T.R.N.C

NEAR EAST UNIVERSITY

INSTITUTE OF HEALTH SCIENCES

Assessing adherence to thrombo-prophylaxis guidelines in patients at risk of developing thromboembolic events at NEU Hospital in Northern Cyprus

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BY:

Abdulhamed Abdulmohemen Tulimt

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Approval

Thesis submitted to the Institute of Health Sciences of Near East University in partial fulfillment of the requirements for the degree of **Master of Science in Clinical Pharmacy.**

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ABSTRACT

Abdulhamed Abdulmohemen Tulimt Assessing adherence to thrombo-prophylaxis guidelines in hospitalized patients at NEU Hospital in Northern Cyprus. Near East University, Institute of Health Sciences, Clinical Pharmacy Master's Thesis', Nicosia, 2015.

Clinical pharmacists are a primary source of scientifically valid information and advice regarding the safe, appropriate, and cost-effective use of medications having wide scope in drug therapy management and optimization using evidence based tools and recommendation. Regarding thromboembolism one of the main cause of morbidity and mortality, despite the presence of effective strategies for prevention of deep vein thrombosis (DVT), a considerable proportion of patients at risk for thromboembolism do not receive prophylaxis during hospitalization while others receive it irrationally though not candidates according evidence based recommendations.

This study aimed to determine the adherence to thrombo-prophylaxis guidelines at Near East University hospital in north Cyprus and to assess rational prescribing of DVT prophylaxis medication in hospitalized patients thus to optimize care and assure rational practices.

The study is an observational prospective 60 days study carried at a tertiary university hospital. Patients from multiple clinics are enrolled to investigate risk for thrombosis and observe rational use of thrombo-prophylaxis for inpatients in healthcare settings using the Caprini's checklist for thrombosis risk assessment in adult patients.

In conclusion, our results suggest that that the Caprini risk assessment model is a practical and effective tool to assess the risk of venous thromboembolism (VTE) among hospitalized patients in North Cyprus, findings of the study show that as globally reported, adherence to VTE prophylaxis at the hospitals to be extremely low.

Key Words: Pharmacy practice, clinical pharmacy, hospital pharmacy, thrombosis, prophylaxis thromboprophylaxis, caprini's checklist, DVT risk.

ÖZET

Abdulhamed Abdulmohemen Tulimt, KKTC'de Yakın Doğu Üniversitesi Hastanesinde yatan hastalarda trombo-profilaksi kılavuzlarına uyumun değerlendirilmesi, Yakın Doğu Üniversitesi, Sağlık Bilimleri Enstitüsü, Klinik Eczacılık Yüksek Lisans Tezi, Lefkoşa, 2015.

Klinik eczacılar, kanıta dayalı kaynakları ve önerileri kullanarak ilaç tedavi yönetimi ve optimizasyonunda ilaçların güvenli, uygun ve maliyet-etkili kullanımı ile ilgili bilimsel geçerliliği olan bilginin primer kaynağıdır. Derin ven trombozunun (DVT) önlenmesi için etkili stratejiler olmasına ragmen tromboembolizm morbidite ve mortalitenin başlıca nedenlerinden biridir, tromboembolizm riski taşıyan hastaların önemli bir kısmı hastanede yattıkları süre boyunca profilaksi almazlarken digger bir kısmı da kanıta dayalı önerilere uymaksızın irrasyonel profilaksi alırlar.

Bu çalışmanın amacı, Kuzey Kıbrıs, Yakın Doğu Üniversitesi Hastanesinde trombo-profilaksi kılavuzlarına uyumun belirlenmesi ve yatan hastalarda DVT profilaksi uygulamasının rasyonel reçetelemesinin değerlendirilmesi böylece tedavinin optimize edilmesi ve rasyonel uygulamanın sağlanmasıdır.

60 gün boyunca yapılan gözlemsel prospektif çalışmada üniversite hastanesinde çeşitli kliniklerde kayıtlı hastalarda trombozis riski araştırılmıştır ve yatan hastalarda, erişkin hastalarda tromboz risk değerlendirilmesi için kullanılan Caprini'nin kontol listesine göre tromboprofilaksinin rasyonelliği gözlemlenmiştir.

Sonuç olarak bulgularımız, yatan hastalarda venöz tromboemboli (VTE) riskinin değerlendirilmesinde Caprini risk değerlendirme modelinin pratik ve etkili bir yöntem olduğunu ve global olarak da gösterildiği gibi Kuzey Kıbrıs'ta da VTE profilaksisine uyumun hastanede oldukça düşük olduğunu göstermiştir.

Anahtar kelimeler: Eczacılık uygulaması, klinik eczacılık, hastane eczacılığı, trombozis, profilaksi, tromboprofilaksi, Caprini'nin kontrol listesi, DVT riski.

Table of Contents

Page

LIST OF ABBREVIATIONS:

DVT: Deep Vein Thrombosis

VTE: Venous Thromboembolism

ACS: Acute coronary syndrome.

ACCP: American College of Chest Physician

AHA: AMERICAN HEART ASSOCIATION.

APA: American Pharmacists Association

ASHAP: The American Society of Health-System Pharmacists

RAM: Risk Assessment Model

CHD: chronic heart disease

COPD: chronic obstructive pulmonary disease

CVD: cardiovascular disease

CP: clinical pharmacist

CPS: clinical pharmacy services

DM: diabetes mellitus

DTP: drug-therapy problem

FDA: Food and drug administration

IFP: International Pharmaceutical Federation

MI: myocardial Infarction

MTM: medication therapy management

NEU: Near East University

RD: respiratory diseases

SD: standard deviation

TRNC: Turkish Republic of North Cyprus.

WHO: World health organization

List of Figures

Page

List of Tables

Page

Introduction

Deep venous thrombosis (DVT) is a life-threatening complication with significant mortality and morbidity. Studies on certain subgroups of injured patients have shown DVT rates as high as 60% and pulmonary embolism (PE) rates of up to 24%. Venous thromboembolism (VTE) is a potentially fatal disorder and a significant worldwide health problem also in elders. Common candidates affected mostly include patients with sustained multiple traumas, undergo major surgery, are immobile for a lengthy period of time, or have a coagulation related disorder. Optimal thromboprophylaxis is highly desirable for different patients. Low-dose heparin (LDH) and sequential compression devices (SCDs) are the most frequently used methods for DVT prevention.

The optimal level of anticoagulation depends upon the underlying condition and guidelines have been proposed by many expert groups. The control of anticoagulation is influenced by many factors including patient factors, setting and drug therapy, and knowledge of these aids accurate control.

Institutions vary in the type of staff who undertakes management of anticoagulant clinics. Examples include consultant hematologists, clinical assistant medical staff, junior medical staff, and pharmacists.

Involvement in anticoagulant therapy is an accepted part of pharmacy practice. Where Pharmacists by applying their pharmacotherapeutic knowledge and using evidence based effective tools can attribute much into anticoagulation management and administration and have been shown to offer a high standard of patient care and an effective use of resources and aid in rational practice.

In this master thesis project we evaluate current practice in providing prophylaxis therapy for patients at risk of developing DVT in a tertiary hospital in northern Cyprus using an evidence based tool for rational prescribing of DVT prophylaxis .

In the first part of literature review, the first chapter provides an overview about VTE etiology consequences and management.
In the second chapter we talk about Prophylaxis therapy, its rational and uses in thromboembolism prevention, then in chapter three we concisely explain DVT risk factors ,and methods of assessing risk in medical practice , currently available tools for assessment of DVT risk and their differences and the role of clinical pharmacist in this .

In the fourth chapter we briefly review trends in practice of thromboprophylaxis guidelines in healthcare settings world widely and compare that to studies done in Turkey.

The second part of this thesis contains sections five to eight which are about our study, its aims, objectives, methodology and results, which at end are summed up with a brief conclusion.

1. OVERVIEW THROMBOEMBOLISM

Venous thromboembolism (VTE) is a potentially fatal disorder and a significant worldwide health problem especially in elders. Common candidates affected mostly include patients with sustained multiple traumas, undergo major surgery, are immobile for a lengthy period of time, or have a coagulation related disorder. (Turpie AGG et al., 2002).

Unfortunately, the disease is often clinically silent, and the first manifestation may be sudden death, it results from clot formation within the venous circulation that manifest as deep vein thrombosis (DVT) and pulmonary embolism (PE). Beside death from PE that can occur within minutes after the onset of symptoms, before even starting to treat, but also long term manifestations could develop as having recurrent thromboembolic events that cause significant suffering and pain to patients.(Turpie AGG et al., 2002) .

Meanwhile the serious sequel of VTE its management is not also far of substantial risks, since Antithrombotic drugs require precise dosing and monitoring via systematic approaches to drug therapy management that can substantially reduce the risks else if undertaken could lead to serious complication, mainly bleeding. (Levine MN et al.,2004 – Chiquette E et al., 1998).

For this, the prevention of VTE in patients at risk is paramount to improving outcomes, while when there is a suspicion of VTE, the rapid and accurate diagnosis of the disorder is critical to making appropriate treatment decisions .

The optimal use of antithrombotic drugs requires not only an in-depth knowledge of their pharmacology and pharmacokinetic properties, but also a comprehensive approach to patient management, an area and scope for clinical pharmacy practice and services to assure rationale anticoagulation medication use .(Geerts WH et al., 2004 -Radley AS et al., 1995) .

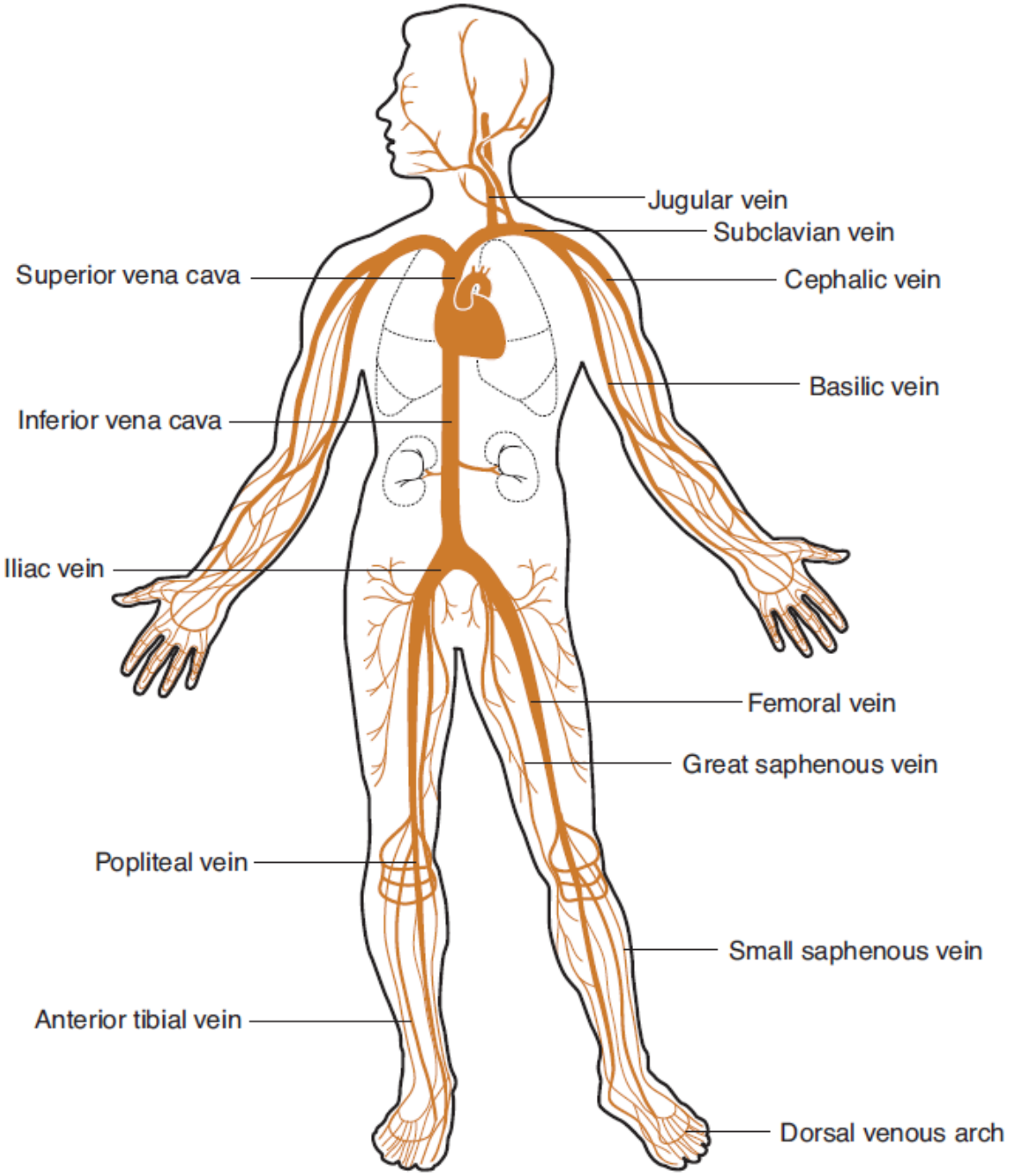

FIGURE 1: Venous circulation (Joseph T. DiPiro et al 2012)

1.1 Epidemiology and Risk Factors

The exact incidence of VTE in the general population is unknown, a significant amount of people around 50% of VTE patients have a silent disease, while in the States its estimated yearly that more than half a million are hospitalized while 60 000 patients die yearly due VTEs.(Buller HR et al., 2004)

The incidence of VTE is higher in men than female, it nearly doubles in each decade of life >50 years old. Estimated direct medical costs of managing VTEs annually are much more than $1 billion. The annual incidence of symptomatic VTE, the collective term used here for deep venous thrombosis, pulmonary embolism or both, is 2-3 per thousand inhabitants. The one-year mortality is 20% after a first VTE. Of the surviving patients 15-25% will experience a recurrent episode of VTE in the three years after the first event. Increase awareness of VTE, coupled with effective prevention, early diagnosis, and optimum treatment; all lead to decline of age-adjusted incidence of PE slightly in the last years.

Extensive studies have been carried on the incidence of VTE in specific high-risk patient populations. Patients undergoing orthopedic procedures involving lower extremities (LE) or those with multiple traumas are at particularly high risk. Incidence of VTE often in such patient groups exceeds 50% when effective prophylaxis is not provided. In patients post major surgery not involving LE, VTE incidence is 20- 40% according to presence of other risk factors e.g. age >60 years.

Other major factors of high incidence of VTE include post MI, CVE, spinal cord injuries, metastatic cancer, hypercoagulability diseases and patients with previous VTE during their lifetime. (Reitsma PH 2015.Geerts WH et al., 2004- Heit JA et al., 2000- Levitan N et al., 1999).

1.2 Consequences and Management

Majority of VTE thrombus begin in the lower extremities although it may form in any part of the venous circulation.

After formation, thrombi lyse, remain asymptomatic, close a vein, and propagate into more proximal veins till becoming an emboli or act in any combination of mentioned consequences. (Kearon C et al., 2003).

DVT or PE most commonly develops in patients with identifiable risk factors during or following a hospitalization. Many, perhaps the majority, of patients have asymptomatic disease but also may suffer long-term consequences, such as the post thrombotic syndrome and recurrent VTE. Many patients develop a symptomatic deep vein thrombosis prior to developing a PE, while many do not. Patients may die suddenly before effective treatment can be initiated.

TABLE 1	Risk Factors for Venous Thromboembolism
Age	Risk doubles with each decade after age 50 y
History of VTE	Strongest known risk factor of DVT and PE
Venous stasis	Major medical illness (e.g., CHF, status post-MI) Major surgery (e.g., general anesthesia >30 minutes) Paralysis (e.g., status post-stroke, spinal cord injury) Polycythemia vera Obesity Varicose veins
Vascular injury	Major orthopedic surgery (e.g., knee and hip replacement) Trauma (especially fractures of the pelvis, hip, or leg) Indwelling venous catheters

Hypercoagulable States	Malignancy, diagnosed or occult Activated protein C resistance/factor V Leiden Prothrombin (G20210A) gene mutation Protein C deficiency-Protein S deficiency Antithrombin deficiency Factor VIII excess (>90th percentile) Factor XI excess (>90th percentile) Antiphospholipid antibodies Dysfibrinogenemia Hyperhomocysteinemia Plasminogen activator inhibitor-1 excess Inflammatory bowel disease Nephrotic syndrome-Pregnancy/postpartum
Drug therapy	Estrogen-containing contraception Estrogen replacement therapy Selective estrogen receptor modulators

Confirming or excluding the diagnosis of VTE is extremely difficult and also to distinguish it from other disorders and additional objective tests are required.

DVT commonly present as unilateral leg pain and swelling or warmth, patient's superficial veins may be dilated and a "palpable cord" may be felt in the affected leg while PE often produces dyspnea, diaphoresis, tachypnea, chest tightness and tachycardia. Hemoptysis, while distressing, occurs in less than one-third of patients. When PE is massive, the patient may complain of dizziness or lightheadedness, cardiovascular collapse, characterized by cyanosis, shock, and oliguria, is an ominous sign.
The patient's neck veins may be distended. In massive PE, the patient may appear cyanotic and may become hypotensive. In such cases, oxygen saturation by pulse oximetry or arterial blood gas will likely indicate that the patient is hypoxic.

Lab tests when carried usually reveal elevated serum concentrations of D-dimer, a by-product of thrombin generation; also elevated erythrocyte sedimentation rate and white blood cell count are common in such patients.

Diagnostic tests:

- Venography or phlebography is the gold standard for the diagnosis of DVT, invasive test involving injection of radiopaque contrast dye into a foot vein. Drawbacks are high cost and effects such as anaphylaxis and nephrotoxicity.
- Pulmonary angiography is the gold standard for the diagnosis of PE. However, it is an invasive test that involves injection of radiopaque contrast dye into the pulmonary artery. The test is expensive and associated with a significant risk of mortality.
- Duplex ultrasonography most commonly used test to diagnosis DVT, It is a non-invasive test that can measure the rate and direction of blood flow and visualize clot formation in proximal veins of the legs. Though with careful clinical assessment may role out or in majority of cases but still not reliable in detecting small blood clots.
- Ventilation–perfusion (V/Q) scan measures the distribution of blood and air flow in the lungs. When there is a large mismatch between blood and air flow in one area of the lung, there is a high probability that the patient has a PE.
- Computerized tomography (CT) scans also among the most commonly used tests to diagnosis PE. Spiral CT scans can detect emboli in the pulmonary arteries.

Management:

Given that VTE can be debilitating or fatal, it is important to treat it quickly and aggressively (Wells PS et al., 2000) .Conversely, because major bleeding induced by antithrombotic drugs can be equally harmful, it is important to avoid treatment when the diagnosis is not a reasonable certainty. Assessment of the patient's status should focus on the search for risk factors in the patient's medical history (see Table 1). Venous thrombosis is uncommon in the absence of risk factors, and the effects of these risks are additive. Even in the presence of mild, seemingly inconsequential symptoms, VTE should be strongly suspected in those with multiple risk factors.

2. PROPHYLAXIS THERAPY: Rational use in thromboembolism prevention

2.1 Definition prophylaxis therapy

The basic meaning of prophylactic is to prevent or protect from. Prophylactic treatment, then, is an approach to preventing a disease or condition before it affects a patient.
The word prophylactic comes from the Greek word prophylaktikós, which means to guard beforehand. Also Known As: preventive treatment (The American Heritage® Stedman's Medical Dictionary 2002, 2001, 1995).

2.2 Rational in medical practice: Example of prophylaxis therapies used in practice

a. Prophylaxis Antibiotics:
Prophylactic antibiotic premedication is when a dentist or physician prescribes antibiotics before certain dental procedures. Antibiotics keep bacteria in the mouth from spreading to other parts of the body.

Certain clinical situations require the use of antibiotics for the prevention rather than the treatment of infections (Figure 2). Because the indiscriminate use of antimicrobial agents can result in bacterial resistance and super-infection, prophylactic use is restricted to clinical situations in which the benefits outweigh the potential risks. The duration of prophylaxis is dictated by the duration of the risk of infection the use of prophylaxis antibiotics in certain circumstances.

Certain dental procedures, such as a root canal or tooth extraction, may allow bacteria from the mouth to enter the bloodstream. Rarely, these bacteria can infect the heart valves and lining of the heart, causing them to become inflamed. This inflammation is called infective endocarditis (IE). IE has the potential to cause catastrophic medical problems, including heart failure and leakage of the heart valves.

When taken before a procedure, antibiotics may prevent bacteria from being released into the bloodstream. This is known as antibiotic prophylaxis.

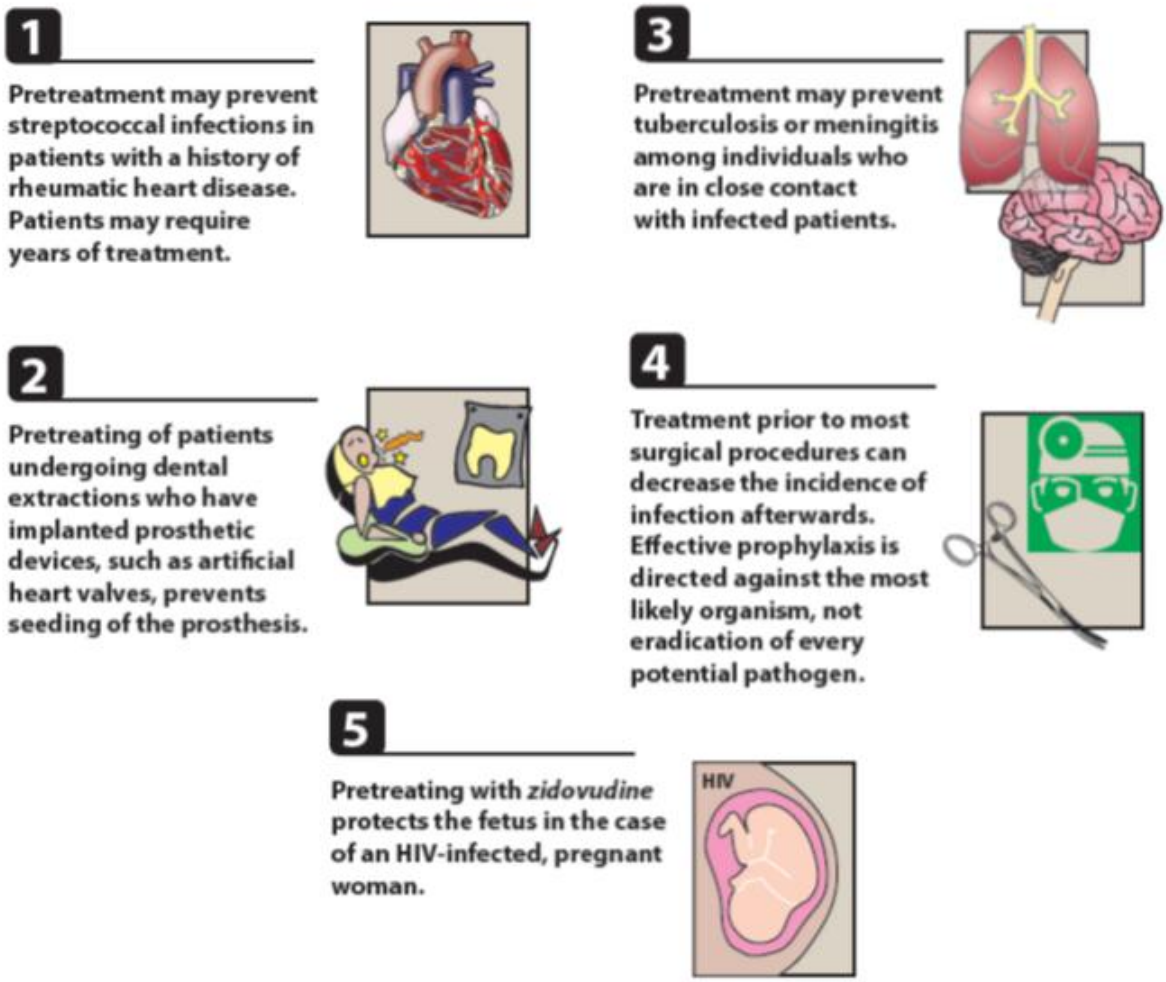

Figure 2: clinical situations in which prophylactic antibiotics are indicated. (Richard A.Harvey –Pamela C.Champe 2009)

On the other side approximately 1 million patients suffer from wound infections each year in the United States. Wound infections are responsible for extension of hospital stay on an average of 1 week and for increase in hospital costs by 20%.

The development of wound infection requires a local inoculum which is sufficient to overcome the local host defense. The development of wound infection depends on microbial virulence factors, the local environment, systemic factors, e.g., comorbidity, and surgical technique.

Antibiotic prophylaxis plays an important part in prevention of wound infections. The efficacy of antibiotic prophylaxis has been demonstrated to be significant; however, antibiotic prophylaxis cannot be a substitute for any other preventive measure. The

scientific basis for the perioperative use of antibiotics was established by Burke .Polk and Stone have confirmed the hypothesis in clinical studies and laid the ground for antibiotic prophylaxis in surgery. (Levine MN et al., 2004. Ansell J et al., 2004. Holzheimer RG et al., 2001).

Beside this urinary tract infection is one of the most common bacterial infections in women, and 50% to 60% of adult women experience a UTI during their lifetime. (Czaja CA, Hooton TM 2006. Foxman et al., 2000).

There are as many options for prevention and management of recurrent UTI as there are studies on the issue. A Cochrane review 22 of 19 trials including 1120 patients showed that antibiotics are better than placebo in reducing the number of clinical and microbiological recurrences in pre- and postmenopausal women with recurrent UTI. Seven trials including 257 patients showed a relative risk of having a clinical UTI of 0.15 (95% CI 0.08 to 0.28) favoring antibiotic over placebo. The number needed to treat to prevent one symptomatic recurrent UTI was 2.2.

Antibiotics reviewed were Fluoroquinolones (Norfloxacin, Ciprofloxacin, and Pefloxacin), Cephalosporin (Cephalexin, Cefaclor), Trimethoprim, Sulfamethoxazole, and Nitrofurantoin. No antibiotic was superior. Choice of antibiotic should rely on community patterns of resistance, adverse events, and local costs. Three main management strategies generally considered are continuous antimicrobial prophylaxis, post-coital prophylaxis, and patient-administered self-treatment. For patients with < 2 UTIs per year, the acute self-treatment may be useful. Patients with > 3 infections annually should be offered a regimen of continuous, low-dose prophylaxis or post-coital prophylaxis. (Stapleton A, Stamm WE 1997)

To sum up prophylaxis antibiotics are well established and used in clinical settings with patients with specific risk factors pre surgery, dental procedures, UTI prevention in recurrence, HIV pregnant ladies to protect fetus, prevention of meningitis and tuberculosis for persons near infected patients and also to prevent rheumatic fever in patients with history of previous rheumatic heart disease which prophylaxis antibiotics are recommended.

b. Stress Ulcer Prophylaxis

Stress ulcer prophylaxis has been an important part of the care for critical illness for over 20 years. (Maynard et al). demonstrated alterations in splanchnic blood flow during acute illness. The physiology of critical illness is frequently complicated with multiple systemic inflammatory abnormalities as well as alterations in hemodynamic status. Systemic hypoperfusion with associated catecholamine search, decreased cardiac output, hypovolemia, vasoconstriction, and inflammatory cytokine release is associated with splanchnic hypoperfusion. (Maynard N et al., 1993).

In comparison to normal patients, critically ill patients may have disturbances in their mucous and bicarbonate protective layer, owing to alterations in mucosal microcirculation (Levy MJ et al., 1997). Overall, the rate of clinically important upper gastrointestinal hemorrhage is low, and is currently rarely seen as a complication of critical illness owing to several potential factors, including strict regimens of prophylaxis. Clinical importance has classically been described as obvious physiologic decline, the requirement of operative for endoscopic intervention, and transfusion requirement. Use of protective agents has historically led to at least a 50% decrease in clinically significant hemorrhage (Cook DJ et al., 1996).

All critically ill patients with associated risk factors should receive chemical prophylaxis for stress ulceration. All agents appear equally adequate for prophylaxis against stress ulceration. The agent of choice should be based upon cost-effective arrangements between vendors and individual hospitals. The duration of treatment is ill-defined, but should be maintained while risk factors are present; the patient is admitted to the intensive care unit, or for a least one week after onset of critical illness. There is currently insufficient evidence to warrant cessation of prophylaxis in the setting of enteral nutrition if other risk factors exist, or to eliminate stress ulcer prophylaxis entirely. (Cook DJ et al., 1996).

2.3 Thromboprophylaxis therapies

Venous thromboembolism is the most common preventable cause of death in surgical patients. Thromboprophylaxis, using mechanical methods to promote venous outflow from the legs and antithrombotic drugs, provides the most effective means of reducing morbidity and mortality in these patients. Despite the evidence supporting thromboprophylaxis, it remains underused because physicians perceive that the risk of venous thromboembolism is not high enough to justify the potential hemorrhagic complications of anticoagulant use.

The risk of venous thromboembolism is determined by patient characteristics and by the type of surgery that is performed. (O'Donnell M, Weitz JI 2003)
Because VTE in hospitalized patients often is asymptomatic, it is inappropriate to rely on early diagnosis. Furthermore, noninvasive tests, such as compression ultrasonography, have limited sensitivity for a diagnosis of asymptomatic DVT. Thromboprophylaxis is, therefore, the most effective strategy to reduce morbidity and mortality from VTE in surgical patients. (O'Donnell M, Weitz JI 2003).

Thromboprophylaxis methods and the American Collage of Chest Physicians (ACCP) Antithrombotic Therapy and Prevention of Thrombosis, 9th end: CHEST Evidence-Based Clinical Practice Guidelines **(**Lansberg MG et al., 2012**).**

Both mechanical and pharmacologic agents can be used for thromboprophylaxis. Mechanical methods serve to prevent venous stagnation in the lower limbs by promoting venous outflow, whereas pharmacologic methods act by attenuating coagulation.
Compression elastic stockings and intermittent pneumatic compression are the mechanical methods used for prophylaxis, whereas anticoagulants, such as unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) and warfarin, or antiplatelet agents, particularly Aspirin, are the pharmacologic agents used for this purpose (Geerts WH et al., 2003).
.
Recent additions to this list include Fondaparinux, which has been licensed in the United States for thromboprophylaxis in high-risk orthopedic patients, and the newest agents the direct thrombin inhibitors. (Arixtra prescribing information 2005).
The (ACCP) recommends thromboprophylaxis for groups of patients for whom the benefits of this intervention appear to outweigh the risks.

Decisions about prescribing thromboprophylaxis for the individual patient are best made by combining knowledge of the literature (including the recommendations provided herein) with clinical judgment, the latter based on specific knowledge about each patient's risk factors for VTE, the potential for adverse consequences with thromboprophylaxis, and the availability of various options within one's center.
Since most thromboprophylaxis studies excluded patients who were at particularly high risk for either VTE or adverse outcomes, their results may not apply to those with previous

VTE or with an increased risk of bleeding. In these circumstances, clinical judgment may appropriately warrant use of a thromboprophylaxis option that differs from the recommended approach.

Mechanical Methods of Thromboprophylaxis:

Early and frequent ambulation of hospitalized patients at risk for VTE is an important principle of patient care. However, many patients cannot be fully ambulatory early after hospital admission or after surgery. Furthermore, the majority of hospital associated, symptomatic thromboembolic events occur after patients have started to ambulate, and mobilization alone does not provide adequate thromboprophylaxis for hospital patients. Specific mechanical methods of thromboprophylaxis, which include graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices, and the venous foot pump (VFP), increase venous outflow and/or reduce stasis within the leg veins. As a group, mechanical thromboprophylaxis modalities have important advantages and limitations. The primary attraction of mechanical thromboprophylaxis is the lack of bleeding potential. These modalities, therefore, have advantages for patients with high bleeding risks. While all three of the mechanical methods of thromboprophylaxis have been shown to reduce the risk of DVT in a number of patient groups, they have been studied much less intensively than anticoagulant-based approaches and they are generally less efficacious than anticoagulant thromboprophylaxis. (Mazzone C et al., 2004. Schulz SL et al., 2005. Urbankova J et al 2005. Agu O et al., 1999).

No mechanical thromboprophylaxis option has been studied in a large enough sample to determine if there is a reduction in the risk of death or PE. Special caution should be exercised when interpreting the reported risk reductions ascribed to mechanical methods of thromboprophylaxis for a number of reasons. First, most trials were not blinded, increasing the chance of diagnostic suspicion bias. Second, in the earlier studies that used fibrinogen leg scanning to screen for DVT, mechanical thromboprophylaxis may have lowered the 10 to 30% false-positive rate seen with the fibrinogen uptake test (FUT) [caused by venous pooling], while the rate remained unchanged in the nonmechanical treatment/control group. (Coe NP et al 1978. Gallus A et al 1983)

Third, a great variety of mechanical devices are available without any accepted physiologic standards and with minimal comparative data. IPC devices differ with respect

to their length (calf only vs calf-plus-thigh), single-chamber vs sequential compression, asymmetric compression vs circumferential compression, and the particular pump parameters (compression/relaxation cycle, cycle duration, pressure generation characteristics). GCS are also heterogeneous with respect to stocking length, ankle pressure, gradients in pressure, and fit. The effects of the specific design features of each of the mechanical devices on the prevention of DVT are unknown. In fact, mechanical thromboprophylaxis methods do not even have to demonstrate that they provide any protection against VTE in order to be approved and marketed.

Although many of these devices have never been assessed in any clinical trial, there is an unsubstantiated assumption that they are all effective and equivalent. Because of relatively poor compliance with optimal fitting and use of all mechanical options, they are unlikely to be as effective in routine clinical practice as in research studies where major efforts are made to optimize proper use.

Finally, the use of all of the mechanical methods of thromboprophylaxis are associated with substantial costs related to their purchase, storage, and maintenance, as well as to their proper fitting and the intensive strategies required to ensure optimal compliance.

In the recommendations that follow, use of mechanical thromboprophylaxis is the preferred option for patients at high risk for bleeding. If the high bleeding risk is temporary, consideration should be given to starting pharmacologic thromboprophylaxis once this risk has decreased. Mechanical thromboprophylaxis may also be considered in combination with anticoagulant thromboprophylaxis to improve efficacy in patient groups for which this additive effect has been demonstrated. In all situations where mechanical thromboprophylaxis is used, clinical staff must carefully select the correct size of the devices, must properly apply them, and must ensure optimal compliance (i.e., they should be removed for only a short time each day when the patient is actually walking or for bathing). Furthermore, care should be taken to ensure that the devices do not actually impede ambulation.

The American College of Chest Physicians (ACCP) recommend that mechanical methods of thromboprophylaxis be used primarily in patients at high risk of bleeding , or possibly as an adjunct to anticoagulant-based thromboprophylaxis.

For patients receiving mechanical methods of thromboprophylaxis, the ACCP recommend that careful attention be directed toward ensuring the proper use of and optimal adherence with, these methods.

Anticoagulants:

UFH and LMWH act as anticoagulants by binding to antithrombin and accelerating the rate at which it inhibits clotting factors, particularly thrombin and activated Factor X (Factor Xa). The interaction of UFH and LMWH with antithrombin is mediated by a unique pentasaccharide sequence found on one-third or one-fifth of the chains of UFH and LMWH, respectively. Fondaparinux, a synthetic analogue of this naturally-occurring pentasaccharide sequence, also acts as an anticoagulant by binding antithrombin. (Hirsh J 1991, Weitz JI 1997, Turpie AG 2001)

LMWH is produced by depolymerizing UFH to generate heparin chains with a mean molecular weight one-third that of UFH (i.e., 5000 Da and 15 000 Da, respectively). The shorter LMWH chains have better bioavailability after subcutaneous injection than the longer chains of UFH, and LMWH has a longer half-life than UFH. LMWH also is associated with a lower incidence of heparin-induced thrombocytopenia.

The anticoagulant profile of LMWH differs from that of UFH. To catalyze Factor Xa inhibition by antithrombin, heparin needs only to bind to antithrombin via its pentasaccharide sequence; an interaction that induces conformation changes in the reactive center loop of antithrombin and accelerates its rate of Factor Xa inactivation. In contrast, to catalyze thrombin inactivation by antithrombin, heparin must bind to both antithrombin and thrombin, thereby bridging inhibitor and enzyme together. Only heparin chains comprising the pentasaccharide and at least 13 additional saccharide units, corresponding to a molecular weight of 5400 Da or higher, are of sufficient length to provide this bridging function. Because at least half the chains of LMWH are too short to provide this bridging function, LMWH has greater inhibitor activity against Factor Xa than thrombin. In contrast, all the chains of UFH are long enough to bridge antithrombin to thrombin, endowing it with equal inhibitory activity against Factor Xa and thrombin.

With a molecular weight of about 1500 Da, fondaparinux is too short to bridge antithrombin to thrombin. Consequently, fondaparinux catalyzes Factor Xa inhibition by antithrombin but has no effect on the rate of thrombin inactivation. Fondaparinux exhibits excellent bioavailability after subcutaneous injection and is given once daily. (Turpie AG 2001)

UFH, LMWH and fondaparinux usually are started postoperatively to reduce the risk of spinal hematoma, a rare, but devastating, complication of spinal puncture for spinal or epidural anesthesia. When these agents are given in prophylactic doses, anticoagulation monitoring is unnecessary. Warfarin also is used for thromboprophylaxis, but it must be monitored so that the dose can be titrated to achieve an International Normalized Ratio (INR) of 2–3.

The ACCP recommend for each of the antithrombotic agents, that clinicians follow manufacturer suggested dosing guidelines.

Also for renal impaired patient's anticoagulant dosing, renal clearance is the primary mode of elimination for several anticoagulants, including LMWH and fondaparinux. With reduced renal function, these drugs may accumulate and increase the risk of bleeding.
There appears to be considerable variability in the relationship between renal impairment and drug accumulation for the various LMWHs, which may be related to the chain length distribution of the different LMWH preparations. (Lim W et al., 2006. Nagge J et al 2002. Grand'Maison A et al., 2005)
Among 120 critical care patients, all of whom had creatinine clearances 30 mL/min, there was no evidence of bioaccumulation of Dalteparin at 5,000 U used as thromboprophylaxis based on serial anti-factor Xa levels. (Douketis J et al 2007)

The ACCP recommend that renal function be considered when making decisions about the use and/or the dose of LMWH, Fondaparinux, and other antithrombotic drugs that are cleared by the kidneys, particularly in elderly patients, patients with diabetes mellitus, and those at high risk for bleeding. Depending on the circumstances, ACCP recommend one of the following options in this situation: avoiding the use of an anticoagulant that bioaccumulates in the presence of renal impairment, using a lower dose of the agent, or monitoring the drug level or its anticoagulant effect.

Antiplatelet drugs

Acetylsalicylic acid inhibits platelets by permanently acetylating cyclooxygenase-1, the enzyme involved in the first step in the synthesis of thromboxane A2, a potent platelet agonist. Because it blocks platelet and megakaryocyte cyclooxygenase-1, its effects persist for the lifetime of the platelets. With a platelet lifespan of about 10 days and 10% replacement of circulating platelets per day, half of the antiplatelet effect of acetylsalicylic acid is reversed within 5–6 days of stopping the drug. (Antiplatelet TrialistsÍ Collaboration.1994).

Thienopyridines, which include Ticlopidine and Clopidogrel, irreversibly inhibit platelet ADP receptors. Both agents must undergo hepatic transformation to generate metabolites that inhibit these receptors. Consequently, their onset of action is delayed unless loading doses are given.

Clopidogrel is replacing Ticlopidine because of safety and convenience advantages. Unlike Tclopidine, neutropenia, thrombocytopenia and thrombotic thrombocytopenic purport are rare complications of Clopidogrel therapy. Furthermore, Clopidogrel can be given once daily, whereas Ticlopidine must be given twice daily. Clopidogrel or Ticlopidine is a reasonable alternative for patients allergic to acetylsalicylic acid. (Antiplatelet TrialistsÍ Collaboration.1994).

Aspirin as Thromboprophylaxis: Aspirin and other antiplatelet drugs are effective at reducing major thrombotic vascular events in patients who are at risk for or who have established atherosclerotic disease. Evidence suggests that antiplatelet agents also provide some protection against VTE in hospitalized patients. However, ACCP do not recommend the use of aspirin alone as prophylaxis against VTE primarily because more effective methods of thromboprophylaxis are readily available. Furthermore, much of the evidence citing a benefit for the use of antiplatelet drugs as VTE thromboprophylaxis is based on methodologically limited studies. For example, the Antiplatelet Trialists' Collaboration meta-analysis pooled data from generally small studies that were conducted _ 30 years ago and that were of variable quality. Only one third of the studies included a group that received aspirin alone; and, of these, generally accepted methods of screening for DVT were performed in only 38%.A number of trials have reported no significant benefit from aspirin VTE prophylaxis or found that aspirin was inferior to other thromboprophylaxis

modalities. (Best AJ et al., 2000- Patrono C et al 2004- Antiplatelet Trialists Collaboration 1994- Lotke PA et al., 1996- Graor RA et al., 1992- Gent M et al., 1996- Westrich GH et al.,1996)

For example, the relative risk reductions (RRRs) for DVT and proximal DVT among patients who have received thromboprophylaxis with a VFP plus aspirin over that with aspirin alone following total knee arthroplasty were 32% and _ 95%, respectively (p _ 0.001 for both comparisons). Among hip fracture surgery patients who were randomized to receive either aspirin or danaparoid, a low-molecular- weight heparinoid, VTE was detected in 44% and 28% of the patients, respectively (p _ 0.028) (Gent M et al., 1996- Westrich GH et al.,1996)

Finally, aspirin use is associated with a small but significant increased risk of major bleeding, especially if combined with other antithrombotic agents. Therefor the ACCP guidelines recommend against the use of aspirin alone as thromboprophylaxis against VTE for any patient group.

3. ASSESSING RISK FACTOR IN PRACTICE:

The concept of risk is an outgrowth of our society's great concern about coping with the dangers of modern life.

Risk factor definition: a factor, such as a habit or an environmental condition that predisposes an individual to develop a particular disease (Collins English Dictionary 2012).

In epidemiology, a risk factor is a variable associated with an increased risk of disease or infection. Sometimes, determinant is also used, being a variable associated with either increased or decreased risk.

Risk factors or determinants are correlational and not necessarily causal, because correlation does not prove causation. For example, being young cannot be said to cause measles, but young people have a higher rate of measles because they are less likely to have developed immunity during a previous epidemic. Statistical methods are frequently used to assess the strength of an association and to provide causal evidence (for example in the study of the link between smoking and lung). Statistical analysis along with the biological sciences can establish that risk factors are causal. Some prefer the term risk factor to mean causal determinants of increased rates of disease, and for unproven links to be called possible risks, associations, etc.

When done thoughtfully and based on research, identification of risk factors can be a strategy for medical screening. (Wald, N J et al 1999).

Mainly taken from risk factors for breast cancer, risk factors can be described in terms of, for example:

- Relative risk, such as "A woman is more than 100 times more likely to develop breast cancer in her 60s than in her 20s.
- Fraction of incidences occurring in the group having the property of or being exposed to the risk factor, such as "99% of breast cancer cases are diagnosed in women" (Giordano SH et al.,2004)
- Increase in incidence in the exposed group, such as "each daily alcoholic beverage increases the incidence of breast cancer by 11 cases per 1000 women".

- Hazard ratio, such as "an increase in both total and invasive breast cancers in women randomized to receive estrogen and progestin for an average of 5 years, with a hazard ratio of 1.24 compared to controls" (Heiss, G et al., 2008).

.The probability of an outcome usually depends on interplay between multiple associated variables. When performing epidemiological to evaluate one or more determinants for a specific outcome, the other determinants may act as confounding factors, and need to be controlled for, e.g. by stratification. The potentially confounding determinants varies with what outcome is studied, but the following general confounders are common to most epidemiological associations, and are the determinants most commonly controlled for in epidemiological studies:

- Age
- Sex or gender
- Ethnicity

Other less commonly adjusted for possible confounders include:

- Social status/income
- Geographic location
- Genetic predisposition
- Gender identity
- Occupation
- Sexual orientation
- Level of chronic stress
- Diet
- Level of physical exercise
- Alcohol consumption and tobacco smoking
- Other social determinants of health

(Case, S.P. and Haines, K.R. 2009)

A risk marker is a variable that is quantitatively associated with a disease or other outcome, but direct alteration of the risk marker does not necessarily alter the risk of the outcome. For example, driving-while-intoxicated (DWI) history is a risk marker for pilots as epidemiologic studies indicate that pilots with a DWI history are significantly more likely

than their counterparts without a DWI history to be involved in aviation crashes. (Case, S.P. and Haines, K.R. 2009)

The term "risk factor" was first coined by former Framingham Heart Study Director, Dr. William B. Kannel in a 1961 article in Annals of Internal Medicine. (Husten, Larry 2011)

3.1 Thromboembolism Risk Stratification

There are two general approaches to making thromboprophylaxis decisions. One approach considers the risk of VTE in each patient, based on their individual predisposing factors and the risk associated with their current illness or procedure. Thromboprophylaxis is then individually prescribed based on the composite risk estimate. Formal risk assessment models (RAMs) for DVT have been proposed to assist with this process. The approach of individual thromboprophylaxis prescribing based on formal RAMs is not used routinely by most clinicians because it has not been adequately validated and is cumbersome. Furthermore, there is little formal understanding of how the various risk factors interact in a quantitative manner to determine the position of each patient along a continuous spectrum of thromboembolic risk. Finally, individual RAMs may not be worth the effort because there are only a limited number of thromboprophylaxis options, and one of the principles of effective thromboprophylaxis is to reduce complexity in decision making. One simplification of the risk assessment process for surgical patients involves assigning them to one of four VTE risk levels based on the type of operation (minor, major), age (_ 40 years, 40 to 60 years, and _ 60 years), and the presence of additional risk factors (such as cancer or previous VTE). Although this classification scheme has been used in some centers, its limitations include risk quantitation that is based on studies that are _ 25 years old, uncertainty about the influence of each factor on overall risk, lack of definitions for minor and major surgery, and arbitrary cutoffs for age and duration of surgery. (Geerts WH et al 2008).

Another approach to making thromboprophylaxis decisions involves implementation of group-specific thromboprophylaxis routinely for all patients who belong to each of the major target groups, for example patients undergoing major general surgery or major orthopedic surgery. At the present time, we support this approach for several reasons. First,

although an increasing number of patient-specific thrombosis risk factors contribute to the substantial variability in VTE rates, the principal factor is the patient's primary reason for hospitalization, whether this is a surgical procedure or an acute medical illness.
Furthermore, at this time, we are not able to confidently identify the small population of patients in the various groups who do not require thromboprophylaxis. An individualized approach to thromboprophylaxis has not been subjected to rigorous clinical evaluation, while group risk assignment and thromboprophylaxis are the basis for most randomized trials of thromboprophylaxis and for evidence- based, clinical practice guidelines.

Third, individualizing thromboprophylaxis is complex and may be associated with suboptimal compliance unless ongoing, institution-wide efforts for implementation are in place. A further simplification of our previous classification system allows clinicians to readily identify the general risk group for their patients and makes general thromboprophylaxis recommendations. (Geerts WH et al 2008).

3.2 present tools for risk assessment in VTE

Worldwide, more than half of the hospitalized patients at high risk do not receive VTE prophylaxis. Accurate assessment of patient VTE risk is critical to improving this situation and increasing compliance with prophylaxis guidelines. (Anderson FA Jr 2007).

There are two general risk assessment approaches, group risk assessment or individual risk assessment. Most recent publications concluded that it may be more appropriate to use the individual risk assessment approach to identify and evaluate all possible risk factors to determine the true extent of risk for a patient and provide appropriate suggestions for prophylactic therapies according to the risk level. Several individualized VTE risk assessment models (RAMs) have been proposed and evaluated clinically, the most notable being those developed by Caprini, Cohen, Kucher, etc.

The Caprini risk assessment model was derived more than a decade ago, based on a combination of clinical experience and published data. The modified versions of the model have been validated in surgical setting and medical environment in western populations. More importantly, the RAM gives appropriate prophylaxis recommendations according to the risk level and score, which is convenient, practical and useful for physicians. This

RAM has been adopted by many individuals and organizations and has been translated into 12 languages. (Caprini JA. 2010)

The **Padua Prediction Score** was used to determine VTE risk in 1180 consecutive medical patients. It was empirically generated by integrating the Kucher_s model with additional items and by slightly modifying the assigned scores in order to permit identification of all those conditions for which the latest international guidelines strongly recommend. Patients were followed for up to 90 days following admission to assess the occurrence of symptomatic VTE. The percent of subjects developing VTE was as follows:

•"Low risk" patients (711): 0.3 percent

•"High risk" patients receiving adequate in-hospital thromboprophylaxis (186): 2.2 percent

•"High risk" patients not receiving adequate in-hospital thromboprophylaxis (283): 11.0 percent. (Barbar S1et al., 2010).

The GENEVA risk score was subject to a multicenter validation study that included 1478 hospitalized medical patients, 43 percent of whom did not receive thromboprophylaxis. Over three percent of high-risk score subjects developed symptomatic VTE or VTE-related death at 90 days, compared to 0.6 percent of low-risk score patients. When only patients who did not receive prophylaxis were considered, these risks were 3.5 and 1.1 percent respectively. (Nendaz M, et al 2014)

3.3 Role of the clinical pharmacist:

Clinical pharmacists are a primary source of scientifically valid information and advice regarding the safe, appropriate, and cost-effective use of medications having wide scope in drug therapy management and optimization using evidence based tools and recommendation. Over the past 40 years, major changes have occurred in the area of anticoagulation management. New strategies have been developed for older anticoagulants, older beliefs have been challenged, new anticoagulants have been introduced, and new indications have been identified for existing anticoagulants. The role of the pharmacist in managing anticoagulant therapy has been established, and clinicians have learned more about the critical importance of medication safety. Advances have spanned from the outpatient setting to the critical care setting. (Maureen A 2007)

Although newer anticoagulants (LMWHs, fondaparinux, DTIs) offer advantages, their lack of complete reversibility can pose challenges in the face of over anticoagulation. Other anticoagulant agents in development include a once-weekly, indirect-acting pentasaccharide inhibitor (Idraparinux), direct acting pentasaccharide inhibitors (Apixaban, Rivaroxaban), soluble Thrombomodulin, and tissue pathway factor inhibitor. Several other major developments in the area of anticoagulation have also occurred. Hypercoagulable states have been identified, along with an understanding of their role in causing thromboembolism. The optimal use of antiplatelet agents (with or without combination anticoagulant therapy) in arterial disease has been further defined. Efforts aimed at public awareness of the signs of stroke have paved the way for the timely use of thrombolytic therapy for acute ischemic stroke. The introduction of newer, longer-acting anticoagulants administered subcutaneously shifted the treatment of venous thromboembolism (VTE) to the outpatient setting. The introduction of warfarin self-monitoring for select patients has allowed for even further empowerment of patients. The introduction of recombinant Factor VIIa for hemophilia patients with inhibitors of Factor VIII or IX was a major breakthrough. Despite the cost and thrombotic risk associated with this agent, its off-label use continues to increase in many clinical settings, including traumatic bleeding and uncontrollable hemorrhage. Understanding the link between activation of inflammation and coagulation led to the development and approval of drotrecogin Alfa, activated for acute severe sepsis. (Rosborough TK et al., 2004- Smythe MA et al., 2001- Kearon C et al 2006).

Over the past 2 decades, the importance of medication safety with anticoagulants became a critical issue for health systems. In the 1980s, the increased incidence of spinal hematomas in patients receiving LMWH and neuraxial anesthesia heightened awareness of the potential significant risks with anticoagulant therapy. The importance of evaluating

hospitalized patients for the risk of VTE has received considerable attention and will continue to be a major area of focus for the healthcare system in the coming decades. VTE is the most common form of preventable hospital death, causing more deaths annually in the US than breast cancer, AIDS, or motor vehicle accidents. (Favaloro EJ et al 2005)

Performance measures that clinical pharmacists can participate in carrying them and are recommended by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and the National Quality Forum include:

- VTE risk assessment/prophylaxis within 24 hours of hospital admission.
- VTE risk assessment/prophylaxis within 24 hours of transfer to the intensive care unit.
- Documentation of inferior vena cava filter indication.
- VTE patients with overlap therapy.
- VTE patients receiving unfractionated heparin with platelet count monitoring.
- VTE patients receiving unfractionated heparin management by monograms/protocol.
- VTE discharge instructions.
- Incidence of potentially preventable hospital-acquired VTE. (Joint Commission 2015)

Over the last 2 decades, the benefit of pharmacist-managed anticoagulant therapy has been well established. In 1985, Drug Intelligence & Clinical Pharmacy published an article on cost justification of a pharmacist-managed anticoagulation clinic. Therapy management by pharmacists resulted in an improvement in the percentage of prothrombin times and INRs in the therapeutic range and a reduction in hospitalizations for thromboembolic or bleeding events. The anticoagulation clinic was found to have a favorable cost: benefit ratio. Numerous publications since that time have also confirmed these benefits. (Gray DR et al., 1985)

The pharmacist's role in managing anticoagulation therapy in the inpatient setting has also been established. An evaluation of over 700 000 Medicare patients from almost 1000 hospitals found that those without pharmacy-directed heparin and warfarin management had higher mortality rates, length of stay, Medicare charges, bleeding rates, and transfusion requirements. Pharmacy-managed anticoagulant therapy improves the quality and safety of such therapy in the inpatient and outpatient setting. (Bond CA, Raehl CL 2004)

As the role of the pharmacist in anticoagulation management continues to evolve, pharmacists must keep current with therapeutic advances. For pharmacists working

primarily in the area of anticoagulation, national certification exams are carried in the states and other pharmacy practice developed countries.

With the current advances in the field of anticoagulation, the future will see an increased focus on patient safety and disease prevention. Quality care as it relates to anticoagulation therapy will be tied to hospital accreditation and reimbursement. New classes of anticoagulants will be introduced, which will heighten the need for reversal agents.

Pharmacists will continue to play a critical role in managing and assessing the outcomes of anticoagulant therapy in the future. The eventual impact of oral DTIs on pharmacist-managed anticoagulation clinics remains to be seen. (Maureen A Smythe 2007)

4. STUDIES DONE ON THROMBOPROPHLAXIS:

4.1 Studies done world widely

The Venous Thromboembolism Prevention Study (VTEPS) Network is a consortium of 5 tertiary referral centers established to examine venous thromboembolism (VTE) in plastic surgery patients. The study report midterm analyses of the study's control group to evaluate the incidence of VTE in patients who receive no chemoprophylaxis, and validate the Caprini Risk Assessment Model (RAM) in plastic surgery patients. (Pannucci CJ et al 2011)

The study design was done by performing medical record review at VTEPS centers for all eligible plastic surgery patients between March 2006 and June 2009. Inclusion criteria were Caprini score _3, surgery under general anesthesia, and postoperative hospital admission. Patients who received chemoprophylaxis were excluded. Dependent variables included symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE) within the first 60 postoperative days and time to DVT or PE.

The study resulted in identifying 1,126 historic control patients. The overall VTE incidence was 1.69%.Approximately 1 in 9 (11.3%) patients with Caprini score _8 had a VTE event. Patients with Caprini score _8 were significantly more likely to develop VTE when compared with patients with Caprini score of 3 to 4 (odds ratio [OR] 20.9, p_0.001), 5 to 6(OR9.9, p_0.001), or 7 to 8(OR4.6, p_0.015). Among patients with Caprini score 7 to 8 or Caprini score_8, VTE risk was not limited to the immediate postoperative period (postoperative days 1-14). In these high-risk patients, more than 50% of VTE events were diagnosed in the late (days 15-60) postoperative period.

The study conclude that the Caprini RAM effectively risk-stratifies plastic and reconstructive surgery patients for VTE risk. Among patients with Caprini score _8, 11.3% have a postoperative VTE when chemoprophylaxis is not provided. In higher risk patients, there was no evidence that VTE risk is limited to the immediate postoperative period.

A second study carried in surgical intensive care unit (SICU) patients which are known to be at high risk for venous thromboembolism (VTE). The 2005 Caprini Risk Assessment Model (RAM) predicts VTE risk in surgical patients. However, a physician's ability to accurately complete this RAM and the effect that inaccurate RAM completion might have on VTE risk remain unknown. (Pannucci CJ et al., 2014)

The study designed to be between 2009 and 2012, physicians completed a 2005 Caprini score for all SICU admissions at our institution. For comparison, they used a previously validated, computer-generated score. Regression-based techniques examined the effect of inadequate risk stratification on inpatient VTE risk, when controlling for other confounders.

Study resulted in among 3,338 consecutive SICU admissions, 55.2% had computer-generated scores that were higher than the physician-reported score, and 20.6% of scores were equal. Computer generated scores were higher than physician-reported scores for both median (6 vs 5) and inter-quartile range (5 to 8 vs 3 to 7). Inter-rater reliability between the 2 scores was poor (kappa ¼ 0.238). Risk score underestimation by _2 points was significantly associated with inpatient VTE (7.67% vs 4.59%, p ¼ 0.002). Regression analysis demonstrated that each additional day's delay in chemoprophylaxis (odds ratio [OR] 1.05, 95% CI 1.01 to 1.08, p ¼ 0.011) and under-risk stratification by _2 points (OR 2.46, 95% CI 1.53 to 3.96, p < 0.001) were independent predictors of inpatient VTE, as were higher admission APACHE score, personal history of VTE, recent pneumonia, and younger age.

The study concluded that physicians under-risk stratify SICU patients when using the 2005 Caprini RAM. As hospitals incorporate electronic medical records into daily practice, computer-calculated Caprini scores may result in more accurate VTE risk stratification. Inadequate VTE risk assessment and delay to chemoprophylaxis carry independent and significant increased risk for VTE.

Also a study considered venous thromboembolism to occur frequently in at risk hospitalized patients, and prophylaxis of VTE is significantly underused. Researchers sought to preliminarily assess the validity of Caprini risk assessment model, a famous individual VTE risk assessment model, in Chinese hospitalized patients with VTE. (Zhou HX et al 2012)

The study was a retrospective study combined with a follow-up study among 347 confirmed VTE patients from a Chinese hospital.

They found compared with the other two risk assessment models (RAMs), Caprini model can classify much more VTE patients into high or highest risk level and the differences were statistically significant (Caprini model vs Kucher model, pb0.0001; Caprini model vs the Padua Prediction Score, pb0.0001). Caprini model exhibited much more effect at assessing patient's VTE risk among surgical patients than nonsurgical patients (average risk score, 5.71±2.54 vs 4.36±2.51, pb0.0001; by Wilcoxon rank sum test, p=0.001 in favor of the prediction effect of the RAM in surgical patients). Kaplan-Meier analysis showed that patients classified into low and highest risk level by Caprini model had increased hazard for VTE recurrence when compared with patients classified into moderate and high risk level, but the result was not statistically significant (p=0.222).

In conclusion the study preliminarily suggests that the Caprini risk assessment model is a practical and effective tool to assess the risk of VTE among unselected Chinese inpatients and may also be useful in predicting the risk of VTE recurrence. However, future studies with control group and prospective validation of the model in Chinese inpatients are needed.

Another study objective was to determine the adherence to thrombosis prophylaxis guidelines in a general hospital as a quality control strategy. In this a random audit of clinical charts was conducted at the Tijuana General Hospital, Baja California, Mexico, to determine the degree of adherence to deep vein thrombosis prophylaxis guidelines. The instrument used was the Caprini's checklist for thrombosis risk assessment in adult patients. The sample included 300 patient charts; 182 (60.7 %) were surgical patients and 118 were medical patients. (Sandoval-Chagoya GA, Laniado-Laborín R 2013)

Forty six patients (15.3 %) received deep vein thrombosis pharmacologic prophylaxis; 27.1 % of medical patients received deep vein thrombosis prophylaxis versus 8.3 % of surgical patients ($p < 0.0001$). The study results show that adherence to DVT prophylaxis at the hospital was extremely low. Only 15.3 % of our patients at risk received treatment, and even patients with very high risk received treatment in less than 25 % of the cases. Study concluded to need for implemented strategies to increase compliance with clinical guidelines.

A study also aimed to test the validity of Caprini risk assessment model in identifying high venous thromboembolism (VTE) risk patients among hospitalized medical patients. (Zhou HX et al 2013)

It was carried as a retrospective case-control study was performed among hospitalized medical patients admitted into West China Hospital, Sichuan University from January 2010 and December 2011. A total of 218 patients with definite VTE during hospitalization were recruited. And 394 controls were randomly selected from the patients without VTE admitted into the same departments within the same period. The risks of both cases and controls were retrospectively assessed with the Caprini risk assessment model.

The average Caprini cumulative risk score in cases was significant higher than that in controls (4.9 ± 2.6 vs 3.2 ± 2.0, P = 0.000). There was no significant difference in the risk of VTE between the patients at a low risk by Caprini model and those at a moderate risk (OR = 1.26, 95%CI: 0.62-2.56). Compared with a low risk, those with a high risk were associated with 2.00-fold increased risk of VTE (95%CI: 1.10-3.61), a highest risk was associated with 5.76-fold increased risk of VTE (95%CI: 3.24-10.24) (both P < 0.05) . When further stratifying the highest risk level with cumulative risk score ≥ 5 into 5-6, 7-8, and ≥ 9 risk level, the patients with score 5-6 were associated with 4.15-fold increased risk of VTE (95%CI: 2.28-7.56), those with score 7-8 11.13-fold increased risk of VTE (95%CI: 4.88-25.36) and those with score ≥ 9 21.00-fold increased risk of VTE (95%CI: 6.34-69.52)compared with low risk counterparts.

the study conclude that Caprini risk assessment model can effectively and quantitatively assess the risk of VTE among hospitalized medical patients based on their individual VTE risk factors.

2.4 Studies done in turkey regarding thromboprophylaxis:

A multi-center study carried also in Turkey Venous **,** entitled Thromboembolism Risk and Thromboprophylaxis Among Hospitalized Patients: Data From the Turkish Arm of the ENDORSE Study, was to evaluate venous thromboembolism (VTE) risk and use of thromboprophylaxis in the acute care hospital setting.(Ongen G et al., 2011)

A total of 1701 patients hospitalized for acute or exacerbated chronic medical illnesses or elective major surgery at 11 different hospitals across Turkey were included in the study. Patients at risk and VTE prophylaxis application were retrospectively identified based on medical charts. According to the American College of Chest Physicians (ACCP) criteria, overall 35.6% (606 of 1701) of the patients were identified to be at VTE risk. Venous thromboembolism-risk was observed in 64.9% of surgical and 23.8% of medical patients, the latter being lower than global Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) study results; while prophylaxis was prescribed in 39.0% and 38.5% of them, respectively. Contraindication to anticoagulant prophylaxis was observed in 8.7% of medical and 8.8% of surgical patients. Study conclude that VTE remains a risk factor among patients hospitalized across Turkey, since identification as well as prophylaxis of patients at VTE risk seems to be neglected.

In a second study which was An observational study for venous thromboembolism risk assessment among hospitalized patients in general surgery clinics across Turkey considered Venous thromboembolism (VTE) to be still remain a significant public health problem due to gaps between recommendations and clinical practice in VTE prophylaxis.(Kurtoglu M 2011).

The researcher claims that the study is the first clinical study designed to evaluate the applicability of a standard 'VTE prophylaxis and risk factor assessment form (VTE-PRAF)' and prescription of VTE prophylaxis among hospitalized patients in the daily practice of general surgeons in Turkey.

A total of 1472 patients (mean age: 52.4 ± 16.9 years; 50.6% were men) were included in cross-sectional (n = 537), first longitudinal (n = 452) or the second longitudinal (n = 483) phases. Data on demographics, hospitalization, surgical intervention and prophylaxis were collected during the cross-sectional phase, whereas utilization of form was evaluated during longitudinal phases.

They found that while 62.1% of patients were identified to be at 'high+ highest' risk, prophylaxis was evident only for 65.9%. Utilization of the form was higher in the second longitudinal phase ($P < 0.001$) but there was no relation between implementation of the form and prophylaxis use. VTE-PRAF was completed for 70.6% and 84.8% of patient who received prophylaxis while it was completed for 50.8% and 50.4% of patients with no prophylaxis, in the first and second longitudinal phases, respectively. Prophylaxis was administered in 58.6% and 62.6% of patients with completed VTE-PRAF in the first and second longitudinal phases, respectively. 'Suggested' and 'used' prophylaxis regimens were significantly more consistent for the cases evaluated with VTE-PRAF ($P< 0.001$).

In Conclusion researchers say based on the use of prophylaxis only for 65.9% of general surgery inpatients at high risk for VTE, low use of prophylaxis is assumed to remain a significant threat to public health across Turkey. Inclusion of a standard VTE-PRAF in the hospital protocol seems to raise clinical awareness of VTE risk assessment and appropriate management in VTE which otherwise well-known to be associated with significant mortality and morbidity. Impact of e-VTE-PRAF is worth investigating.

5. THE STUDY OBJECTIVE, AIMS, RATUIONAL, AND DESIGN

5.1 Objectives Aims and Rationale:

Clinical pharmacists are a primary source of scientifically valid information and advice regarding the safe, appropriate, and cost-effective use of medications having wide scope in drug Information and utilization, evaluation and selection medication therapy management and finally disease State Management, this made clinical pharmacists to have a wide efficient practice in many specialties in implementing rational drug use and optimizing the use of medications.

Worldwide, more than half of the hospitalized patients at high risk do not receive VTE prophylaxis. Accurate assessment of patient VTE risk is critical to improve this situation and increasing compliance with prophylaxis guidelines.

Most recent publications concluded that it may be more appropriate to use the individual risk assessment approach to identify and evaluate all possible risk factors to determine the true extent of risk for a patient and provide appropriate suggestions for prophylactic therapies according to the risk level.

More than Eleven different guidelines exist including both local and international ones for thromboprophylaxis from the following associations were included: The American College of Chest Physicians (ACCP) , the American Academy of Orthopaedic Surgeons (AAOS) , the Cardiovascular Disease Educational and Research Trust (ICS) , the National Institute for Clinical health and Excellence (NICE, United Kingdom), the Scottish Intercollegiate Guidelines Network (SIGN), Die Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF, Germany) , a Sociedade Brasileira de Angiologia e CirurgiaVascular (SBACV) , the South African Society of Thrombosis and Haemostasis , Medical Front International Limited (Japan) , the French Society for Anaesthesiology and Intensive Care (SFAR) and the Australia and New Zealand working party on the management and prevention of venous thromboembolism .

The importance of evaluating hospitalized patients for the risk of VTE has received considerable attention and will continue to be a major area of focus for the healthcare system in the coming decades. VTE is the most common form of preventable hospital death, causing more deaths annually in the US than breast cancer, AIDS, or motor vehicle accidents.

In spite of increasing evidence that a substantial proportion of patients admitted to departments of internal medicine show a high risk of venous thromboembolic (VTE) complications, the administration of thromboprophylaxis in these patients continues to be largely underused. There are two general approaches to making thromboprophylaxis decisions. One approach considers the risk of VTE in each patient, based on their individual predisposing factors and the risk associated with their current illness or procedure.

In order to help stratify the risk of VTE in hospitalized medical patients, Formal risk assessment models (RAMs) for DVT have been proposed to assist with this process Several individualized VTE risk assessment models (RAMs) have been proposed and evaluated clinically, the most notable being those developed by Caprini, Cohen, Kucher, etc.

The Caprini risk score is a risk assessment tool for the occurrence of venous thromboembolism among surgical patients first and later validated for other settings. The Caprini risk score includes 39 variables and it is derived from a prospective study of 538 general surgery patients.

The scoring system consists of a comprehensive list of risk factors that have been shown by evidence based publications to be associated with the development of deep vein thrombosis (DVT). Each risk factor is further classified according to the relative likelihood of causing a DVT compared to each other. Factors with a score of one are the least powerful causes of DVT compared to others with a higher point score. This intuitively correct approach to risk assessment has now been validated by comparing the patient scores to the proven DVT incidence in these individuals within 30 days of surgery. It is very important to identify all of the factors in a given patient since missing one or more factors may not identify the appropriate level of risk for the patient.

This tool and other interventions aid in rationalizing drug use and could be introduced by specialized clinical pharmacists' promoting optimum care health and wellbeing.

The role of the pharmacist in managing anticoagulant therapy is well established as new strategies have been developed for older anticoagulants, older beliefs have been challenged, new anticoagulants have been introduced, and new indications have been identified for existing anticoagulants, and clinicians have learned more about the critical importance of medication safety.

However Anticoagulants pharmacist is not a common practice in hospitals in Turkey and Turkish Republic of North Cyprus (TRNC) though currently pharmacy regulations and education in turkey and North Cyprus are shifting in favour of more clinical care based practice and education.

To our knowledge, at the time this thesis was prepared, the clinical pharmacy services introduced by master students at Near East University Hospital, was the only established clinical pharmacy practice all over Cyprus. The aim of this study is to evaluate current thromboprophylaxis practice at a university hospital in north Cyprus investigating management of patients in general ward having low risk medium, and high risk of developing DVT and determine the adherence to thrombo-prophylaxis guidelines and to assess rational prescribing of DVT prophylaxis medication in hospitalized patients thus to optimize care and assure rational practices.

The significance is to assess gaps in current management and patient care using assessment tools used by clinical pharmacists and compares that to current practice at hospitals in TRNC.so to optimize care and assure rational practices.

5.2 Materials and Methods

5.2.1 Subjects and setting:

The Study was carried out in the general ward from 01 February 2015, to 30 March, 2015 at Near East University Hospital, the largest and one of the leading medical facilities in Nicosia, Cyprus. It offers extensive medical services with its highly experienced specialist staff to patients from all over the world. The Hospital of Near East University has a 56,000 square-meter closed area comprising 209 private, single patient rooms, 8 operating theatres, 30-bed Intensive Care Unit, 17-bed Neonatal Intensive Care Unit and more than 30 different clinics and departments. The study is carried in the general ward including patients from cardiology, internal and geriatric clinics.

All inpatients admitted to general ward where included except some patients of physicians not intending to participate with their patients. 8 physicians' four consultants and four senior residents were in charge of the patients.

5.2.2 Study Design:

The Study is an observational prospective study carried at a tertiary university hospital for inpatients and documented over a period of two months. Patients where enrolled from the general ward with multiple pathologies and enrolled to investigate risk for thrombosis and observe rational use of thrombo-prophylaxis for inpatients in this healthcare settings using the Caprini's checklist for thrombosis risk assessment in adult hospitalized patients.

5.2.3 Data collection:

Patients data regarding presence of thrombosis risk factors were collected, documented and registered in a work sheet along with the involved patient information and current clinical status.

Specially designed forms were filled for each patient, collecting information of patient age; complain, medical history, family history, medications use history, presence of different levels of risk factors, labs taken during their hospital stay and medications given during their hospital stay and on discharge.

5.2.4 Risk assessment model

The RAM adopted in this study (The Caprini risk score) is a risk assessment tool for the occurrence of venous thromboembolism among hospitalised and surgical patients. The Caprini risk score includes 20 variables and it is validated and used world widely in many healthcare settings for DVT risk assessment. The scoring system consists of a comprehensive list of risk factors that have been shown by evidence based publications to be associated with the development of deep vein thrombosis (DVT). Each risk factor is further classified according to the relative likelihood of causing a DVT compared to each other. Factors with a score of one are the least powerful causes of DVT compared to others with a higher point score. By this it permits identification of all those conditions for which the latest international guidelines strongly recommend thromboprophylaxis.

5.2.5 Data analysis and validation:

Data analysis was performed using Statistical Package for Social Sciences (SPSS, version15). Descriptive statistics which examined DVT incidence were generated and were stratified by the level of risk and various risk factors. Chi-square test was used as appropriate for categorized data.

5.2.6 Ethical Considerations:

Confidentiality was assured during the study and also patient's privacy, a Letter of ethical clearance was submitted to the Institutional Review Board (IRB) of Near East University Hospital who assigned this research as being only observational study and thus regarded as not needing ethical approval. Only Initials were used during the study without recording patients address or other related not clinical important personal information.

6. Results:

45 patients were enrolled into the study; patients were enrolled from patients of three physicians from three clinics that accepted to carry the study, the clinics were cardiology internal and geriatric clinic, with an average age of patients 70.8 years a median of (71) and mode of (71). The average number of medications is almost 9 medications for each patient, nearly 53% of patients were males while 47% were females.Table 2 shows the main demographic and clinical characteristics of the study patients.

Table 3 shows stratification of levels of risk among sampled patients, of the 45 patients assessed, 68.88% of patients were identified as having moderate level of risk, and 24.4% patients were identified as having high level of risk, and only 4.45% and 2.22% with very low and low level of risk respectively.

The distribution of RAM items and risk factors among sampled patients is shown in Table 4 .The major risk factors identified in the sampled patients included Age 41-60 years (11.11%); Swollen legs (6.66%) Obesity (BMI>25) (2.22%); Serious lung disease including pneumonia (15.55%); Acute myocardial infarction (2.22%); Congestive heart failure (2.22%); Medical patient currently at bed rest (95.55%); Abnormal pulmonary function (COPD) (15.55%) Age 61-74 years (51.11%); Patient confined to bed (8.88%); Major surgery> 45 minutes (4.44%); Age 75 years or older (33.33%).

Thromboprophylaxis was provided rationally to only about 36% of patients who received adequate thromboprophylaxis, alone or associated with compression elastic stockings during the hospitalization period, while the remaining 64% either did not receive any form of prophylaxis (68% of irrational managed) or received inadequate prophylaxis (12%) (e.g. compression stockings alone or insufficient doses of Enoxaparin) while more than 20% took more thromboprophylaxis than indicated (either taking increased dose or taking medicine while only compression stockings indicated). 60% of high risk patients did not have enough thromboprophylaxis needing both compression devices and an antithrombotic agent. Table 7 shows proposed management for sampled patients according to their Caprini score.

No significant difference was present among genders in level of risk (Table 5). 33 Patients aged above 65 years 75% of them belonging to moderate risk group while other 25% were assigned high risk group which represent almost 3 quarters of total number of patients assigned to this risk category (table 6).

TABLE 2: Demographics, contraindications and rationality according to Caprini RAM			
Clinics	Cardio	İnternal	Geriatric
Number	n(20) (44.44%)	n(5) (11.11%)	n(20) (44.44%)
Average age		70.88	
Average number of drugs :		8.93	
Total number of patients		n(45)	
Rational managed cases		n(16) (35.55%)	
İrrational cases		n(29) (64.44%)	
Males		n(24) (53.33%)	
Females		n(21) (46.67%)	
Patients with no need for prophylaxis(total)	Contraindication	contraindication managed Rational	contraindication managed İrrational
n(2) (4.44%)	n(9) (20%)	n(8) (17.77%)	n(1) (2.22%)

TABLE 3: Stratification of levels of risk among sampled patients				
LEVEL OF RISK	A	B	C	D
	n(2) (4.45%)	n(1) (2.22%)	n(31) (71.11%)	n(10) (22.22%)
A: very low level of risk B: low level of risk C: moderate level of risk D: high level of				

TABLE 4 : Distribution of risk factors among sampled patients	
Name of risk factor	Number of patients have it
Age 41-60 years	n(5) (11.11%)
Swollen legs	n(3) (6.66%)
Obesity (BMI>25)	n(1) (2.22%)
Serious lung disease including pneumonia	n(7) (15.55%)
Acute myocardial infarction	n(1) (2.22%)
Congestive heart failure	n(1) (2.22%)
Medical patient currently at bed rest	n(43) (95.55%)
Abnormal pulmonary function (COPD)	n(7) (15.55%)
Age 61-74 years	n(23) (51.11%)
Patient confined to bed	n(4) (8.88%)
Major surgery> 45 minutes	n(2) (4.44%)
Age 75 years or older	n(15) (33.33%)

TABLE 5 : Stratification of levels of risk according to gender		
	Male	Female
A : very low level of risk	n(2) (8.33%)	n(0) (0%)
B: low level of risk	n(0) (0%)	n(1) (4.76%)
C: moderate level of risk	n(16) (66.66%)	n(15) (71.43%)
D: high level of risk	n(6) (25%)	n(5) (23.80%)
Note :the percentage taken from total number of male or female not from the total number of patients		

TABLE 6: Stratification of levels of risk according to age groups			
	Under 50	50-64	Above 65
A	n(2) (4.45%)	n(0) (0%)	n(0) (0%)
B	n(0) (0%)	n(1) (2.22%)	n(0) (0%)
C	n(1) (2.22%)	n(6) (13.33%)	n(25) (55.55%)
D	n(0) (0%)	n(2) (4.45%)	n(8) (17.78%)

TABLE 7 : Proposed management for sampled patients according to their Caprini score		
Rational	n(16)	(35.55%)
SCD only	n(1)	(2.22%)
Medication	n(11)	(24.44%)
Medication + SCD	n(7)	(15.55%)
Needs for SCD even with presence of medication	n(1)	(2.22%)
Increase dose	n(1)	(2.22%)
Decrease dose	n(6)	(13.35%)
Decrease dose + needs for SCD	n(2)	(4.45%)

-Patient with contraindication were significantly more managed rationally than patients with no contraindication (p=0.000)

-while elderly patient 65 and more had less chance of over dosing, younger patients less than 65 had higher chances of being over dosed that may lead to bleeding chances (p=0.016)

-No significant difference was found between males and females in rational management (p=0.360), and nor in proposed type of management (p=1.000)

7. Discussion:

Venous thromboembolism is the most common preventable cause of death in surgical patients. Thromboprophylaxis, using mechanical methods to promote venous outflow from the legs and antithrombotic drugs, provides the most effective means of reducing morbidity and mortality in these patients. Thromboprophylaxis is, therefore, the most effective strategy to reduce morbidity and mortality from VTE in high risk patients (O'Donnell M, Weitz JI 2003). Despite this it remains underused because physicians perceive that the risk of venous thromboembolism is not high enough to justify the potential hemorrhagic complications of anticoagulant use (O'Donnell M, Weitz JI 2003). The risk of venous thromboembolism is determined by patient characteristics, clinical state and intended operation. Appropriate selection of hospitalized medical patients for VTE prophylaxis is an important unresolved issue. The simple 40-point RAM adopted at our study clearly discriminated between hospitalized medical patients at high and low risk of VTE complications.

Indeed, after introducing the RAM to patients of three clinics, cardiology, internal and geriatrics, rationally managed cases were about 36% of patients who received adequate thromboprophylaxis, alone or associated with compression elastic stockings during the hospitalization period, while the remaining 64% were identified irrational either due not receiving any form of prophylaxis (68% of irrational managed) or received inadequate prophylaxis (12%) while more than 20% took more thromboprophylaxis than indicated , these findings are important though less compared to other researchers in other countries who found that adherence to DVT prophylaxis at hospitals to be extremely low where 85 % of patients at risk did not received recommended therapy, and even patients with very high risk received treatment in less than 25 % of the cases compared to 40 % in our study. Also in turkey researchers found that venous thromboembolism-risk was observed in

64.9% of surgical and 23.8% of medical patients, and prophylaxis was prescribed in 39.0% and 38.5% of them respectively, which almost resembles our study findings.
As a result, the majority of both fatal and non-fatal PE episodes that are nowadays encountered in clinical practice arise in medical settings (Cohen AT et al., 2007)

Other studies in turkey reported that contraindication to anticoagulant prophylaxis was observed in 8.7% of medical and 8.8% of surgical patients while we identified 20% in which almost 90% were not given thromboprophylaxis while 10% were provided though contraindicated proposing these patients to a high risk of bleeding.

Our findings show how Caprini RAM have the potential to identify virtually all those medical patients for whom the latest international guidelines strongly recommend thromboprophylaxis and also aid in guiding therapy in hospitalized patients who are world widely under treated as reported by many researchers, this approach we used can lead to a definitely higher degree of protection against thromboembolic complications and on the same time without any apparent increase in the bleeding risk but instead also it helps in identification of groups that thromboprophylaxis doesn't suit.

Mis dosing was also one of the errors we found in the sampled group, more than 17% of the patients were taking higher doses of anticoagulants than what they need, anticoagulants misuse can lead to complications that range between nosebleeds ,blood in urine or tarry stools ,or may precede to bruising or petechial formations followed by frank bleeding. Thus correct prophylaxis doses should be administered as shown in table 8.

TABLE 8 prophylaxis doses	
Drug	Thromboprophylaxis doses
Unfractionated heparin (UFH)	• SubQ 5000 units every 8-12 hours
Enoxaparin (Lovenox) (Clexane)	• SubQ 40mg once daily (6-11 days). • Abdominal surgery 40 mg once daily with initial dose within given 2 hours prior tosurgery • knee replacement surgery : 30 mg every 12 hours • BMI > 40 increasing the prophylactic dose by 30%.
Dalteparin (Fragmin)	• Immobility during acute illness: 5000 units daily. • Low to moderate DVT risk: 2500 units 1-2 hours prior surgery then once daily for 5 -10 days. • High DVT risk: 5000 units prior surgery then once daily for 5 -10 days.
Fondaparinux sodium (Arixtra)	• 2.5 mg subcutaneously once daily starting 6 to 8 hours after surgery.
Recommended doses of anticoagulants for thromboprophylaxis. Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; June 10, 2015	

Our findings are fully consistent with other national and international reports, and confirm that, despite present evidence suggesting the strong advantage of thromboprophylaxis in high-risk medical patients (Lansberg MG et al., 2012), this practice continues to be largely under-implemented. (Chopard P et al.,2005- Goldhaber SZ et al.,2000- Cohen AT et al 2008- Tapson VF et al.,2007- Kucher N et al., 2009)

Adoption of electronic tools was found to be effective in encouraging physicians to use prophylaxis at least amongst subgroups of patients at high risk of thrombotic complications. (Kucher N et al., 2005 - Lecumberri R et al., 2008)

Electronic alerting systems, however, require sophisticated technology infrastructure and considerable financial resources, and are thus unlikely to find widespread acceptance while clinical pharmacists at hospitals , being a primary source of scientifically valid information and advice regarding the safe, appropriate, and cost-effective use of medications having wide scope in drug therapy management and optimization using evidence based tools and recommendation can utilize RAMs such as the Caprini checklist a self-explanatory, easy, suitable and effective RAM as shown in multiple literature (Caprini JA. 2010) and has the potential to aid clinicians in managing their patients without the need for supplementary electronic tools, and may result in rational implementation of antithrombotic prophylaxis in hospitals.

The pharmacist's role in managing anticoagulation therapy in the inpatient setting has also been established. An evaluation of over 700 000 Medicare patients from almost 1000 hospitals found that those without pharmacy-directed heparin and warfarin management had higher mortality rates, length of stay, Medicare charges, bleeding rates, and transfusion requirements. Pharmacy-managed anticoagulant therapy improves the quality and safety of such therapy in the inpatient and outpatient setting.(Bond CA, Raehl CL 2004)

Strengths and limitations

The strength of our investigation lies in that beside of being the first of its kind in North Cyprus and Turkey, the tool used is a world widely well validated and adopted, the RAM we used in this study has a scoring system that identifies all those medical conditions for which the latest international guidelines strongly recommend thromboprophylaxis (Lansberg MG et al., 2012). Clinical pharmacists in managing and guiding therapy have the advantage of being drug experts specialized in rationalizing drug use and thus can largely attribute in guiding anticoagulant therapy which is not yet evaluated in Turkey and North Cyprus. Patients were recruited in this study from multiple clinics served by more than 15 physicians, while the study findings were comparable to others carried elsewhere in china, Mexico, Europe and Turkey.

Also a few study limitations deserve attention. Firstly and most importantly, patients were not followed up for complications post hospital discharge , the numbers sampled also were few compared to the numbers enrolled in other comparable studies ,this could be overcome in the future by recruiting patients also from other centers in Turkey and North Cyprus so to achieve more precision and validity for our findings.

Future studies should be carried in multi settings including surgery, patients could be recruited from multi centers, a pharmacist interventional arm should be compared to usual care, patients should be followed post hospitalization for three months to follow up complications of VTE development or bleeding, also VTE could be diagnosed and confirmed using diagnostic procedures for identifying VTE beside clinical signs and symptoms to assure more surrogate endpoints.

8. Conclusion

In conclusion, our results suggest that that the Caprini risk assessment model is a practical and effective tool to assess the risk of VTE among hospitalized patients in North Cyprus , findings of the study show that as globally reported, adherence to VTE prophylaxis at hospitals to be extremely low and that despite present evidence suggesting the strong advantage of thromboprophylaxis in high-risk medical patients; this practice continues to be largely under-implemented and clinical pharmacists at hospitals , being a primary source of scientifically valid information and advice regarding the safe, appropriate, and cost-effective use of medications can utilize RAMs such as the Caprini checklist and thus aid clinicians in rational implementation of antithrombotic prophylaxis in hospitals.

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Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Swollen legs (current)
- ❑ Varicose veins
- ❑ Obesity (BMI >25)
- ❑ Minor surgery planned
- ❑ Sepsis (<1 month)
- ❑ Acute myocardial infarction
- ❑ Congestive heart failure (<1 month)
- ❑ Medical patient currently at bed rest
- ❑ History of inflammatory bowel disease
- ❑ History of prior major surgery (<1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Serious Lung disease including pneumonia (<1 month)
- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant
- ❑ Other risk factors_____

Subtotal:

Each Risk Factor Represents 2 Points

- ❑ Age 61-74 years
- ❑ Arthroscopic surgery
- ❑ Malignancy (present or previous)
- ❑ Laparoscopic surgery (>45 minutes)
- ❑ Patient confined to bed (>72 hours)
- ❑ Immobilizing plaster cast (<1 month)
- ❑ Central venous access
- ❑ Major surgery (>45 minutes)

Subtotal:

Each Risk Factor Represents 3 Points

- ❑ Age 75 years or older
- ❑ History of DVT/PE
- ❑ Positive Factor V Leiden
- ❑ Elevated serum homocysteine
- ❑ Heparin-induced thrombocytopenia (HIT)
  (Do not use heparin or any low molecular weight heparin)
- ❑ Elevated anticardiolipin antibodies
- ❑ Other congenital or acquired thrombophilia

If yes: Type_____

- ❑ **Family History of thrombosis***
- ❑ Positive Prothrombin 20210A
- ❑ Positive Lupus anticoagulant

Subtotal:

* **most frequently missed risk factor**

Each Risk Factor Represents 5 Points

- ❑ Stroke (<1 month)
- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (<1 month)
- ❑ Acute spinal cord injury (paralysis) (<1 month)
- ❑ Multiple trauma (<1 month)

Subtotal:

TOTAL RISK FACTOR SCORE:

FACTORS ASSOCIATED WITH INCREASED BLEEDING

Patient may not be a candidate for anticoagulant therapy & SCDs should be considered.

Active Bleed, Ingestion of Oral Anticoagulants, Administration of glycoprotein IIb/IIIa inhibitors, History of heparin induced thrombocytopenia

CLINICAL CONSIDERATIONS FOR THE USE OF SEQUENTIAL COMPRESSION DEVICES (SCD)

Patient may not be a candidate for SCDs & alternative prophylactic measures should be considered.

Patients with Severe Peripheral Arterial Disease, CHF, Acute Superficial DVT

Total Risk Factor Score	Risk Level	Prophylaxis Regimen
0	VERY LOW	❑ Early ambulation
1-2	LOW	❑ Sequential Compression Device (SCD)
3-4	MODERATE	Choose **ONE** of the following medications +/- compression devices: ❑ Sequential Compression Device (SCD) - Optional ❑ Heparin 5000 units SQ TID ❑ Enoxaparin/Lovenox: ❑ 40mg SQ daily (WT < 150kg, CrCl > 30mL/min) ❑ 30mg SQ daily (WT < 150kg, CrCl = 10-29mL/min) ❑ 30mg SQ BID (WT > 150kg, CrCl > 30mL/min) (Please refer to Dosing Guidelines on the back of this form)
5 or more	HIGH	Choose **ONE** of the following medications **PLUS** compression devices: ❑ Sequential Compression Device (SCD) ❑ Heparin 5000 units SQ TID **(Preferred with Epidurals)** ❑ Enoxaparin/Lovenox **(Preferred)**: ❑ 40mg SQ daily (WT < 150kg, CrCl > 30mL/min) ❑ 30mg SQ daily (WT < 150kg, CrCl = 10-29mL/min) ❑ 30mg SQ BID (WT > 150kg, CrCl > 30mL/min) (Please refer to Dosing Guidelines on the back of this form)