Thromboprophylaxis: medical recommendations and hospital programs

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Abstract

Venous thromboembolism (VTE) is the most preventable cause of in-hospital death. Hospital-related VTE is associated with over 50% of VTE episodes occurring either during or after hospitalization. Selective thromboprophylaxis is the recommended approach for inpatients. Patient selection for thromboprophylaxis requires VTE risk stratification, including either the baseline disease plus additional risk factors or risk assessment standardized models (RAM). Risk categories guide the thromboprophylaxis selection to include general, mechanical, pharmacological, or combination measures. Although thromboprophylactic protocols have been available for decades, many patients at risk (20% to 75%) still do not receive the recommended thromboprophylaxis. This study purpose is to alert to the relevance of thromboprophylaxis and to guide the strategies to arrange hospital thromboprophylaxis programs in Brazilian settings.

Keywords: Venous thromboembolism; risk factors; hospitalization; primary prevention.

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Introduction

Venous thromboembolism (VTE) comprises both deep venous thrombosis (DVT) and pulmonary embolism (PE)[1-6]. VTE is the main preventable cause of in-hospital death, and venous thromboprophylaxis is the initial strategy to improve safety of hospitalized patients[7,8]. However, even after decades of disclosure of thromboprophylactic regimens, a significant proportion of patients at thromboembolic risk does not receive thromboprophylaxis during hospitalization[9-12]. VTE diagnosis in hospitalized patients might require clinical search for a second disease in a patient already ill, new tests and differential diagnoses, extended hospitalization, among other problems[8,13,14]. Over a half thromboembolic events occurring in the community are associated with hospitalization or previous institutionalizations[15]. This study purpose is to discuss the need for implementing hospital thromboprophylaxis prevention programs and explain the principles of current thromboprophylactic recommendations.

Terminology definitions

Venous thrombosis results from the process of thrombi formation within the veins. In most cases, venous thrombosis develops in lower limbs, more precisely in the drainage area between deep muscles and thus is called DVT. The cut-off point for the affected area location is the highest level the thrombus has reached, being proximal when it goes beyond the popliteal region and distal if it is confined to the calf. Over DVT course, a thrombus ascending extension to the popliteal region and/or to the groin (proximal extension) can occur[14,16-18]. In the thrombus extension phase, the clot is friable and could break up, creating fragments (emboli). Thrombus migration to the lung could block the pulmonary artery or its branches, leading to PE[14,16-18]. The PE localization will be central, segmentar or subsegmentar, according to the most proximal affected extremity[19]. Both processes, DVT and PE, by being continuous from a pathological perspective, can be grouped as VTE[18,20]. The preventive measures for VTE are termed thromboprophylaxis or venous thromboprophylaxis[13].

Patients suffering from a VTE episode have a high recurrence risk and the possibility of late complications, such as post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH). The risk for thromboembolic recurrence is higher over the first months following the initial event, being 7% to 14% over the first three months and up to 30% within eight years[21-23]. PTS is characterized by chronic swelling of the affected leg, venous valvular function loss, cutaneous discoloration and ulceration. PTS affects 2% to 10% of patients suffering from VTE, and may develop in up to 10 years after VTE until becoming clinically detectable[17,24]. On the other hand, up to 4% of patients with VTE can develop CTEPH over the first 2 years from the initial embolic event[25]. These complications reduce the quality of life and are associated with morbidity, resulting in economic burden for the health system[26].

Venous thromboembolism diagnosis

Generally, patients with DVT present with a painful or sore venous area, erythema or swelling in the affected limb. Physical examination enables the identification of palpable venous chords representing a thrombosed vein or a superficial vein dilatation. Differential diagnosis of DVT includes ruptured Baker's cyst, muscular and tendinous tears, infeccious cellulites, among others[17-18]. The purely clinical diagnosis of DVT, based on signs and symptoms, is inaccurate and insensitive, with only one-third or less of clinical suspicion being confirmed through imaging studies[18,27]. A meta-analysis of a clinical evaluation to diagnose DVT showed that confirmation is more frequent in the presence of malignity [likelihood rate (LR) = 2.7], previous VTE (LR = 2.3), recent immobilization (LR = 2.0), recent surgery (LR = 1.8) and calf circumference difference (LR = 1.8). On the other hand, only the absence of swelling (LR = 0.7) and the difference between calf circumference (LR = 0.6) contributed to rule out DVT diagnosis[28].

Patients with suspect DVT can be evaluated by the application of clinical probability models. The probabilistic modeling helps to guide medical management according to the clinical probability calculated[18,29].

Until very recently, contrast-enhanced phlebography was considered the gold standard of DVT diagnosis. However, apart from being an invasive test, phlebography still requires a trained practicioner to be done, and this practitioner is seldom available in emergency rooms even in hospitals. Still, phlebography cannot be repeated many times to monitor the developmento of DVT. In a significant ratio of symptomatic patients, podal vein puncture for contrast medium injection is not feasible because of swelling, pain, or difficult approach[16]. Another possible problem of phlebography is that it can not visualize the distal venous system, or detect clinically insignificant thrombi[16].

Alternative studies for DVT tracking include radionuclide imaging with labeled fibrinogen and venous ultrasound. Both present low sensitivity to distal DVT[16]. Meta-analysis of orthopedic patients applying isotope methods shows 45% sensitivity for lower limb DVT and 92% especificity[16].

Duplex ultrasonography scan presents 39% sensitivity and 98% specificity in symptomatic hospitalized patients. In patients undergoing arthroplasty, the numbers decrease to 13% and 92%, respectively[16]. The ultrasound test performance in defining symptomatic DVT is better in proximal DVT[30].

The computed tomography phlebography shows similar results to ultrasound tests in DVT concerning clinical significance. In hospitals, the diagnostic imaging

technique chosen for DVT usually follows criteria of patient safety, cost of diagnostic technique, and time to have the exam done[16].

Over the last decade, laboratory tests to detect D-dimers (DD) in the diagnostic strategy of DVT were introduced. This measure goal was to improve the accuracy of noninvasive clinical diagnostic strategy. DD test can be especially useful when there is a low clinical probability of DVT for a patient. In this setting, a negative result indicates a low clinical probability of DVT, which is sufficient to exclude the diagnosis, even in the absence of an imaging study. However, as it is poorly specific, positive results can occur in postoperative states, severe infections, and neoplasms, even in the absence of VTE[18,27,31]. Even the Wells' model of structured clinical rules for DVT alone is inappropriate to define or exclude the DVT diagnosis. However, this model is accurate and safe enough to guide the subsequent diagnostic procedure[27,32]. Thus, excluding DVT diagnostic can be possible in certain clinical circumstances without resorting to an imaging study.

DD test can also be useful in patients with high clinical probability of DVT and ultrasound negative results. In this case, a negative DD test would avoid a repeated assessment by imaging studies the following weeks. These strategies are economically sparing and assure diagnostic safety for the patient[27,32]. Variations of DD laboratorial performance can allow patients in a intermediate risk category to have DVT diagnosis excluded without undergoing imaging studies[29]. However, only imaging studies usually can confirm the diagnosis, especially lower limb ultrasonography[27,32].

Clinically, PE may present a clinical condition of sudden dyspnea, occasionally associated with hemoptysis, pleuritic chest pain, arterial hypotension or, in extreme cases, circulatory shock resulting from acute right heart failure. The most prevalent PE symptoms are dyspnea (present in 73% of patients), pleuritic pain (69%) and cough (37%). The most important signs are tachypnea (70%), rales (51%), and tachycardia (30%). Cardiorespiratory arrest and circulatory collapse can develop in severe cases. Electrocardiographic signs include sinus tachycardia and, less often, atrial fibrillation, right bundle-branch block or other right ventricular strain findings, such as a $S_1Q_3L_3$ pattern. In a meta-analysis of PE diagnostic clinical evaluation, syncope alone (LR = 2.4), shock (LR=4.1), thrombophlebitis (LR=2.2), concomitant DVT (LR=2.1), lower limb swelling (LR=2.1), sudden dyspnea (LR=1.8), active neoplasm (LR=1.7), recent surgery (LR=1.6), hemoptysis (LR=1.6), and lower limb pain (LR=1.6) showed to be valuable for confirming PE. On the other hand, the absence of sudden dyspnea (LR=0.4) and the absence of any dyspnea (LR=0.5) or tachypnea (LR=0.6) contribute to rule out DVT[33].

Patients with suspect PE represent a medical urgency due to high mortality and morbidity related. Many patients do not present DVT symptoms in lower limbs, although conversely many symptomatic DVTs are associated with asymptomatic PE. Similarly to DVT, PE models of clinical probability were developed to help the diagnostic approach[1-3,18,34,35].

Pulmonary angiography is the gold standard test to diagnose PE, although it is an invasive procedure associated with increased morbidity and mortality.[36]

Pulmonary scan is a more widespread diagnostic procedure and traditionally constitutes an objective study to diagnose PE. A normal pulmonary scan practically rules out PE. However, PE could be present in cases of low- or intermediate probability pulmonary scan. In this context, other exams can be required. Excluding low- or intermediate probability patients, a high probability pulmonary scan sensitivity is 77.4%, while a normal or low probabilility pulmonary scan specificity is 97.7%. The percentage of patients with confirmed or ruled out diagnosis using pulmonary scan is 73.5%[37].

Recently, the pulmonary spiral computed tomography (multislice pulmonary helical computed tomography or computed angiotomography), by employing contrast media, gained acceptance in diagnosing PE, as it has the advantage of evaluating other pulmonary structures and other thoracic organs at the same time it evaluates the possibility of PE[18,27,31].

The pulmonary scan was not considered an inferior diagnostic method compared to angiotomography[38]. Meta-analysis by Hayashino *et al.*[39] suggested the angiotomography presents higher discriminatory power to rule out PE compared to pulmonary scan in patients with low PE probability. On the other hand, in patients with high PE probability, the methods seem equivalent[39].

A meta-analysis studying PE diagnosis calculated positive LRs in 18.3 for high probability pulmonary scan and 24.1 for pulmonary angiotomography ,16.0 for lower limb ultrasonography. The negative LR for normal pulmonary scan was 0.05. For negative pulmonary angiotomography and negative ultrasonography, the negative LR is 0.04 for both. A DD result below 500 mg/L presents negative LR 0.08.[35] The diagnostic approach to PE can be directed to the different categories of clinical risks, with later definition of diagnostic procedure[1-3,34,35].

Venous thromboembolism epidemiology

VTE is a public health matter. In the United States there are at least 200,000 new cases diagnosed annually[40]. The annual incidence in the United States is calculated as one case per 1,000 in the population, with one-third corresponding to PE.[4] In Europe, the annual estimates of symptomatic VTE incidence are 1.48 cases per 1,000 population for DTV and 0.95 per 1,000 population for PE[20].

VTE occurs in community patients (primary care level), but it is much more prevalent in hospitalized patients (tertiary care level). Sixty to 70% of all VTE population burden is estimated as being associated with hospitalization[15,34,41,42]. Although most medical studies of VTE in hospitalized patients focus the patient status during hospitalization, the fact that the patient has been hospitalized is, per se, a risk factor for VTE after discharge, with most symptomatic VTEs associated with hospitalizations occurring after discharge[13,42,43]. Some studies show VTE after discharge is up to three times as frequent as during hospitalization[43]. Although many authors define thromboembolic risk is higher within 4 weeks from hospitalization, this risk can persist for up to 3 months[42,43]. Thus, the separation between hospital-acquired VTE and community-acquired VTE is to some extent artificial[43].

Although VTE risk during hospitalization is historically associated with surgical complications, more than a half (50% to 75%) fatal hospital thromboembolic events occur in medical patients, since their number is superior to that of surgical patients[44-46]. In 2003, for instance, from 38 million hospital discharges from departments of medical urgencies in the United States, 24 million were medical hospitalizations while 8 million were surgical hospitalizations.

Surgical procedures increase VTE risk, with an OR of 21.7[22]. Even in gynecological surgeries, OR can reach a value of 11[22]. The length of surgery is to be considered, with an operative time longer than 30 minutes seeming to be the cut-off value for thromboembolic risk definition[17]. The surgical procedures performed under general anesthesia have a two-fold higher thrombotic risk, compared to epidural and spinal anesthesia[17].

Between 40% and 80% of patients hospitalized for major orthopedic surgery receiving no prophylaxis present with documented thromboembolic events. Up to 10% of these patients have fatal PE[17]. But the VTE incidence in hospitalized patients in medical or general surgery unities varies from 10% to 40% in the absence of thromboprophylaxis[8]. Similar proportions are found in patients after a stroke. Up to a quarter of patients with an acute myocardial infarction may suffer VTE with no thromboprophylaxis[18]. When patients are grouped by clinics and they are given no thromboprophylaxis, VTE risk can be considerable, as it is demonstrated in Table 1.

Among hospital discharges in 944 intensive care unities in the United States, postoperative VTE has been the second leading cause for complications and the third leading cause for mortality and excess cost[8]. After adjusting for comorbidities, survival after PE is three months shorter than after DVT[47].

In the United Kingdom, VTE is associated with the death of 25,000 to 32,000 inpatients annually and is the immediate cause of death in 10% of all patients who die in hospital[14]. In one-fifth or VTE patients, the clinical events will develop so rapidly that no medical intervention can be allowed[40]. In about 70% to 80% of patients dying in a hospital as a result of PE, this initial diagnosis was not considered prior to death[13].

Table 1 – Venous thromboembolism risk for patients admitted to hospital wards for different medical conditions without thromboprophylaxis[8,13]

Hospital ward	Venous thromboembolism incidence (%)
Medical clinic	10 to 20
General Surgery	15 to 40
Major gynecologic surgery	15 to 40
Neurosurgery	15 to 40
Stroke	20 to 50
Hip or knee replacement	40 to 60
Major trauma	40 to 80
Spinal cord injury	60 to 80
Intensive Care	10 to 80

In a postmortem study with 1,234 patients dying up to 30 days after a surgery, PE proportion was 32%, with PE being considered death cause in 29% of PE patients[13]. Risk factors for early mortality in hospitalized patients include recurrent episode of PE, old age, neoplasm, and underlying cardiovascular disease[18]. Despite the advances in care and the reduced length of stay in the hospital contribute to mitigate some of the VTE risk factors, inpatients currently may present higher VTE risk than in the past because of the current population older age. The population aging favors increased neoplasm prevalence, more intensive antineoplastic therapies, more extended and complex surgical procedures, and ultimately longer stays in hospital[13].

It is simplest to define clinically the patients at risk for VTE than identifying asymptomatic DVT and PE in hospitalized patients with other diseases. VTE is a clinically difficult secondary diagnosis, remaining occult or being diagnosed as another disease, such as cellulitis, venous insufficiency, tendinitis, pneumonia, myocardial infarction, and viral pleurisy among others[43]. Although venous thromboprophylaxis studies use accurate diagnostic strategies, most events are caused by distal DVT often silent. In 10% to 20% of patients with distal DVT, a thrombus proximal extension occurs. There is an association between asymptomatic DVT and later development of symptomatic PE. Thus, even asymptomatic DVT cases require clinical care[13].

VTE is a clinical condition of high cost to health systems. Most patients require one or more imaging diagnostic studies, treatment with injectable anticoagulant drugs, such as unfractionated heparin (UFH) or low molecular weight heparins (LMWH), and a potentially long stay in the hospital[48]. After hospital discharge, the patient will still use oral anticoagulant for a varying period, depending on the event clinical circumstance[49]. There is still the possibility of recurrence and sequels, such as PTS and CTEPH[49].

In 1993, the annual burden in the United Kingdom from postsurgical VTE therapy was 223 million pounds[14]. The total annual cost both direct and indirect from VTE treatment is estimated at 640 million pounds[14]. In the United States, the annual expenditures with each VTE event vary from US$7,594 to US$16,644[26].

Venous thromboembolism risk factors

Different VTE risk factors can lead to a hypercoagulable or prothrombotic state, to a vascular pooling or to venous endothelium damage, as described in Virchow's triad[18]. VTE episodes can be elicited by risk (physiological or pathological) situations or associated diseases (secondary VTE) or be unrelated to any condition (idiopathic VTE). VTE risk factors are identified in 50% to 75% of inpatients, with about 40% of them presenting three or more risk factors[8].

Age-associated VTE risk is similar to an exponential function, varying from one event per 10,000 people/year in patients under 40 years to one event per 1,000 people/year at the seventh decade. Above 80 years of age, the risk can increase to one in 100 patients-year[17]. The mean VTE diagnosis age is 62 years old, with 44% presenting PE and 14% DVT-associated PE[50]. The PE proportion among those having VTE increases with age in males and females. TVE risk is growing important as a public health issue due to population aging.

There seems to be a VTE incidence variation according to ethnicity. Some studies suggest a higher VTE incidence in Caucasians and in Afro-descendants, with an intermediate incidence among Hispanics and a low incidence in Asians[40].

Another risk factor is malignancy. Up to 20% of community-acquired VTE are associated to neoplasms[8]. Cancer and VTE association can be caused by antineoplastic surgeries, immobilization, chemotherapy use, hormone therapy use, central catheter implants, and bedridden condition[8]. Often, a neoplasm is still occult at the moment VTE occurs, being detected only during clinical follow-up (paraneoplastic syndrome). The main malignancies associated with VTE are hematological, renal, ovarian, pancreatic, gastrointestinal and pulmonary in nature[18]. OR values between 2 and 9 are representative of the association between VTE and malignancy[22,51].

VTE risk is higher in patients with hereditary thrombophilias, including several hemostatic defects, such as activated protein C resistance, natural anticoagulant deficiencies, such as protein S, C, and antithrombin, and prothrombotic mutations known as factor V Leiden and prothrombin gene *G20210A* mutation[17,18,52,53]. Acquired thrombophilias, such as the antiphospholipid syndrome, characterized by the presence of antiphospholipid antibodies – lupus anticoagulant and anticardiolipin antibodies – are also associated with higher VTE risk[17,18,52,53]. Other determinants less evaluated clinically, include increased factor VIII, fribinogen, factor IX, factor XI, and homocysteine levels among others[18,53]. The magnitude of the association between VTE and thrombophilia, in OR, varies between 2 and 9[51].

Obesity, defined as body mass index above 30 kg/m^2, increases VTE risk by up to three times. This increase may be due to immobilization or coagulation activation[17,51].

Varicose veins increase VTE risk by 1.5 times when associated with major surgeries or large orthopedic surgeries (hip and knee replacement, hip fracture surgery). However, risk seems to be reduced in patients undergoing varicose vein repair surgery[17]. Another study suggested the presence of varicose veins is a relatively low-risk factor, with OR below 2[51].

Immobilization due to lower limb paralysis, casts or bed confinement for longer than three days increases thrombotic risk up to ten times, with a cumulative effect in time[17]. In other studies, a long bedridden condition was considered a relatively low-risk factor, with OR < 2. Lower limb paralysis associated with a neurological condition, on the other hand, has an OR of approximately 3[22,51]. There is an increased VTE risk with an OR < 2 in individuals who remain seated for a long time, such as in long air travel[51].

Severe trauma and spinal cord injury increase VTE risk by over 10 times[22,51].

Other risk factors include congestive heart failure, early period (three weeks) after acute myocardial infarction and stroke, in addition to severe infections, polycythemia, multiple myeloma, chronic inflammatory bowel diseases (ulcerative retocolitis or ileitis), nephrotic syndrome among others[17,51].

Pregnancy, specially the postpartum period, increases thrombotic risk by 2 to 20 times[22,51,54]. Combined oral contraceptives, hormone replacement therapy, raloxifene, and tamoxifen increase thromboembolic risk by three times. There is no evidence that low-dose progestogens used alone as contraceptives favor VTE[17].

Acute medical disease, such as respiratory insufficiency and congestive heart failure, increase thrombotic risk by up to 10 times[17,51]. A previous VTE is also an important thromboembolic risk factor, with OR between 2 and 9[51]. There also seems to be an associations between thrombophlebitis and VTE, with a population study indicating OR 4.5[22]. Indwelling central vein catheter and pacemaker insertion are associated with venous thromboembolic risk, with OR 5.6[22].

Thromboembolic risk stratification in hospitalized patients

Fatal PE prevention should not be the only thromboprophylaxis purpose, with proximal or distal DVT and PE prevention being important additional purposes, whether they are symptomatic or not, because of their morbidity, cost, and hospital length of stay[8].

The thromboprophylaxis recommendation in hospitalized patients is based on studies monitoring asymptomatic and symptomatic DVT occurrence. Profound DVT, identified by imaging study in screening risk groups, has an incidence 10 to 30-fold higher than that found in symptomatic DVT studies[55]. Such a result tends to overrate thromboprophylaxis cost-effectiveness and benefits. Based on symptomatic patient studies, the number necessary to avoid a VTE is high, i.e., ranging from 150 to 1,600, and the cost-effectiveness ratio is unreliable[55]. On the other hand, although the number of VTE cases grows quite a lot by including asymptomatic cases, the clinical significance of asymptomatic VTE prevention is unknown[16]. The inclusion of asymptomatic DVT as an endpoint in thromboprophylaxis studies has been rejected specially in orthopedic surgeries due to the discrepancy between DVT phlebographic prevalence and the low risk for symptomatic VTE, even in high thromboembolic risk patients[17]. The Scottish Intercollegiate Guideline Network (SIGN) claims that reducing asymptomatic DVT also reduces symptomatic DVT, asymptomatic and symptomatic PE, including fatal PE[17].

VTE risk factors can be basically grouped in two ways. The most usual way is grouping risk factors into risk categories, i.e., inpatients, defined conditions, medical wards or surgical wards[8,13]. This process, in surgical patients, involves risk factors allocation into three or four risk categories based on surgery type (e.g., minor or major surgery), patient's age (adult or elderly), presence of additional risk factors (e.g., neoplasm, trauma, comorbidity or previous VTE, among others). There is great variability among different proposals and even among thromboprophylactic regimens[14,50]. Even after identification of TVE group risks, it is not possible to predict the individual patient in any risk group who will develop the thromboembolic event[13].

The recommendations from the 8th American College of Chest Physicians (ACCP) Consensus Conference support this approach[8,13]. In short, the classification of low thromboembolic risk patients includes those undergoing minor surgeries or patients with medical conditions, but entirely ambulatory. Intermediate (moderate)-risk patients comprise those undergoing open general, gynecologic or urologic surgeries, and medical patients with restricted mobility with no free ambulation. High-risk patients include those undergoing a major orthopedic surgery, multiple trauma cases, and those with spinal cord injury[8,13]. This approach has been suggested and updated for many years, but the attending physicians have not adhered to it[10-12,56,57].

The other approach used for thromboprophylaxis in hospitalized patients is the generation of formal models to assess VTE risk. This approach is standardized and assesses a list of risk factors in all patients. Thromboembolic risk factors are then grouped into risk categories and thromboprophylaxis is suggested for each risk category. This approach is more difficult to implant than the previous one, as it requires information technology or systematic organization of patients' information flow. Many argue that this approach has not been formally tested and that there is no formal understanding about interaction among several risk factors to define the patient status inside the thromboembolic risk spectrum. Another argument against this approach is that the individual prophylactic strategy has not undergone strict clinical assessment, with risk individualization being logistically complex[8,13].

The development of either local or nationwide clinical recommendations for thromboprophylaxis has still been controversial. However, the use of specific updated recommendations for thromboprophylaxis is suggested for every hospital care setting[10,17,56,57]. Table 2 summarizes the main pharmacological thromboprophylaxis regimens.

Table 2 – Recommendation of heparin thromboprophylactic regimen for medical and surgical inpatients[40]

Heparin type	Regimen
Unfractionated heparin	3,500 to 5,000 units SC q8 or 12h or 7,500 units SC q12h
Low molecular weight heparin	
Enoxaparin	30 mg SC q12h starting 12 to 24h before the surgery or 40 mg/day SC starting 10 to 12h before the surgery
Dalteparin	5,000 units SC starting 12h before the surgery
Nadroparin	40 U anti Xa/kg SC for 3 days starting 2h before the surgery and then 60 units anti Xa/kg SC for day

SC: subcutaneous route.

International studies on thromboprophylaxis

Endorse

This study, the International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE), collects information on thromboprophylactic practices and compares VTE risk in different inpatient populations over 40 years of age and admitted to medical wards or over 18 years of age andadmitted to surgical wards. It is a multicentric cross-sectional study with 358 hospitals participating, designed to measure the prevalence of VTE and risk factors, and the recommended thromboprophylaxis is based on the 7th 2004 ACCP Consensus Statement. The results reported in 2008 included 68,183 patients, with 30,827 (45%) of them being surgical patients. The mean percentage of patients at risk for VTE is 51.8%, ranging among countries from 35.6% to 72.6%. Among patients at risk, 19,842 (64.4%) are from surgical wards. Among surgical patients at risk, 11,613 (58.5%) were receiving the recommended thromboprophylaxis. The variation between countries was 0.2% to 92.1%. Among medical patients at risk for VTE, 6,119 (39.5%) patients were given the advocated thromboprophylaxis. The variation between countries was 1% to 70.4%[11].

In January 2010, Kakkar *et al.*[12] updated data on surgical ward inpatients and applied multivariate analysis for thromboprophylaxis used. It included 18,461 patients, 17,084 (92.5%) of which were considered at risk for VTE. The thromboprophylaxis was used in 10,638 (62.3%) patients at risk. The use of thromboprophylaxis varied with the type of major surgery from 86% for orthopedic surgery to 53.8% in urology/gynecology and to 53.6% in other surgeries. Major orthopedic surgery was the procedure most strongly associated with thromboprophylaxis. Hip replacement was associated with OR = 6.2, followed by knee replacement, with OR = 5.9[12].

Improve

Another International Initiative, the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) assessed thromboprophylactic practices in medical inpatients at risk for VTE. It is an observational study, in which hospitals registered the first 10 medical patients acutely ill every month. The treatment was defined by the attending physician. The analysis of 15,156 patients from 52 hospitals in 12 countries between July 2002 and September 2006 shows that 50% of patients were receiving pharmacological or mechanical thromboprophylaxis. In the United States, 52% of patients (in other countries, 43% of patients) should havereceived thromboprophylaxis according to the ACCP recommendations. Only 60% of patients at risk in both country categories received thromboprophylaxis. Unfractionated heparins were the most often used pharmacological approaches in the United States (21%), while low-molecular weight heparins were more often used in other countries (40%). There was also a variation regarding graded compression stockings and intermittent pneumatic compression (IPC) between the United States and the other countries[10].

Proposals regarding thromboprophylaxis programs

Proposal of the 8th American College of Chest Physicians Consensus Meeting

The latest ACCP publication presents the evidence-based recommendations[8]. The most important according to the recommendation level and study quality are shown in Table 3.

Some class societies, such as those in the fields of Orthopedics, Anesthesiology, Oncology, Gynecology and Obstetrics, adopt standard recommendations for thromboprophylaxis[58-62].

Table 3 – Main prophylactic recommendations according to the 8th American College of Chest Physicians Consensus Meeting[8,80]

Recommendation (recommendation level and evidence degree)*
1) Every hospital should develop a formal strategy for venous thromboprophylaxis (1A)
2) Do not use salicylates alone for thromboprophylaxis (1A)
3) Use mechanical methods in high bleeding risk patients (1A)
4) Use mechanical methods to assist pharmacological thromboprophylaxis in mid- or high thromboembolic risk patients and high bleeding risk (2A)
5) Use LMWH, UFH minidose or pentasaccharide in patients undergoing large surgeries (1A)
6) Use routine thromboprophylaxis for all patients undergoing large gynecological or urological surgeries with LMWH, UFH minidose, pentasaccharide, or mechanical methods (1A)
7) Apply as a routine LMWH pentasaccharide or oral anticoagulants with a target-INR 2.5 (range from 2-3) to patients undergoing elective hip or knee replacement (1A)
8) Apply as a routine pentasaccharide (1A), LMWH (1B), oral anticoagulants with a target-INR 2.5 (recommendation 1B) or UFH (1B) to patients with hip fractures.
9) Maintain thromboprophylaxis for at least 10 days in patients undergoing major orthopedic surgeries (1A). In hip replacement and hip fracture, prophylaxis should be extended for over 10 days up to 35 days (1A).
10) Apply thromboprophylaxis to every patient with major trauma and spinal cord injury (1A)
11) Use thromboprophylaxis with LMWH, UFH or pentasaccharide in patients admitted to hospital with acute medical disease (1A)
12) Evaluate venous thromboembolic risk in all patients admitted to an Intensive Care Unit and apply thromboprophylaxis to most patients (1A)

*Notes: Level 1 recommendation refers to a robust recommendation in which the benefits overcome risks and cost. Level 2 indicates patient individual values might cause different choices, representing weaker recommendations than at level 1. It further indicates the risks, benefits, and cost magnitude is less well defined than at Level 1 recommendation. Evidence level may originate from high-, mid- or low-quality studies, indicated by letters A, B or C, respectively. UFH: unfractionated heparin; LMWH: low molecular weight heparin.

Caprini's proposal

This is a standard risk assessment model (RAM) originally proposed in the 80s and recently revised[63,64]. Caprini recommends the universal thromboembolic risk assessment applying the Evanston Northwestern Healthcare's Thrombosis Risk Factor Assessment scores in a standard form. This tool lists several VTE risk factors and can be completed by a health team member based on a patient's interview[64]. The tool recommends assigning weights from 1 to 5 to each risk factor. A cumulative score of all identified risk factors with their respective weights is used to stratify for each patient's thromboembolic risk and indicate the recommended thromboprophylaxis[64]. The model rationale is to associate thromboprophylactic regimens with thromboembolic risk categories. In the original study, 538 surgical patients were prospectively assessed according to the presence of 20 risk factors. The presence of each risk factor was given one point. The total score defines the thromboembolic risk category as low-(below two), mid-(between two and four) or high-risk (5). General care steps are recommended for all risk categories, and pharmacological thromboprophylaxis is recommended for mid- and high-risk patients in varying dosages.

The revised tool classifies thromboembolic risk factors with a score of 1 to 5. Risk factors classified as equivalent to 1 point are considered relatively minor factors, while those with a higher score are considered more important factors regarding thromboembolic risk. The cumulative score for a all risk factors determines the patient's thromboembolic risk range. The protocol recommends that patients with a cumulative score above two should be given either pharmacological or mechanical thromboprophylaxis. Patients with cumulative score 5 should be given pharmacological prophylaxis alone or associated with mechanical methods[64].

National Institute for Clinical Excellence Proposal

According to the National Institute for Clinical Excellence recommendations[65], the priorities for implantation of thromboprophylactic recommendations in surgical patients are:

– patient assessment to identify the thromboembolic risk;

– health professionals should provide the patient with oral and written information about VTE risk and thromboprophylaxis effectiveness before the surgery;

– selected patients should be offered graded compression stockings since admission. Stockings must follow technical compression standards. Patients should be instructed on the way of dealing with the stockings, and health team should encourage and monitor their use;

– use of IPC or foot devices as an alternative or in association with graded compression stockings;

– high thromboembolic risk patients and orthopedic surgical patients should be offered pharmacological thromboprophylaxis with LMWH associated with mechanical thromboprophylaxis. Pentasaccharide can be used as an alternative to LMWH;

- maintenance of thromboprophylaxis medication for 4 weeks after hip surgery

– favor regional anesthesia over general anesthesia;

– promote the patient ambulation as soon as possible after surgery[65].

Brazilian thromboprophylaxis Studies

In Brazil, PE and DVT diagnosis and Treatment guidelines approaching thromboembolic risk factors, risk stratification, and thromboprophylactic recommendation are supported by the Brazilian Medical Association (Associação Médica Brasileira – AMA)[66-68].

Deheinzelein *et al.* described the thromboembolic risk and application of thromboprophylactic strategies in four facilities in São Paulo with 1,454 patients (589 surgical patients and 865 medical patients). This study using Caprini's risk stratification showed 29% of high VTE risk patients were not given thromboprophylaxis. Still 27% of low thromboembolic risk patients were given the prescribed thromboprophylaxis[69].

Another study, developed from October 1995 to August 1999 in a public Brazilian Navy hospital in Rio de Janeiro, enrolled 18,690 patients[70,71]. By adopting Caprini's risk stratification, 4.7% of patients were classified as high-risk patients, 8,012 (42.9%) as intermediate-risk patients, and 52.4% as low-risk patients. The recommended prophylaxis was adopted in 47.1% of high-risk patients. On the other hand, 4.6% of low-risk patients were given pharmacological prophylaxis even with no indication[70,71].

Over a thromboprophylaxis assessment in a university hospital, Franco *et al.*[72] developed a cross-sectional study in seven wards at *Conjunto Hospitalar de Sorocaba* from August 2004 to August 2005. When stratifying for DVT risk, clinical and surgical factors derived from Caprini's model were investigated. Two hundred and sixteen medical records, 121 from surgical wards, 31 from medical wards, 31 from an intensive care unit, and 33 from gynecology/obstetrics wards were analyzed. Thromboprophylaxis was prescribed in 57 (26%), with 51 (89%) receiving a correct prescription. The most used prophylactic method was pharmacological; 49 from 57 patients used LMWH. Compression stockings were used in five patients, early ambulation in seven and IPC was not used.

Pereira *et al.*[73] performed, from March to May 2007, a prospective study with inpatients at Roraima General Hospital. The purpose was to find thromboprophylaxis applied to inpatients. The thromboembolic risk stratification followed Caprini's model. From 850 patients, 557 (66.7%) were medical patients. Overall, 353 patients (41.6% of the total) were low-risk patients, 411 (48.3%) were intermediate-risk patients, and 86 (10.1%) were high-risk patients for VTE. Only 24% of patients who should receive pharmacological thromboprophylaxis actually received it[73].

Another cross-sectional observational study on thromboprophylactic practice included 1,036 patients in three Manaus hospitals from January to March 2006. The risk stratification used was Caprini's proposal. The VTE risk was high in 50.6% of hospitalizations, intermediate in 18.6% of the hospitalizations and low in 30.8% of the patients. In 74% of moderate- or high-risk patients, pharmacological thromboprophylaxis was not used[74].

More recently, Rocha *et al.*[68] created venous thromboprophylaxis formal structures to apply the venous thromboprophylaxis Brazilian guidelines supported by AMB to medical patients from four hospitals in Bahia. The intervention included the disclosure of guideline through lectures and algorithms. The study design was cross-sectional with a thromboprophylaxis assessment both before and after the intervention. The authors concluded that thromboprophylaxis is underused in Brazilian hospitals and that the disclosure strategy and the continued education program are insufficient to improve the correct thromboprophylaxis indication[75].

Another retrospective study also assessed the national guideline implantation for surgical patients in a university hospital[76]. The project disclosure involved an algorithm adoption, consensus meetings, disclosure in a healthcare team meeting and an introduction letter from the hospital administrative staff. The adherence to thromboprophylaxis was inappropriate, although compression stockings have been more often prescribed[76].

Strategy for in-hospital thromboprophylaxis implantation

There are strong scientific arguments for thromboprophylaxis program implantation in hospitals[7,8,43,56,57]. The United State Agency for Health Care Research and Quality recently developed an administrative method of evaluation for a hospital thromboprophylaxis program implantation[77]. Based on the intervention effectiveness and cost-effectiveness, the thromboprophylaxis in selected patients was the most outstanding step as an in-hospital practice to protect patients[7].

National recommendations as the National Institute for Clinical Excellence's (NICE) for healthcare services in England and Scotland[17,65] were issued after more than a half of deceased patients from PE were found not to have received thromboprophylaxis although they showed risk factors and had no contraindication to standard thromboprophylaxis[14,17].

Passive protocol delivery and thromboprophylactic strategy disclosure were unlikely to succeed[8,17]. Thromboembolic risk simple models integrated with in-hospital prescriptions are a key strategy to increase inpatient protection. This approach should generate electronic alerts regarding non-venous thromboprophylaxis prescription in patients at risk. This strategy should be complemented by the formation of specific multidisciplinary teams for venous thromboprophylaxis, by the thromboprophylaxis process monitoring and by thromboprophylaxis prescription control through an internal audit[78,79]. National collaborations can accelerate the use of venous thromboprophylaxis. Adoption of stimuli to prescribe thromboprophylaxis was also suggested. Possibly regulatory steps in addition to local actions are required as in the United Kingdom[14]. Therefore, hospitals should have proven active thromboprophylaxis program according to predetermined standards.

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