Deep-vein thrombosis and prevention of post-thrombotic syndrome

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Introduction

Deep-vein thrombosis (DVT) refers to the formation of a thrombus in one of the deep veins of the body, usually in the leg, resulting in leg pain, tenderness, and swelling. The clinical course of DVT may be complicated by the potentially fatal conditions of pulmonary embolism (PE), recurrent DVT and in the long term by the emergence of post-thrombotic syndrome (PTS). In its presentation, PTS is typified by a variety of symptoms and signs that can be systematically assessed, including edema, skin induration, hyperpigmentation, pain, pruritus, and paresthesia (Table 1). The most severe form of the syndrome will manifest as venous ulcers.[1]

As both a frequent and chronic complication of DVT, PTS interferes with patients' daily life, function and health. The syndrome can have a profoundly adverse effect on quality of life, limiting physical activity, interfering with work and social activities, causing psychological distress and changing patients' health perceptions.[2] Furthermore, PTS carries a high cost of medical care, with costs amounting to about 75% of the cost of a primary DVT.[3]

There are currently limited options for treating PTS and most are aimed at the prevention or treatment of leg ulcers.[4] Indeed the treatment of established PTS is described as frustrating for patients and physicians alike, with current therapies and management only able to improve or stabilize symptoms in around half of all patient cases.[4,5]

Despite extensive study of DVT and its prevention and treatment in recent years, PTS has received little attention from clinicians and researchers.[4] The syndrome has

rarely been included as an outcome measure in DVT trials, and continues to be an underdiagnosed, underappreciated and often overlooked morbid consequence of DVT. There is poor appreciation of the burden posed by PTS and a prevailing perception that the condition is an inevitable and untreatable consequence of DVT.[4]

Prophylaxis with anticoagulant therapy is known to reduce the rate of DVT and its reoccurrence, and consensus guidelines on the prevention of venous thromboembolism have been formulated based on a strong body of evidence.[6,7] The prevention of DVT in the first place may therefore offer the best opportunities for optimal patient care and avoidance of PTS and venous ulcers.

Risk of venous thromboembolism, recurrence, PTS and venous ulcers

Venous thromboembolism (VTE) is a major health problem. Recent estimates suggest that the total annual number of nonfatal, symptomatic VTE events in the United States exceeds 600,000, more than half of which are DVT.[8] Individual risk for DVT varies according to clinical situation, as shown in Table 2,[6] and potential of additional VTE risk factors including an acute infectious disease, cancer, age greater than 75 years, stroke, immobilization and previous history of VTE.[9,10]

Data from a population-based cohort study in the United States reveal that the risk for VTE recurrence after a first episode is high. As many as 5% of patients with a first VTE experience a recurrent event within 30 days, around 17% have a recurrence within 2 years and 30% within 10 years.[11] The hazard of recurrence is highest in the first 6–12

months after the initial event, with hazard rate per 1000 person-days ranging from 30 recurrent VTE events at 7 days to 50 events at 30 days, and 10 at 6 months and 1 year.[11]

In a group of 335 consecutive patients who experienced symptomatic thrombosis, PTS occurred in 23% within 2 years of the VTE event, with a strong association between the development of ipsilateral recurrent DVT and risk for PTS.[12] Severe cases of PTS had manifested in 9% of patients after 5 years.[12] A recent meta-analysis has also shown that in patients in whom postoperative DVT was asymptomatic, the relative risk of developing PTS is 1.58 times (95% Confidence Interval [CI] 1.24–2.02) the risk in patients without evidence of DVT ($P < 0.0005$).[13] This highlights that even silent DVT predisposes the patient to the later threat of chronic PTS and risk for venous ulceration.

To date, specific patient risk factors for developing PTS have not been clearly established, but it has emerged that many patients with chronic venous ulceration have unsuspected PTS.[14,15] Several risk factors have been put forward, of which only recurrent DVT has clearly been identified as increasing the risk of PTS as much as 6-fold (Table 3).[4]

The annual incidence of venous ulceration is estimated to be at least 0.3%, of which around one quarter of cases can be linked with a DVT history.[16,17] Both clinical and subclinical VTE appear to be significant predisposing factors for the development of chronic venous insufficiency and venous ulcers.[18-20] Indeed, patients with a DVT history have been shown to be 2.4-fold (95% CI 1.7–3.2) more likely to develop venous stasis with its associated risk for venous ulcer formation.[19]

Thromboprophylaxis: reducing the incidence of VTE and long-term complications

There is a compelling body of evidence that the incidence of VTE, and thereby its long-term complications, can be drastically reduced by providing effective thromboprophylaxis to patients at known risk for VTE.[6,7] Many studies of VTE prophylaxis have focused more on surgical rather than medical patients because of the very high risk of VTE following major surgical procedures. However, the absolute numbers of potentially at-risk patients reveal high numbers of medical patients who are candidates for VTE prophylaxis in accord with current guidelines on VTE prevention.[6,7,21] Of an estimated 13.4 million US residents who meet the current American College of Chest Physicians (ACCP) guideline defined risks for VTE each year, 7.6 million (57%) are medical patients.[21]

Despite internationally recognized guideline recommendations and government-backed initiatives in support of wider adoption of VTE prophylaxis in at-risk groups, the reality is that prophylaxis for VTE continues to be underutilized in clinical practice in both surgical and medical patient groups. [6,7,22,23,24] A recent multicenter study in Canada revealed that while most patients hospitalized for medical illness had indications for thromboprophylaxis, only 16% received prophylaxis deemed appropriate to reduce the risk of VTE.[24] In a Spanish study, it was noted that appropriate adherence to all guideline recommendations on VTE prophylaxis was observed in only 42% of patients with risk factors, with dosage of thromboprophylaxis often inappropriate according to patients' relative risk.[23]

Reasons for underprophylaxis of hospitalized patients may relate to an underestimation of VTE risk, since VTE events often arise after hospital discharge and VTE is often clinically silent, or to emergence of symptoms that are not immediately detected or detectable during patient follow-up. Inadequate levels of prophylaxis not only increase the risk of occurrence of thrombosis, but also increase the risk of PTS and, in this way, venous ulceration.[4] The key to optimal VTE prevention lies in better assessment of patient risk and appropriate intervention. Indeed in the United States, the National Quality Forum (NQF) identifies VTE risk assessment among its 30 practices for improving patient safety, highlighting the need to evaluate all patients for VTE risk on hospital admission and stressing the need for appropriate methods to prevent VTE, a recommendation supported by the Agency for Healthcare Research and Quality (AHRQ) as well.[22]

Risk Assessment Model (RAM)

There is a body of literature and evidence regarding VTE risk factors and guidance on patient risk assessment to support clinicians and surgeons in identifying patients at risk of VTE in daily practice. The ACCP guidelines approach to risk assessment is to define patients as belonging to one of four broad categories of VTE risk — low, moderate, high and highest risk.[7] However, the ACCP approach of broad risk categories and its lack of specification of what constitutes “other risk factors”, does not provide an immediately accessible model for application in clinical practice and there have therefore been attempts to develop more practical risk assessment models and tools.

For example, using a computerized alert program, it is possible to encourage greater and more successful use of prophylaxis among at-risk patients.[25] In a study conducted at a large US hospital, an alert system linked to the inpatient database used eight common risk factors to determine each patient's risk status and then prompt clinicians to use thromboprophylaxis. This approach resulted in a 41% reduction in the rate of venographically confirmed VTE at 90 days compared with clinician-based judgment alone ($P = 0.001$).[25]

A risk assessment model based on detailed evaluation of a patient's exposing risk factors associated with the clinical setting and predisposing risk factors for VTE has been devised based on previous models and real clinical data[10] (Figure 1). The model requires that a form is completed on hospital entry to allow physicians to score thrombosis risk and select and prescribe the most appropriate prophylaxis according to whether the patient falls into a low, moderate, high or highest risk category. Through this model, the appropriate selection of prophylaxis per patient is based on a risk factor score, and the type, duration and intensity of prophylaxis is based on patient need.

Methods of thromboprophylaxis

A range of drugs are available for VTE prophylaxis including warfarin, unfractionated heparin (UFH), the low molecular weight heparins (LMWHs) enoxaparin and dalteparin, and the pentasaccharide fondaparinux (Table 4).

Warfarin

Data from the Global Orthopaedic Registry (GLORY) of in-hospital management and outcomes following elective total hip and knee replacement reveal that, as a contemporary choice for primary VTE prophylaxis, warfarin use is restricted almost entirely to the United States.[26] While 58% of orthopedic patients in GLORY in the United States received warfarin in hospital, the use of this vitamin K antagonist has largely been abandoned in Europe in favor of 92% use of LMWH.[26]

Although warfarin therapy has the convenience of oral administration, its use is complicated by the difficulty in reaching and maintaining target International Normalized Ratio (INR) levels — a process which may take between 1 and 12 days.[27] Drug levels must be monitored to ensure a balance between treatment efficacy and safety, specifically concerns over bleeding, and there is a need for frequent drug monitoring to avoid the many common drug and food interactions with warfarin.[28]

Underanticoagulation with warfarin is common and it has been shown that achieving a target INR of 2–3 is important throughout the period of patients' highest risk. For example, in a study of 125 patients undergoing total hip replacement, achievement of target INR over the entire 4 weeks post-operation was vital to providing adequate DVT prophylaxis with warfarin.[29] This study found not only that average INR values were higher among patients who did not develop DVT, but also demonstrated that a larger proportion of the patients who developed DVT were outside the therapeutic INR range during the third (73% versus 39%, $P < 0.001$) and fourth postoperative weeks (89% versus 39%, $P < 0.001$).

Unfractionated heparin

Seminal studies of heparin-based VTE prophylaxis have shown the beneficial effects of low-dose unfractionated heparin (UFH) administered subcutaneously twice or three times daily in patients undergoing major surgery.[30,31] One of the first studies to demonstrate the preventive benefits of UFH was an international multicenter study comparing low-dose UFH given three times daily with no specific prophylaxis in 4121 elective surgical patients, where rates of postoperative DVT fell from 24.6% to 7.7% ($P < 0.005$).[30] An early systematic review of studies with UFH for VTE prevention confirmed that perioperative UFH reduced the risk of DVT following general, orthopedic, and urologic surgery by 68% compared with control ($P < 0.001$), but that overall excessive bleeding or need for transfusion was increased relatively by between 50% and 66% in patients given UFH.[31]

Low-dose UFH (5000 U) given twice daily has not been found as effective in reducing DVT rates in medical patients at risk of VTE, despite early reports that this form of prophylaxis reduced mortality.[32] The Heparin Prophylaxis Study group which assessed the effects of low-dose UFH twice daily as VTE prophylaxis in patients with infectious disease also found that while UFH appeared to delay time to fatal PE in this group of medical patients it had no effect on overall rate of fatal PE.[33]

Indeed, although UFH twice daily is commonly used in clinical practice, a recent evaluation showed that there is no large, well conducted, placebo-controlled trial to support the use of UFH twice daily for VTE prevention in hospitalized medical patients.[34] Future large-scale controlled studies in this field are unlikely given the known incidence of complications associated with UFH compared with LMWHs. While more frequent

dosing of UFH (three times daily) may offer more effective VTE prophylaxis in medical patients, such a regimen would be associated with a higher risk of bleeding.[34]

Another factor playing against widespread use of UFH for VTE prophylaxis is the risk of heparin-induced thrombocytopenia (HIT). A recent meta-analysis of published study data spanning 20 years and including 2478 patients found that HIT occurs in around 2.6% of patients given UFH thromboprophylaxis compared with 10-fold lower rates at 0.2% during use of LMWH to prevent VTE (Odds ratio [OR] 0.10, 95% CI 0.03–0.33).[35]

Prophylaxis with enoxaparin, dalteparin or fondaparinux reduces the rate of DVT very effectively, and requires less frequent administration than use of UFH, making these drugs preferred options for the prevention of VTE (initial and recurrent episodes).

Low-molecular-weight heparin

A strong body of evidence supports the role of LMWH in the prevention of VTE in a wide range of patients at moderate to highest risk for thrombosis associated with surgery, medical conditions and known VTE risk factors. A meta-analysis of randomized trials in orthopedic surgery comparing warfarin with other forms of VTE prophylaxis has shown the superior efficacy profile of LMWH relative to warfarin in preventing DVT (Risk reduction [RR] 1.51, 95% CI 1.27, 1.79, $P < 0.001$).[36] On an individual trial basis, for example in 1472 patients undergoing total hip arthroplasty (THA), pre- and postoperative dalteparin (initial dose 2500 IU, followed by 5000 IU once daily) for 6 ± 2 days was associated with lower rates of DVT of 10.7% and 13.1%, respectively, compared to 24% with warfarin ($P < 0.001$).[37] Extended dalteparin out-of-hospital to 35 days in 569

patients further reduced the cumulative incidence of DVT to 19.7% compared to 36.7% in the warfarin/placebo group ($P < 0.001$).[38]

Extending enoxaparin prophylaxis (40 mg once daily) with 21 days, after an initial course of 7–10 days, in 435 patients undergoing THA resulted in a VTE rate of 8.0% compared with 23.3% ($P < 0.001$) in the enoxaparin/placebo group.[39] Enoxaparin (30 mg twice daily) for 4–14 days has also been shown to reduce the incidence of VTE after total knee arthroplasty (TKA) in a study of 349 patients, with VTE rates of 25% in the enoxaparin group compared with 45% in the warfarin group ($P = 0.0001$) and no difference in major bleeding rates.[40] Prolonging enoxaparin for three weeks had no significant benefit in TKA patients.[39]

In a meta-analysis of 51 studies comparing LMWH with UFH for prevention of VTE in over 48,000 general surgery patients, LMWH was at least as effective and safe as UFH in preventing VTE, with a suggested benefit in reducing overall clinical VTE events (RR 0.71, 95% CI 0.51–0.99).[41] To highlight one of the 51 studies included in this meta-analysis, the Enoxaparin and Cancer (ENOXACAN) study demonstrated that enoxaparin 40 mg once daily was at least as effective and safe as UFH three times in 1115 patients undergoing elective surgery for cancer. The incidence rate of VTE was 14.7% in the enoxaparin group and 18.2% with UFH (OR 0.78, 95% CI 0.51-1.19), with no differences in bleeding complications.[42] Extending enoxaparin for another 21 days after an initial 6–10 days in the ENOXACAN–II study resulted in a VTE rate of 4.8% compared to 12.0% in the enoxaparin/placebo group ($P = 0.02$).[43]

A number of key trials have shown that LMWH reduces VTE incidence compared with placebo in medical patients at risk for VTE and associated complications, without

compromising safety.[6] In addition, LMWH is at least as effective and safe as UFH three times daily in this patient population.

In the Prophylaxis in Medical Patients with Enoxaparin (MEDENOX) trial, comparing once daily subcutaneous enoxaparin 20 mg or 40 mg with placebo for 6 to 14 days in a cohort of 1102 acutely ill hospitalized medical patients, enoxaparin 40 mg significantly reduced VTE to 5.5% compared with an incidence of 14.9% in the placebo group ($P < 0.001$).[44] This reduction in rate of VTE linked with medical illness and hospitalization was achieved with a similar rate of adverse events with LMWH or placebo.

Another large-scale study in 3706 acutely ill medical patients — the Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT) — also demonstrated the efficacy and safety benefits of dalteparin over placebo.[45] Medically ill patients assigned to dalteparin 5000 IU daily for 14 days had a rate of VTE of 2.77% compared with 4.96% in the placebo group in the 90 days of follow-up, representing an absolute risk reduction of 2.19% and a relative risk reduction of 45% ($P = 0.0015$). This reduction in VTE was achieved without a significant increase in the risk of major bleeding.[45]

A study which compared the effects of enoxaparin with UFH prophylaxis in medical patients with heart failure or severe respiratory disease was the Thromboembolism-Prevention in Cardiac or Respiratory Disease With Enoxaparin (THE-PRINCE) study.[46] This multicenter, open study randomized 665 patients to receive either enoxaparin 40 mg once daily or UFH (5000 IU three times daily) for 10–12 days. The incidence of VTE was 10.4% with UFH and 8.4% with enoxaparin ($P = 0.015$, for

equivalence). The use of enoxaparin was associated with fewer deaths, a lower rate of bleeding complications, and fewer adverse events (45.8% versus 53.8%, $P = 0.044$) than UFH prophylaxis in this patient group.[46]

To date, LMWH has been used in an estimated 1.3 million patients worldwide for prevention of VTE, with the class recognized to have an excellent track record of no recalls due to lack of efficacy or safety concerns. Within the class, the LMWH enoxaparin is both the most widely used and most studied of the available drugs and evidence relating to this LMWH is widely cited in current guidelines and consensus publications concerning recommendations for use of LMWH for VTE prevention.[6,7]

Fondaparinux

Fondaparinux is a pentasaccharide molecule and the first in a novel class of synthetic antithrombotic drugs. A meta-analysis of data from four randomized double-blind studies evaluating the role of fondaparinux (2.5 mg once daily) in VTE prevention in 7344 patients undergoing major orthopedic surgery showed a significant reduction in the incidence of total VTE (6.8%) at day 11 compared with enoxaparin (13.7%) ($P < 0.001$). However, fondaparinux was not associated with a difference in the rate of symptomatic VTE and PE (0.6% versus 0.4%, $P = 0.25$), and increased the rate of major bleeding (2.7% versus 1.7%, $P = 0.008$).[47]

The PENTasaccharide in HIp-FRActure Surgery Plus (PENTHIFRA Plus) study evaluated the efficacy and safety of extending fondaparinux prophylaxis for up to 3 weeks after hip surgery in a group of 656 patients.[48] All patients received fondaparinux for 6–8 days after surgery, and subsequently one group was assigned to extended

prophylaxis with fondaparinux while another received placebo for 3 weeks. Extended fondaparinux was reported to reduce the incidence of postoperative VTE by 96% from 35% to 1.4% in these high-risk patients ($P < 0.001$). Again there was a trend towards more major bleeding in patients receiving fondaparinux (2.4% versus 0.6%, $P = 0.06$).[48]

In 2048 high-risk abdominal surgery patients in the PEntasaccharide GenerAl SUrgery Study (PEGASUS), which compared fondaparinux 2.5 mg and dalteparin 5000 IU for 5–9 days, the rate of VTE observed up to day 10 was similar between treatment groups, at 4.6% in the fondaparinux group compared with 6.1% in the dalteparin group ($P = 0.144$).[49]

Fondaparinux has also been compared with placebo in hospitalized medical patients. In the ARixtra for ThromboEmbolism prevention in a Medical Indications Study (ARTEMIS), the efficacy and safety of 2.5 mg of fondaparinux once daily for 6–14 days were compared with that of placebo in a group of 849 elderly, acutely ill patients with conditions requiring hospitalization and bed rest.[50] VTE was detected in 10.5% of placebo patients and this rate was reduced by 46.7% to 5.6% in patients given fondaparinux ($P = 0.029$) with no apparent increase in bleeding risk.[50]

The evidence to date suggests promise for this novel drug against preventable VTE, but until further data accumulate, fondaparinux should be reserved for use in selected patients.

Mechanical methods of prophylaxis

Mechanical methods of prophylaxis have a long history in VTE prevention. A recent meta-analysis of data from 15 clinical studies, assessing the efficacy of intermittent

pneumatic compression (IPC) for DVT prevention in 2270 surgical patients, showed that IPC reduces the risk of DVT by 60% compared with no prophylaxis ($P < 0.001$).[51] When mechanical prophylaxis (pneumatic compression stockings) was combined with pharmacological prophylaxis (low-dose UFH) in 2551 patients undergoing cardiac surgery, reductions in VTE risk were greater still with a further 62% reduction in DVT over use of mechanical methods alone ($P < 0.001$).[52]

Preliminary data from the safety study of fondaparinux sodium to prevent venous thromboembolic events (APOLLO) which evaluates the combined effect of fondaparinux and IPC versus IPC alone for prevention of VTE after major abdominal surgery, suggest that this combination of mechanical and pharmacological prophylaxis can effect high rates of VTE reduction 32 days after surgery, reducing VTE incidence to 1.7%, a 70% reduction over use of IPC alone ($P = 0.004$).[53]

Although mechanical devices do not provide sufficient protection against VTE in moderate to high-risk patients on their own, they may be used to complement or replace pharmacoprophylaxis in certain patient groups in whom pharmacological prophylaxis is contraindicated. Compression devices and vena cava filters may be indicated as methods to reduce the risk of VTE in patients with known contraindications to anticoagulant therapy, in selected trauma cases where bleeding risk is high, or to complement anticoagulant prophylaxis during procedures where there is a very high risk of VTE.[6,7]

Remaining issues in the prevention of post-thrombotic syndrome

There is a robust body of evidence to support the use of prophylaxis to reduce the incidence of DVT but to date, little to none of the research and study of VTE prevention has included collection of data that demonstrate a direct impact of primary DVT prevention on PTS rates.

Although prophylaxis can help reduce the incidence of DVT, its use to prevent PTS and venous ulceration is also limited by the fact that measures to reduce DVT do not eliminate it completely. Furthermore, not all DVT can be predicted based on risk assessment. The risk of recurrence of DVT following an initial symptomatic DVT event can be reduced through long-term use of secondary prophylaxis, for which warfarin is generally used because of its ease of oral administration. As demonstrated in a meta-analysis, LMWH is an alternative option, being at least as effective as and perhaps favorable to warfarin in terms of VTE recurrence (OR 0.70; 95% CI 0.42–1.16) and resulting in less bleeding complications (OR 0.38, 95% CI 0.15–0.94).[54]

There is evidence that the use of therapeutic compression stockings reduces the incidence of PTS after symptomatic DVT.[55-57] In 325 outpatients with a first episode of DVT, graded compression stockings for at least 2 years were associated with a lower incidence of mild-to-moderate PTS at 20% compared to 47% in the control group without stockings ($P < 0.001$), as well as a lower incidence of severe PTS (11% versus 23%, $P < 0.001$).[56] In a review on the value of graduated compression stockings, the pooled incidence of PTS of three studies was significantly reduced from 54% to 25.2% (RR 0.47, 95% 0.36-0.61), as well as the incidence of recurrent asymptomatic DVT (RR 0.20, 95% CI 0.06-0.64).[57] Thus, available data strongly suggest that after DVT, mechanical stockings can reduce the incidence of PTS and should therefore be used together with

DVT prevention to reduce the burden posed by PTS.[55] In contrast, there is less evidence to suggest that the intensity of warfarin anticoagulation has any important impact on incidence of PTS after DVT.[15]

Clearly, more studies are needed to address the prevention and treatment of PTS in order that evidence-based data and results can be included in future guideline recommendations for improved patient care and management.

Conclusion

Until such time as effective treatments for PTS and its potential manifestation of venous ulceration have been found, prevention of the syndrome remains the key to reducing the impact of this condition on both patients and society. Therapeutic compression stockings associated to the anticoagulant treatment after an incident of DVT may have a role in reducing the risks of progression to PTS, but better still is prevention of VTE whenever possible. Identifying patients at risk of VTE is possible and great progress has been made in terms of accurate risk assessment of individual patients that in turn allows the best and most appropriate use of available methods of VTE prophylaxis. By providing more at-risk patients with appropriate, clinically proven anticoagulant therapy during periods of high risk, the incidence of DVT and consequently its long-term complications can be reduced. Prevention of venous diseases with the potential to progress to PTS, particularly DVT prevention, may lead to a reduction in the incidence of venous ulcers.

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Table 1. Clinical scale for post-thrombotic syndrome (PTS) according to Villalta et al.[1]

PTS symptoms	Pain
	Cramps
	Heaviness
	Pruritus
	Paresthesia
PTS signs	Edema
	Skin induration
	Hyperpigmentation
	Ectasia
	Redness
	Pain during calf compression
PTS score*	
0–4	No PTS
5–14	Mild PTS
≥ 15, or presence of ulcer	Severe PTS

*PTS score is based on cumulative rating of the 5 symptoms and 6 signs, with each rated as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe).

Table 2. Risk of deep-vein thrombosis (DVT) in different patient populations[6]

	Probability of DVT without prophylaxis (%)
Surgical	
Elective hip replacement	51 (48–54)
Total knee replacement	47 (42–51)
Hip fracture	44 (40–47)
General surgery	25 (24–26)
Gynecological surgery (malignancy)	22 (17–26)
Gynecological surgery (benign disease)	14 (11–17)
Medical	
General medical	12 (10–14)
Stroke	56 (51–61)
Myocardial infarction	22 (16–28)
Spinal cord injury	35 (31–39)
Medical intensive care	25 (19–32)

95% Confidence intervals in parentheses.

Table 3. Proposed risk factors for post-thrombotic syndrome (PTS)[4]

Proposed risk factor	Association with PTS
Recurrent DVT	Clearly identified risk factor, up to 6-fold increase
Asymptomatic DVT	Identified risk factor, 1.6-fold increase
Characteristics of the initial DVT; distal DVT	Distal DVT appears to be associated with PTS, although some studies suggest that the site of the initial thrombus is not predictive, or that the risk is higher in patients with proximal rather than distal DVT
Patient characteristics	Factors **predictive** of PTS (as identified in retrospective studies): • Increasing age • Female gender • Hormone therapy • Varicose veins • Abdominal surgery • Increased body mass index Factors **not predictive** of PTS (as identified in prospective studies): • Gender • Delay in initiating treatment for DVT • Risk factors for thrombosis • Family history of thrombosis • Intensity of warfarin anticoagulation

DVT = deep-vein thrombosis.

Table 4. Summary of methods of thromboprophylaxis and guideline recommendations in patients at risk of venous thromboembolism (VTE) (for further details, see Geerts et al.[7] and Nicolaides et al.[6])

Prophylaxis method	Patient population	Dosing	Duration
Warfarin	Orthopedic surgery (THA, TKA, HFS)	INR target 2.5 (range 2–3)	TKA: 10 days, THA and HFS: 28–35 days
UFH	General surgery	Moderate risk: 5000 units twice or three times daily High risk: 5000 units three times daily	No recommendation available
	Medical conditions	At risk: 5000 units three times daily	No recommendation available
LMWH	General surgery	Moderate and high risk: enoxaparin 40 mg once daily, dalteparin 5000 units once daily	5–10 days
	Orthopedic surgery (THA,	Enoxaparin 30 mg	TKA: 10 days,

	TKA, HFS)	twice daily, enoxaparin 40 mg once daily when started pre-operatively (THA only), dalteparin 5000 units once daily	THA and HFS: 28–35 days
	Medical conditions	At risk: enoxaparin 40 mg once daily, dalteparin 5000 units once daily	6–14 days
Fondaparinux	Orthopedic surgery (THA, TKA, HFS)	2.5 mg once daily	TKA: 10 days, THA and HFS: 28–35 days
Mechanical methods	Low-risk patients, patients with contraindication to pharmacological prophylaxis, in addition to pharmacological prophylaxis in high-risk patients	–	–

HFS = hip fracture surgery; INR = international normalized ratio; THA = total hip arthroplasty; TKA = total knee arthroplasty.

Figure 1. Risk assessment model. (Updated from Caprini et al.[10]

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Venous Thromboembolism Risk Factor Assessment

Patient's Name:_____ Age: ___ Sex: ___ Wgt:___lbs **Joseph A. Caprini, MD, MS, FACS, RVT**

Choose All That Apply

Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Minor surgery planned
- ❑ History of prior major surgery
- ❑ Varicose veins
- ❑ History of inflammatory bowel disease
- ❑ Swollen legs (current)
- ❑ Obesity (BMI >30)
- ❑ Acute myocardial infarction (< I month)
- ❑ Congestive heart failure (< 1 month)
- ❑ Sepsis (< 1 month)
- ❑ Serious lung disease incl. pneumonia (< 1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Medical patient currently at bed rest
- ❑ Leg plaster cast or brace
- ❑ Other risk factors_____

Each Risk Factor Represents 2 Points

- ❑ Age 60-74 years
- ❑ Major surgery (> 60 minutes)
- ❑ Arthroscopic surgery (> 60 minutes)
- ❑ Laparoscopic surgery (> 60 minutes)
- ❑ Previous malignancy
- ❑ Central venous access
- ❑ Morbid obesity (BMI >40)

Each Risk Factor Represents 3 Points

- ❑ Age over 75 years
- ❑ Major surgery lasting 2-3 hours
- ❑ BMI > 50 (venous stasis syndrome)
- ❑ History of SVT, DVT/PE
- ❑ **Family history of DVT/PE**
- ❑ Present cancer or chemotherapy
- ❑ Positive Factor V Leiden
- ❑ Positive Prothrombin 20210A
- ❑ Elevated serum homocysteine
- ❑ Positive Lupus anticoagulant
- ❑ Elevated anticardiolipin antibodies
- ❑ Heparin-induced thrombocytopenia (HIT)
- ❑ Other thrombophilia
  Type_____

resents 5 Points

xtremity arthroplasty
ure (< 1 month)

onth)
y (paralysis)(< 1

over 3 hours

For Women Only (Each Represents 1 Point)
❑ 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

Total Risk Factor Score ☐

Please see Following Page for Prophylaxis Safety Considerations

Revised November 4, 2006

VTE Risk and Suggested Prophylaxis For Surgical Patients

Total Risk Factor Score	Incidence of DVT	Risk Level	Prophylaxis Regimen	Legend
0-1	<10%	Low Risk	No specific measures; early ambulation	**ES** - Elastic Stockings **IPC** - Intermittent Pneumatic Compression **LDUH** - Low Dose Unfractionated Heparin **LMWH** - Low Molecular Weight Heparin **FXa I** - Factor X Inhibitor
2	10-20%	Moderate Risk	ES, IPC, LDUH (5000U BID), or LWMH (<3400 U)	
3-4	20-40%	High Risk	IPC, LDUH (5000U TID), or LMWH (>3400U)	
5 or more	40-80% 1-5% mortality	Highest Risk	Pharmacological: LDUH, LMWH (>3400 U)*, Warfarin*, or FXa I* alone *or* in combination with ES or IPC	

*Use for major orthopedic surgery

Prophylaxis Safety Considerations: Check box if answer is 'YES'

Anticoagulants: Factors Associated with Increased Bleeding
❑ Is patient experiencing any active bleeding?
❑ Does patient have (or has had history of) heparin-induced thrombocytopenia?
❑ Is patient's platelet count <100,000/mm^3?
❑ Is patient taking oral anticoagulants, platelet inhibitors (e.g., NSAIDS, Clopidogrel, Salicylates)?
❑ Is patient's creatinine clearance abnormal? If yes, please indicate value _____
If any of the above boxes are checked, the patient may not be a candidate for anticoagulant therapy and you should consider alternative prophylactic measures: elastic stockings and/or IPC
Intermittent Pneumatic Compression (IPC)
❑ Does patient have severe peripheral arterial disease?
❑ Does patient have congestive heart failure?
❑ Does patient have an acute superficial/deep vein thrombosis?
If any of the above boxes are checked, then patient may not be a candidate for intermittent compression therapy and you should consider alternative prophylactic measures.

Based on: Geerts WH et al: Prevention of Venous Thromboembolism. Chest 2004;126(suppl 3):338S-400S; Nicolaides AN et al: 2001 International Consensus Statement: Prevention of Venous Thromboembolism, Guidelines According to Scientific Evidence.; Arcelus JI, Caprini JA, Traverso CI. International perspective on venous thromboembolism prophylaxis in surgery. Semin Thromb Hemost 1991;17(4):322-5.; Borow M, Goldson HJ. Postoperative venous thrombosis. Evaluation of five methods of treatment. Am J Surg 1981;141(2):245-51.; Caprini JA, Arcelus I, Traverso CI, et al. Clinical assessment of venous thromboembolic risk in surgical patients. Semin Thromb Hemost 1991;17(suppl 3):304-12.; Caprini JA, Arcelus JI et al: State-of-the-Art Venous Thromboembolism Prophylaxis. Scope 2001; 8: 228-240.; Caprini JA, Arcelus JI, Reyna JJ. Effective risk stratification of surgical and nonsurgical patients for venous thromboembolic disease. *Seminars in Hematology*, April 2001;38(2)Suppl 5:12-19.; Caprini, JA. Thrombosis risk assessment as a guide to quality patient care, Dis Mon 2005;51:70-78.; Oger E: Incidence of Venous Thromboembolism: A Community-based Study in Western France. Thromb Haemost 2000; 657-660.; Turpie AG, Bauer KA, Eriksson BI, et al. Fondaparinux vs. Enoxaparin for the Prevention of Venous Thromboembolism in Major Orthopedic Surgery: A Meta-analysis of 4 Randomized Double-Blind Studies. Arch Intern Med 2002; 162(16):1833-40.; Ringley et al: Evalution of intermittent pneumatic compression boots in congestive heart failure. American Surgeon 2002; 68(3): 286-9.; Morris et al. Effects of supine intermittent compression on arterial inflow to the lower limb. Archives of Surgery 2002. 137(11):1269-73.; Sugarman HJ et al, Ann Surg: 234 (1) 41-46, 2001

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Examiner_____Date_____