postpartum period | Estrogen-containing oral contraceptives or hormone replacement therapy | Selective estrogen receptor modulators | Erythropoiesis-stimulating agents | Acute medical illness | Inflammatory bowel disease | Nephrotic syndrome | Myeloproliferative disorders | Paroxysmal nocturnal hemoglobinuria | Obesity | Central venous catheterization | Inherited or acquired thrombophilia |
|--------------------------------------------|--------------------------------------------------|--------------------------------------|----------------------------|------------------------------------------------------------------|-------------------------------------------------|----------------|----------------|-----------------------------------|--------------------------------------|-----------------------------------|-------------------------------|-----------------------------|-----------------------------|-----------------------------|--------------------------------|---------|-----------------------------|--------------------------------|


of procoagulant factors (Fibrinogen, prothrombin, factor VIII, IX, XI), increased basal procoagulant activity, impaired fibrinolysis and increased basal innate immunity activity and reactivity predisposes to thrombosis (thrombophilia). Inherited thrombophilias interact with clinical risk factors (eg. Pregnancy, hormone therapy, surgery) to increase the risk of incident thrombembolism. Genetic interaction increases the incidence of incident and recurrent VTE.

**WESTERN SCENARIO**

VTE among whites is 108 per 100,000 person-years with about 250,000 incident cases occurring annually among US whites. The incidence appears to be similar or higher among Blacks and lower among ASIAN and Native Americans. The incidence among US – Blacks is about 78 per 100,000, suggesting that about 27000 incident VTE cases occur annually among US Blacks. Recent data suggests that more than 900 000 incident or recurrent, fatal and non fatal VTE occur in the US annually. The incidence of VTE has not changed significantly over the last 25 years.

**INDIAN SCENARIO**

The prevailing belief that VTE in the ASIAN population is less than in the western population has been disproved by recent studies and there appears no reason to believe that it should be any different in India. The incidence of VTE in India is highly underestimated because of lack of adequate studies highlighting the incidence of VTE especially in medical patients, existence of a few but conflicting studies in post surgical patients and paucity of data from autopsied patients as autopsy is being done in very few institutions in India.

Jain et al conducted a prospective study in post – surgical patients with total knee (26 patients) and hip arthroplasty (45 patients), and showed a very low incidence (2/71) of DVT. They concluded that the incidence of DVT in Indian patients is very low in comparison to west and emphasized the fact that no thromboprophylaxis is needed in Indian patients undergoing total Hip / Knee arthroplasty if they have no known risk factors for DVT. Vijayaraghavan et al did a retrospective study on DVT in the South Indian population and showed an incidence of 1.79 / 1,000 population. Agarwal et al conducted a study in patients undergoing total hip / knee arthroplasty and revealed an overall incidence of DVT in 60% cases in the non prophylaxis group. This data was comparable to the data from other parts of Asia and West and emphasized the need of thromboprophylaxis. The Smart Study Group conducted a prospective observational study on Asian patients (2420 Patients) undergoing major orthopaedic surgery without thromboprophylaxis and revealed symptomatic VTE in 2.3% patients and sudden death in 1.2% patients. Progressive registry on venous thromboembolic events (PROVE) conducted in 19 countries enrolled 3526 patients with symptomatic DVT, out of which 667 were from India. DVT was found proximally and in the calf in 54% of Indian patients which is comparable to western date. Sharma et al in a prospective study of 112 patients who underwent surgery for fractures around hip joint found a 19.6% incidence of DVT. A prospective study conducted in PGIMER, Chandigarh by Nagi et al, revealed 8% incidence of DVT after major orthopaedic surgery.

Bhan et al, in a multicentric study, found an incidence of 23.34% of DVT in the nonprophylaxis group as compared to nil in the group which received mechanical prophylaxis. Lee et al conducted a retrospective study in CMC Vellore from (1996-2005) to determine the incidence of VTE among hospitalized patients and showed an overall incidence of confirmed DVTs to be 17.46 per 10,000 admissions with 64% being non surgical non trauma patients. PE was diagnosed in 14.9% of the study patients. Mortality in those with confirmed PE was 13.5%. A recently published study from Dept. of Medicine, AIIMS, New Delhi by Pandey et al, 75% of the patients admitted to Medicine ward and medicine ICU had the highest risk for DVT and PE. Only 12.5% had DVT prophylaxis within first two days of admission. They emphasized the need to aggressively implement DVT risk stratification strategy in medical patients and provide prophylaxis unless contraindicated. Shead et al found a 28% incidence of post operative DVT in 50 patients above 50 years of age in South India.

Autopsy provides the final diagnosis of PE. Shead et al showed major PE to have occurred in 1.9% cases in a retrospective analysis of autopsy examination performed on 432 patients dying postoperatively and stressed on the disproportion between the frequent occurrence of post operative DVT and the low incidence of PE at autopsy. In the study by Kakkar and Vasishta the overall incidence of PE in medical autopsies (all three groups – fatal, contributory and incidental) was 15.9%. Incidence of PE contributing significantly to the death of the patient (fatal and contributory) was 12.6%. Thus PE very significantly contributed
to death in 79.24% (126/159) of above group of patients. Bergqvist and Lindblad\(^a\) found an incidence of 23.6% PE at autopsy in surgical patients half of whom were not operated upon. Rubenstein et al\(^a\) found an incidence of 3.4% (Fatal and contributory) at autopsy in medical patients. Stein et al\(^a\) found an incidence of 0.23% of acute pulmonary embolism in tertiary care general hospital but a previous study by Datta et al\(^a\) from the same institute found an incidence of 3.1% at autopsy, but their study was purely based on gross morbid anatomical analysis only. Antemortem diagnosis of PE has been poor in various studies carried out in different parts of the world\(^a\). Kakkar and Vasistha\(^a\) found that PE affected younger population as 79.87% of the overall patients, 66.67% of the fatal group and 73% of combined group. This is in contrast to western studies where young adults or adolescents were occasionally affected.

**DIAGNOSIS OF VTE & PE**

It is difficult to establish an accurate diagnosis of VTE because of its nonspecific history, and clinical findings and the lack of simple, conclusive, low cost, low risk test for establishing a diagnosis. Major PE remains undiagnosed in around 40 – 70% cases because of such reasons. A clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians summarize, the current approaches for the diagnosis of VTE / PE 24.

**Recommendation 1**: Validated clinical prediction rules should be used to estimate pretest probability of VTE, both DVT and PE and for the basis of interpretation of subsequent tests.

**Recommendation 2**: In appropriately selected patients with
Thromboembolism Risk Stratification:

There are two general approaches in making thromboprophylaxis decision. One is “individualized” risk stratification and other is “group-specific” risk stratification. At present American College of Chest Physicians recommends “group specific risk stratification”.

8th ACCP Guidelines for Thromboprophylaxis:

According to the guidelines issued by 8th American College of Chest Physicians (ACCP) consensus on Antithrombotic and thrombolytic therapy.

i. For every general hospital, a formal active strategy that addresses the prevention of VTE be developed (Grade IA).

ii. Mechanical methods of thromboprophylaxis be sued primarily in patients at high risk for bleeding (Grade IA) or possible an adjunct to anticoagulant - based thromboprophylaxis (Grade 2A).

iii. For acutely ill medical patients admitted to hospital with CHF or severe respiratory disease or who are confined to bed and have one or more additional risk factors including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, thromboprophylaxis with low molecular weight heparin - LMWH (Grade IA), low dose unfractionated heparin- LDUH (Grade –IA), or fondaparinux (Grade IA) is recommended for patients having contraindication to anticoagulant prophylaxis, the optimal use of mechanical thromboprophylaxis with graduated compression stocking (GCS) or Intermittent pneumatic compression (IPC) is recommended (Grade IA).

iv. For patients admitted to a critical care unit, routine assessment for VTE risk and routine thromboprophylaxis in most is recommended. (Grade IA). Patients at moderate risk of VTE thromboprophylaxis using LMWH or LDUH is recommended (Grade IA).

Table 4: Approximate Risk of DVT in Hospitalized Patients*

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>DVT Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical patients</td>
<td>10 – 20</td>
</tr>
<tr>
<td>General Surgery</td>
<td>15 – 40</td>
</tr>
<tr>
<td>Major gynecologic surgery</td>
<td>15 – 40</td>
</tr>
<tr>
<td>Major urologic surgery</td>
<td>15 – 40</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>15 – 40</td>
</tr>
<tr>
<td>Stroke</td>
<td>20 – 50</td>
</tr>
<tr>
<td>Hip or knee arthroplasty, HFS*</td>
<td>40-60</td>
</tr>
<tr>
<td>Major trauma</td>
<td>40-80</td>
</tr>
<tr>
<td>SCI*</td>
<td>60-80</td>
</tr>
<tr>
<td>Critical Care patients</td>
<td>- 80</td>
</tr>
</tbody>
</table>

Rates based on objective diagnostic screening of asymptomatic DVT in patients not receiving thromboprophylaxis.


Table 5: Rationale of Thromboprophylaxis in Hospitalized Patients

<table>
<thead>
<tr>
<th>High prevalence of VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almost all hospitalized patients have one or more risk factors for VTE DVT is common in many hospitalized patient groups. Hospital – acquired VTE and PE are usually clinically silent It is difficult to predict which at – risk patients will develop Symptomatic thromboembolic complications. Screening at –risk patients using physical examination or Noninvasive testing is neither cost-effective nor effective</td>
</tr>
<tr>
<td>Adverse consequences of unprevented VTE</td>
</tr>
<tr>
<td>Symptomatic DVT and PE</td>
</tr>
<tr>
<td>Fatal PE</td>
</tr>
<tr>
<td>Cost of investigating symptomatic patients</td>
</tr>
<tr>
<td>Risk and costs of treating unprevented VTE</td>
</tr>
<tr>
<td>Increased future risk of recurrent VTE</td>
</tr>
<tr>
<td>Chronic postthrombotic syndrome</td>
</tr>
<tr>
<td>Efficacy and effectiveness of thromboprophylaxis</td>
</tr>
<tr>
<td>Thromboprophylaxis is highly efficacious at preventing DVT and proximal DVT</td>
</tr>
<tr>
<td>Thromboprophylaxis is highly effective at preventing Symptomatic VTE and fatal PE</td>
</tr>
<tr>
<td>The prevention of DVT also prevents PE</td>
</tr>
<tr>
<td>Cost effectiveness of thromboprophylaxis has repeatedly been demonstrated.</td>
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</tbody>
</table>

v. Patients who are at higher risk, thromboprophylaxis using LMWH is recommended (Grade IA). Patients who are at high risk for bleeding, optimal use of mechanical thromboprophylaxis with GCS and / or IPC at least until the bleeding risk decreases is recommended (Grade IA). When bleeding risk decreases, pharmacologic thromboprophylaxis be substituted for or added to mechanical thromboprophylaxis (Grade IC).

vi. Use of aspirin alone as thromboprophylaxis against VTE for any patient group is not recommended (Grade IA)

vii. Hence, for Indian patients it is advisable to follow the ACCP recommendations for VTE prophylaxis. However, in resource limited settings UFH is likely to be more cost effective than LMWHs.

8th ACCP Guidelines for Antithrombotic Therapy for VTE:

1. For patients with objectively confirmed DVT /PE, anticoagulant therapy with SC LMWH, monitored IV or SC UFH, unmonitored weight based SC UFH or SC fondaparinux is recommended (all Grade IA). For patients with a high clinical suspicion of DVT / PE treatment with anticoagulants while awaiting the outcome of diagnostic tests (Grade IC). For patients with confirmed PE early evaluation of the risk to benefits of thrombolytic therapy is recommended (Grade IC). For those with haemodynamic compromise short course thrombolytic therapy is recommended (grade IB) and for those with non-massive PE use of thrombolytic...
therapy is not recommended (Grade IB).

2. In acute DVT /PE, initial treatment with LMWH, UFH, or Fondaparinux for at least 5 days rather than a shorter period is recommended (Grade I C) and initiation of vitamin K antagonists (VKAs) together with LMWH, UFH, or fondaparinux on the first treatment day and discontinuation of these heparin preparations when the INR is > 2.0 for at least 24 hrs (Grade IA).

3. For patients of DVT / PE secondary to a transient risk factor (reversible), treatment with a Vit K antagonist for 3 months is recommended (Grade IA) and then all patients are evaluated for the risks to benefits of indefinite therapy (Grade IC). Indefinite anticoagulation therapy is recommended for first unprovoked proximal DVT or PE and low risk of bleeding when this is consistent with patients preference (Grade IA) and for most patients with a second unprovoked DVT (Grade IA).

4. Dose of VKA be adjusted to maintain a target INR of 2.5 (INR range 2.0 – 3.0) for all treatment durations (Grade IA).

5. For prevention of post thrombotic syndrome (PTS) after proximal DVT, use of an elastic compression stocking is recommended (Grade IA).

6. For DVT of upper extremity, similar treatment as for DVT of leg is recommended (Grade IC).

7. Selected patients with lower extremity (Grade 2B) and upper extremity (Grade 2 C) DVT, thrombus removal using catheter based thrombolytic techniques may be considered.

8. For extensive superficial vein thrombosis, treatment with prophylactic or intermediate doses LMWH or intermediate doses UFH for 4 weeks is recommended (Grade IB).

**ROLE OF STATINS IN PREVENTION OF VTE**:  
Jupiter trial, a randomized trial reveals that rosuvastatin (20mg / day) was associated with a significant reduction in the risk of VTE, an independent benefit of statin use. During a median follow up period of 1.9 years (maximum 5 years) the rates of VTE were 0.18 and 0.32 events per 100 person – years in rosuvastatin and placebo groups respectively. The rates of PE were 0.09 and 0.12 events per 100 person years in the rosuvastatin and placebo groups respectively. Rosuvastatin apart from its favourable lipid profile and anti-inflammatory properties inhibits isoprenylation of signalling proteins, reduces tissue factor expression and thrombin generation, attenuates fibrinogen cleavage and activation of factor V & VII. Statins augment the activity of transcription factor Kruppel - like factor 2 (KLF-2) promoting thrombomodulin expression on endothelial cells, thereby enhancing the activity of the protein-C – anticoagulant pathway.

**CONCLUSION**

VTE is a major public health issue globally. Incidence of VTE in the Indian sub-continent is underestimated. Indian scenario is very much like that of the western scenario. Despite solid scientific evidences, VTE prophylaxis remain under- used even in premier institutes. Hospital wide strategies to assess patients’ VTE risk should be implemented, together with measures that ensure that at-risk patients receive appropriate VTE prophylaxis.

**REFERENCES**


