Venous thromboembolism prophylaxis using the Caprini score

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ABSTRACT

Venous thromboembolism (VTE) including pulmonary embolism (PE) and deep vein thrombosis (DVT) is one of the leading causes of preventable cardiovascular disease in the United States (US) and is the number one preventable cause of death following a surgical procedure. Post-operative VTE is associated with multiple short and long-term complications. We will focus on reviewing the many faces of VTE in detail as they represent common challenging scenarios in clinical practice.© 2018 Elsevier Inc. All rights reserved.

PART ONE: THE MANY FACES OF VENOUS THROMBOEMBOLISM INCLUDING RISK FACTORS

Introduction

Venous thromboembolism (VTE) is the number one preventable cause of death following a surgical procedure.1 Anticoagulant prophylaxis postoperatively saves lives without increasing bleeding deaths.2 Surgeons are understandably reluctant to employ these drugs for fear of bleeding complications which in some cases can result in poor clinical outcomes.1 This review will demonstrate the value of individual risk assessment to tailor the use of anticoagulant

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prophylaxis. Patients with a low risk for thrombotic complications can be spared from the use of anticoagulants without increasing thrombosis event rates and death from this serious disorder. High-risk patients who are at great risk for developing thrombotic episodes including death can be targeted using appropriate drug regimes. These patients need drug prophylaxis for the entire period they are at risk in order to achieve the best results. Randomized control trial data from 160 centers over a 30-year period in 43,000 patients demonstrate that 7–10 days of anticoagulants is the proper course of prophylaxis to prevent most VTE events. However, thirty days of prophylaxis has been shown to be more effective and is recommended for the highest risk patients especially those with cancer and a previous VTE. The popular policy of administering anticoagulants only during hospitalization or until the patient is ambulatory has not been proven to prevent most thrombotic events. A significant number of patients develop VTE after discharge from the hospital and often are not protected with anticoagulants. The most powerful risk associated with surgical patients is a history or family history of thrombosis. These patients are particularly prone to fatal VTE events and often patients are not specifically queried about this history. Those identified with this past history are often not protected due to the perceived low risk of simple surgical procedures. Understanding that a minor surgical procedure may be associated with a major thrombotic risk is not well understood. The incidence of fatal VTE events even in young people having so called “minor surgical procedures” is far too common and almost totally preventable if their risk was properly assessed. The administration of appropriate anticoagulant prophylaxis for the period of time that they remain at-risk is relatively uncommon. This review will discuss these issues and illustrate the value of these principles based on the vast body of available literature that exists today.

Major public health concern

The precise number of people affected by DVT/PE is unknown, although as many as 600,000 people could be affected (1 to 2 per 1,000) each year in the United States. Estimates suggest that 60,000–100,000 Americans die of DVT/PE including 10 to 30% of people who will die within one month of diagnosis. Sudden death is the first symptom in about 25% of people who have a PE. Among people who have had a DVT, one-half will have long-term complications including the post-thrombotic syndrome, which presents with swelling, pain, discoloration, and scaling in the affected limb. A number of other complications can also occur and will be subsequently described. One-third of people with DVT/PE will have a recurrence within 10 years. Approximately 5 to 8% of the U.S. population has one of several genetic risk factors (inherited thrombophilias) that increase the risk for thrombosis.

Venous thromboembolism (VTE) is a major health problem, with over one million events every year in Europe. The annual incidence of fatal pulmonary emboli across Western Europe was estimated via an epidemiological model when the annual estimates for symptomatic VTE events were estimated to be 465,715 (404,664–538,189) cases of deep-vein thrombosis, 295,982 (242,450–360,363) cases of pulmonary embolism (PE), and 370,012 (300,193–483,108) VTE-related deaths. Of these deaths, an estimated 27,473 (7%) were diagnosed as being ante-mortem; 126,145 (34%) were sudden fatal PE, and 217,394 (59%) followed undiagnosed PE. Almost three-quarters of all VTE-related deaths were from hospital-acquired VTE. The estimated total number of VTE events (DVT and PE: 148 per 100,000 and 95 per 100,000, respectively) in the EU is higher than that reported for US communities. Sandler et al demonstrated that pulmonary embolism is a frequent complication in hospital patients with 10% of 2388 patients who underwent autopsy having died from PE.

Need for increased awareness

The International Society of Hemostasis and Thrombosis reported on the occasion of World Thrombosis Day (October 13th). This date was chosen since it was Professor Virchow’s birthday. “Thrombosis including VTE, ischemic heart disease, and ischemic stroke is a major contributor
to the global health burden.” The authors estimate that one of every 4 deaths worldwide are due to these thrombotic events. In the US alone, the Center for Disease Control and Prevention estimated that there were more than 500,000 adult hospitalizations with the diagnosis of VTE each year from 2007–2009. VTE is responsible for more deaths each year than breast cancer, HIV disease, and motor vehicle crashes combined. Furthermore, approximately 60% of VTE cases are associated with a recent hospital stay, and the World Health Organization (WHO) patient safety program found that hospital-associated VTE was the leading cause of death and disability associated with hospitalization among all countries and accounted for more deaths and disability than nosocomial pneumonia, catheter-related bloodstream infections and adverse drug events. Public awareness of VTE remains low with only 44% and 54% of respondents in a global survey were aware that most cases are preventable. An important education goal of the World Thrombosis Day is to equip patients and family with the adequate knowledge to advocate for VTE prevention especially in high risk settings like hospitalization.16

The many faces of VTE

There is a group of physicians who believe the only important postoperative venous thrombotic issue is symptomatic and fatal pulmonary emboli during hospitalization.17 The following section summarizes the numerous issues associated with a postoperative thrombosis including short and long-term complications. These issues represent compelling rationale to prevent “The Many Faces Of VTE” rather than just focus on only one aspect of this enormous health problem.

Pulmonary emboli (PE)

Pulmonary emboli (PE) represent the most dramatic of the thrombotic events and fatal emboli are seen in 1–5% of those with > 4 risk factors. One-third of all fatal events present as sudden death. The mortality in those that survive the initial event approaches 17% at 3 months.18,19 Non-fatal pulmonary emboli may be severe and some massive events may dictate fibrinolytic therapy occasionally associated with serious bleeding. The Pulmonary Embolism Response Team concept (PERT) represents integrated and multidisciplinary teams designed to provide the best standard of care for patients suffering from acute PE. These teams are becoming more common in clinical practice and it may soon become a new standard of care in patients with PE. Kabherl et al reported on a 30 month follow up on patients for whom PERT was activated. Even though PERT was initially conceptualized for patients with higher risk PE they found out that the PERT team was incredibly valuable for patients with low risk PE or with complex/unstable issues without confirmed PE. PERT has the ability to quickly mobilize resources that benefit patients, save lives, and provide efficient and prompt care.20

Chronic pulmonary hypertension

One of the most serious consequences that patients who suffer and survive a PE is chronic pulmonary hypertension. Chronic thromboembolic pulmonary hypertension (CTEPH) etiology remains poorly understood but is thought to most often result from obstruction of the pulmonary vascular bed by non-resolving thromboemboli.21,22 Chronic emboli can result after acute or recurrent PE or DVT. Increased pulmonary vascular resistance (PVR) leads to progressive pulmonary hypertension and right heart failure. In the non-occluded areas, pulmonary arteriopathy manifests in small to medium-sized muscular pulmonary arteries as intimal cellular proliferation with focal disruption of the internal elastic lamina and media by “glomeruloid” small vascular channels. These channels ramify into alveolar septal capillaries, can be indistinguishable from pulmonary arterial hypertension (PAH) and can contribute to disease progression.23 The incidence of CTEPH is unknown, and it remains controversial if CTEPH is a direct consequence of acute PE, but studies suggest that incidence of CTEPH may be 1%–3.8% within 2 years of acute pulmonary embolism.22 A prospective international registry reported a history of PE
in 74.8%, and a history of DVT in 56.1% of CTEPH patients, thus labeling CTEPH as a chronic complication of VTE. Some risk factors for CTEPH and VTE include: previous splenectomy, infected ventriculo-atrial shunts, indwelling venous catheters and leads, thyroid replacement therapy, cancer, and chronic inflammatory states.

Symptoms are absent in the initial phases of CTEPH and once symptomatic, symptoms are nonspecific and clinically indistinguishable from PAH, PE, or acute PE superimposed on pre-existing CTEPH. Right-sided heart failure can manifest at later stages of the disease secondary to right ventricular functional impairment. The incidence after a PE remains low, thus routine screening for CTEPH is not feasible.

Without treatment, the prognosis of CTEPH is poor and depends on the hemodynamic severity of pulmonary HTN. In contrast with other pulmonary hypertension subgroups CTEPH is potentially curable by surgical intervention. Pepke-Zaba et al reported results from an international prospective registry of 679 newly diagnosed patients (≤6 months) who were followed for 2 years. 427 patients (62.9%) were considered operable while 247 (36.4%) were non-operable, and 5 (0.7%) had no operability data.

Operable patients did not differ from non-operable patients relative to symptoms, New York Heart Association class, and hemodynamics. At the time of CTEPH diagnosis, 37.7% of patients initiated at least 1 pulmonary arterial hypertension–targeted therapy (28.3% operable, 53.8% non-operable). Pulmonary endarterectomy was performed with a 4.7% documented mortality rate. This study concluded that given the similarities between the groups, careful diagnostic workup is necessary to assess which patients will be good candidates for operative procedures. They also noticed that patients in the operable group were more likely to have thromboembolic disorders. This registry data highlights the importance of previous venous thromboembolism events as a causal factor for the development of CTEPH, along with a significant role for associated medical risk factors as coexisting mechanisms in the disease process. The registry data also indicate that, although pulmonary endarterectomy can be performed with a low in-hospital mortality rate, operability rates may vary considerably across centers and countries.

Removal of the obstructive material from the pulmonary vasculature is the treatment of choice to alleviate pulmonary obstruction and reduce resistance, but in 50% of patients the obstructions are technically inaccessible, or the risk/benefit ratio is unfavorable. Lately, balloon pulmonary angioplasty (BPA) has emerged as a valuable treatment option for inoperable CTEPH.

The ELOPE study indicates that almost half of PE patients can be considered to have a post-PE syndrome characterized by exercise limitation at 1 year which impairs their quality of life (QOL) and degree of dyspnea. Predictors of post-PE syndrome include male sex, younger age, higher BMI and smoking. Cardiopulmonary exercise testing (CPET) or 6-minute-walk test (6MWT) at 1 month many help to identify patients with higher risk for post-PE syndrome at 1 year.

Deep vein thrombosis (DVT)

Deep vein thrombosis (DVT) is a serious and sometimes life-changing event for many patients. Major DVT requires appropriate anticoagulation treatment for months or in many cases for years when the event results from an unknown cause. The use of anticoagulants may dictate refraining from contact sports, or activities such as skiing, and other winter sports for fear of excessive bleeding in case of injury. Rarely the use of anticoagulants may be associated with heparin-induced thrombocytopenia with or without thrombosis. Warfarin-induced skin necrosis is also a rare but potentially devastating complication. Venous gangrene with limb loss may be a result of these complications.

Silent venous thromboembolism

Borow reported that 66% of patients having surgery who had a previous DVT suffer a recurrent event without postoperative prophylaxis. The incidence of recurrent DVT in those with
previous asymptomatic events is unknown but likely to be greater than those without that history. One study enrolled 150 high-risk patients in an internal medicine service with consecutive hospitalization for another diagnosis, not DVT, who underwent Doppler US of the lower extremities. Four and one-half percent of patients were diagnosed with proximal DVT and 16% with distal DVT (dDVT). Female sex, elevated age and renal and electrolyte abnormalities were significantly associated with dDVT (p = 0.014, p = 0.009 and p = 0.046, respectively). Decreased mobility was independently associated with dDVT [OR 7.97 (95% CI 2.42–26.27), p = 0.001]. A high mortality rate, for non-VTE-related causes, was found, especially in the first week, among dDVT patients.33 Another study evaluated 294 patients over a 24-month period in a surgical intensive care unit. Prevalence of DVT was 7.5% in this population and no clinical signs of DVT were present. DVT was identified within major vessels including iliac vein 1.7%, common femoral vein 2.7%, superficial femoral vein 2% and popliteal vein 1%. In this study age, APACHE II score ≥12 and emergent procedure were identified as risk factors for presence of DVT.34 Another study included 71 patients who underwent total hip arthroplasty (THA) and 30 patients who underwent total knee arthroplasty to study the prevention of asymptomatic DVT with fondaparinux prophylaxis. In patients who received fondaparinux for 14 days after THA surgery, the incidence of DVT was 0% on the day of the surgery, 13.6% at day 1, 27.1% at day 4, and 11.9% at day 14. In patients who received fondaparinux for 14 days after TKA surgery, the incidence of DVT was 4.2% on the day of surgery, 50.0% at day 1, 58.3% at day 4, and 20.8% at day 14. The incidence of DVT after THA or TKA surgery at day 14 was significantly reduced compared to that at day 4.35 Asymptomatic DVT remains an understudied entity and more data is necessary to understand its prevalence and clinical significance.

Post-Thrombotic syndrome (PTS)

Incidence ranges from 25–50% following DVT and the clinical manifestations may not be apparent for 2–5 years after the DVT. In a considerable portion of patients, the thrombus fails to resolve resulting in obstructive changes or valvular incompetence years after the event.22 This syndrome can occur in cases of not only proximal DVT but calf DVT and asymptomatic DVT.

Chronic complications from DVT and/or PE can occur. PTS is associated with symptoms and signs that can vary between patients but most frequently include: pain, heaviness, cramps and persistent swelling of the affected extremity. Edema, telangiectasia, hyperpigmentation, lipodermatosclerosis and ulceration might be present. Prognosis depends on the affected anatomic segment and the patency of the involved vessel.22 Proximal DVT has an increased risk for developing PTS compared with calf or popliteal vein DVT.22,36 Illofemoral DVT carries a higher risk of recurrence, and the incidence of PTS is high despite anticoagulation.37 PTS is diagnosed based on clinical symptoms and venous duplex US. Symptoms can be exacerbated by exercise and improve with rest.22 Different scoring systems for PTS exist including The Villalta scale, Ginsberg score, and Brandjes score.38 The Villalta score combined with a venous disease-specific quality-of-life questionnaire is considered the current gold standard for diagnosis and classification of PTS.38

Use of elastic compression stockings (ECS) after DVT is the first treatment choice to prevent PTS by reducing leg edema, promoting venous blood return and improving venous pump function.22 Several studies have shown the benefits of using ECS.39 Brandjes et al. observed a 50% reduction in the incidence of PTS due to ECS.40 Elastic compression stockings are also helpful once PTS has developed as they increase fibrinolytic activity, stimulate collateral formation and help prevent venous ulceration.22,41 Aspirin 300 mg daily was tested in a small RCT and improved rates of ulcer healing.42 Pentoxifylline is a xanthine derivative that has been used for several decades in the symptomatic management of intermittent claudication.43 It also influences microcirculatory blood flow and oxygenation in ischemic tissues even though the mechanism is uncertain.44 In a Cochrane literature review of 12 trials 864 participants were included to assess the role of pentoxifylline in treating venous leg ulcers. Pentoxifylline is more effective than placebo in terms of complete ulcer healing (RR 1.70, 95% CI 1.30 to 2.24). Pentoxifylline plus
compression stockings is more effective than placebo plus compression (RR 1.56, 95% CI 1.14 to 2.13). Pentoxifylline in the absence of compression appears to be more effective than placebo or no treatment (RR 2.25, 95% CI 1.49 to 3.39). More adverse effects were reported in people receiving pentoxifylline (RR 1.56, 95% CI 1.10 to 2.22). Nearly three-quarters (72%) of the reported adverse effects were gastrointestinal including nausea, indigestion and diarrhea.44

Several years ago a large placebo controlled randomized trial was published indicating that ECS do not prevent PTS in the first 2 years in patients with a first proximal DVT. The authors conclude—“ECS did not prevent PTS after a first proximal DVT, hence our findings do not support routine wearing of ECS after DVT.” This statement is misleading since many physicians routinely prescribe ECS to control the acute symptoms of pain, swelling, heaviness, and other symptoms frequently associated with acute DVT. I would have preferred a statement saying that the trial does not support the routine use of ECS to prevent PTS, but these stockings may indeed be useful to control the patient’s symptoms. A number of methodological issues exist with this trial and are best summarized in an editorial commenting on this trial.46 It is apparent that more research is needed to identify the role of ECS for the prevention of PTS.

In selected patients with PTS surgical or endovascular treatments can be performed to relieve symptoms.22 Percutaneous transdermal recanalization of the iliac venous outflow tract by stent angioplasty is an emerging trend for treatment of PTS.22 The CaVent study tested Catheter-directed thrombolysis (CDT) using Alteplase to reduce PTS and the absolute risk reduction was 14.4%.47 PTS has been associated with higher healthcare expenses and worse quality of life of patients and its adverse impact is comparable with diabetes and congestive heart failure.22,48,49 A large NIH supported clinical trial has recently been completed comparing standard anticoagulation to pharmaco-mechanical fibrinolysis. (catheter-mediated or device-mediated intra-thrombus delivery of recombinant tissue plasminogen activator and thrombus aspiration or maceration, with or without stenting). The primary outcome was development of the post-thrombotic syndrome between 6 and 24 months of follow-up. The study showed that the addition of pharmaco-mechanical catheter-directed thrombolysis to anticoagulation did not result in a lower risk of the post-thrombotic syndrome but did result in a higher risk of major bleeding.50

**Venous insufficiency-induced lymphedema**

Lymphedema is classified into primary and secondary types. Primary lymphatic dysfunction is of congenital or idiopathic origin. Secondary lymphedema is from damage to lymphatic structures from parasites, surgery, radiation, infection, most commonly cellulitis or chronic venous hypertension due to chronic venous disease (CVD).51,52 Up to 1/3 of patients with CVD will have lymphatic dysfunction by isotope lymphangiography suggesting that secondary lymphedema is probably more common than the primary variety. Treatment of lymphedema is a necessary step when treating extremity ulcers.51,53 Raju et al concluded that clinical features, isotope lymphangiography, routine duplex imaging, and venography (sensitivity 61%) cannot reliably rule out a venous cause for lymphedema and suggested that intravascular ultrasound IVUS (sensitivity 88%) be routinely used. Swelling improved significantly after stent placement with significant pain relief [complete swelling relief was 16% and 44% (P < 0.001); pain relief at 40 months was 87% and 83%, respectively (P = 0.3), with 65% and 71%, experiencing complete pain relief in the abnormal and normal lymphangiographic groups].51

Compression stockings can be helpful for lymphedema management.51 There is little data about the optimal amount of pressure needed for edema reduction. The International Society of Lymphology recommends the highest level tolerated; however, Partsch suggests that even low pressures can achieve significant lymphedema reduction.53 Inelastic compression bandages should be applied at the start of treatment for patients with chronic edema, as they provide high pressures both when standing and walking. They also have a strong massaging effect and offer intermittent compression during walking and a low pressure when lying down, and tend to be well tolerated by the patient over time due to the reduction in edema which decreases the leg circumference. However, inelastic systems retain stiffness, thereby maintaining effective
pressure in the upright position for several days.\textsuperscript{53} The commonly used elastic (ACE) bandages are ineffective for reducing edema, and swelling may increase with these bandages in place.\textsuperscript{54}

One of the major issues with compression stockings is noncompliance among patients even in the presence of severe symptoms, and medical supervision and patient education have not resulted in better compliance. Manual drainage and decongestive therapy are effective techniques when properly administered. Massage techniques do not correct the basic pathology, however, and intensive lifelong daily compliance is necessary. In venous lymphedema, it is best used in conjunction with correction of venous pathology.\textsuperscript{53}

A most important compression modality for the treatment of leg swelling including lymphedema is Velcro compression. A number of devices are available which consist of overlapping Velcro straps made from inelastic material. They are quite easy to apply and remove, and as the leg swelling decreases they can be tightened to further reduce leg swelling.

Paradoxical embolus

Paradoxical embolism (PDE) describes the passage of venous or right-sided cardiac thrombus into the arterial systemic circulation.\textsuperscript{55} PDE should be suspected in cases where ischemic stroke occurs in the absence of conventional risk factors for cerebral vascular disease indicating an alternative mechanism. Forty percent of strokes have no identifiable or proven cause. This occurs most commonly through an intracardiac defect at the atrial level, but it can also occur via interventricular or pulmonary arteriovenous malformations.\textsuperscript{55,56} It has been suggested that PDE could account for as many as 47,000 unexplained ischemic strokes in young patients each year. In a small retrospective study with 13 patients with PDE, saline solution contrast echocardiography was used as a useful method to demonstrate patent foramen ovale (PFO). Treatment varied, but all patients received anticoagulation initially with heparin. The duration of therapy was individualized with patients receiving 6–12 months of anticoagulation. Surgical embolectomy was performed for 8 patients presenting with limb-threatened ischemia. Intravenous unfractionated heparin was administered followed by oral anticoagulation. An IVF filter was placed below the renal veins and no acute limb loss was reported. One patient had surgical closure of PFO with right atrial thrombectomy.\textsuperscript{55} PFO rates are higher in cryptogenic stroke than in the general population. In a meta-analysis of 23 case-control studies the odds ratio for PFO in cryptogenic stroke patients compared with those with stroke from known cause was 2.9 (95% CI 2.1–4.0) which was similar to Handek et al who prospectively studied 503 consecutive acute stroke patients and observed that compared with stroke from a determined cause, the PFO rate in cryptogenic stroke is significantly greater.\textsuperscript{56,57} Another prospective study of 504 patients investigated the presence of patent foramen ovale (PFO) in patients younger and older than 55. Two hundred twenty seven patients with cryptogenic stroke were compared with 276 patients with known causes of stroke. All patients received transesophageal echocardiogram for PFO evaluation including the 131 younger patients.

Concluding that there is an association between the presence of patent foramen ovale and cryptogenic stroke between both older and younger patients odds ratio, 3.70; 95% CI, 1.42 to 9.65; \(P=0.008\) and the older group (odds ratio, 3.00; 95% CI, 1.73 to 5.23; \(P<0.001\).\textsuperscript{57}

The above data reflect the enormous burden on society as a result of the many faces of VTE, and these disorders provide compelling evidence for employing appropriate thrombosis prophylaxis to patients based on their level of risk. Balancing the risks of thrombosis and bleeding in each individual is critical to minimize adverse postoperative events. The authors wish to emphasize that deaths from prophylactic anticoagulation are extremely rare, while deaths from withholding anticoagulation for “at-risk” patients are common. Data published over the last 4 decades will support these strong statements.

Risk assessment

Evaluation of the individual patient represents a complex problem. A list of individual risk factors that are associated with VTE have been known for a long time.\textsuperscript{19} Over the years new
factors have appeared that increase the risk of a thrombotic event. It is a daunting task to review all of these factors but if one fails to account for a potentially important risk factor, appropriate prophylaxis for that level of risk may not be prescribed. The result may be a serious or fatal VTE event. Complicating this analysis is that the tendency of these factors to result in thrombosis varies; i.e., bedrest is not as strong a risk factor as cancer or major surgery. A past history of VTE was identified as one of the greatest risks for developing a VTE postoperatively.\(^7\) Borow (1981) found that in patients not receiving prophylaxis, there was a 66% chance of recurrent thrombosis postoperatively in those with a past VTE history. Young age is associated with a minimal increase in risk compared to older patients where the risk is quite substantial.\(^58\) Howel et al demonstrated that congestive heart failure was an independent risk factor for VTE, and the risk increased with decreasing left ventricular ejection fraction.\(^59\) Summarizing, the more risk factors present the higher incidence of VTE. The more potent the risk factor, the more likely a VTE will result. A past history of VTE or current malignancy are among the most powerful risk factors that may result in a postoperative thrombotic event.

For many years there was little understanding of how these various risk factors interact in a quantitative manner to determine the position of each patient along a continuous spectrum of thromboembolic risk. During this era, clinical trial data in specific surgical populations was used to estimate risk according to the type and complexity of the surgical procedure.\(^60\)

Consensus guidelines vs. Clinical judgment

We discourage blindly following consensus guidelines without first determining whether the patients in studies used to develop the guidelines fit a particular patient in question. As seen in the quote below the guidelines emphasize the importance of careful clinical analysis of the patients’ risk before deciding about the prophylaxis strategy for that individual. This means one may not follow the guideline recommendations for an individual patient because their risk profile has not been tested in clinical trials. These trials commonly exclude very high-risk patients especially those with a history or family history of thrombosis, or multiple comorbidities. These patients must be protected due to their level of risk. The Caprini score provides an acceptable method to calculate individual risk, and recommend a prophylactic program tied to the final score. The Boston Hospital system described later in the chapter is a good example of how this system works.\(^61\)

The CHEST Guidelines included the following statement: “In this review, thromboprophylaxis is recommended 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.”\(^62\)

The following quote from the CHEST 2012 guidelines may help to clarify the spirit of this discussion.\(^63\) “A Cochrane systematic review analyzed data from six randomized trials involving close to 1,500 patients who required lower-leg immobilization for at least 1 week and comparing once-daily LMWH vs no thromboprophylaxis continued, typically, until the cast or brace was removed.\(^127\) We identified an additional multicenter study that has remained published only in abstract form \(^128\) and updated the meta-analysis by performing our own analysis. We did not extract the data found in the Cochrane review. PE was diagnosed in two of 585 patients in the placebo group and one of 576 in the LMWH group. Results failed to demonstrate or exclude a beneficial effect of LMWH on symptomatic DVT (RR, 0.34; 95% CI, 0.09–1.28), and two major bleeding events were seen with
**LMWH vs none in the placebo group.** The patient population was quite heterogeneous, and patients with a higher risk for VTE were excluded. Detailed information was not provided with regard to immobility."

Based on that text the summary statement in the guidelines is as follows:

“3.0. We suggest no prophylaxis rather than pharmacologic thromboprophylaxis in patients with isolated lower-leg injuries requiring leg immobilization (Grade 2C).”

Let us now try to apply those guidelines to an individual patient.

**Clinical vignette**

A 60-year-old male was struck by a car while riding his bicycle. He suffered a compound fracture of the ankle involving both bones and requires an external fixator to stabilize the fracture until the wound heals and definitive surgery can be done. His mother had a DVT and his sister suffered a non-fatal pulmonary embolus. Patient has limited mobility due to the hardware and painful nature of the injury.

He is very high-risk due to the nature of his injury, marked immobility, and family history of thrombosis. Anticoagulant prophylaxis in my view is required in this situation and selecting an approach not recommended in the guidelines may be life-saving.

The patient had a pulmonary embolus and died 10 days after the injury. He did not receive anticoagulant prophylaxis. The surgeon defended his approach stating the guidelines do not recommend anticoagulant prophylaxis. Hypothetically if you were that surgeon would you provide prophylaxis to a future patient you encounter with the same set of clinical circumstances? This type of patient with these characteristics has not been tested in clinical trials. The clinician must use judgment, knowledge of risk factors, experience, and in some cases common sense to provide protection for the patient. In the final analysis, the decision to use anticoagulant prophylaxis is based on carefully weighing the evidence for thrombosis vs. bleeding, and providing the safest course of action for the patient. It also stands to reason, but not often mentioned, that the prophylaxis for thrombosis needs to be continued as long as the patient remains at risk. In the case of braces and casts that period continues until these devices have been removed and the patient is ambulating normally.

Those who have practiced for any length of time fully realize that individual patient decisions are based on clinical judgment and experience as well as the guidelines. When the individual patient does not fit the criteria outlined in the guidelines, or when following the guidelines results in a poor clinical outcome, a different course of action is warranted. Clinical experience over the years continues to refine this process.

**Risk factors associated with the development of VTE**

**Age**

Borow (1981) studied the relationship of age to the development of DVT and found a linear relationship. The incidence of DVT in those 40–60 years of age was 20%, and in those 61–70 years of age the incidence was 36.4%, while when patients 71 years of age or more this incidence rose to 62.5%. He also reported that in patients receiving prophylaxis the incidence of DVT although lower overall, doubled in patients 61–70 years, and tripled in those 71 years of age and above.

Anderson and colleagues conducted a community-wide study in 16 short-stay hospitals to examine the incidence and case-fatality rates of DVT and PE in patients during an 18-month period starting in July 1985. There were 151,349 acute-care discharges from the 16 hospitals and VTE was found in 1372 patients (0.9%). Furthermore, the proportion of patients with clinically suspected DVT in whom the diagnosis was confirmed by objective testing increased with the
number of risk factors. The incidence of thrombosis was 100% in patients who had 5 risk factors and were suspected clinically of having a DVT. They found that the incidence rates of DVT and PE increased exponentially with age. These incidence rates increase with age and rising Caprini score that assigns points based on the age of the patient beginning with age over 40 years.

**Obesity**

Obesity is a common finding in the population with a prevalence of 20–25% and has been defined as a body mass index (BMI) $\geq 30$ kg/m$^2$. Studies have shown that the risk of thrombosis is increased twofold in these patients. On the other hand, women with a BMI $> 25$ kg/m$^2$ are at increased risk for developing thrombosis, and if they are taking oral contraceptive a synergistic effect occurs increasing their risk by 10-fold. The thrombotic risk is increased with advanced age, but adjustment for clotting factor levels were shown not to affect the risk estimate for obesity.\(^{64}\) White and colleagues, using an administration database in patients who underwent total hip arthroplasty, found that a body-mass index of 25 kg/m$^2$ or greater was associated with subsequent re-hospitalization for thromboembolism.\(^{65}\)

Obesity has emerged as a global health issue and there is moderate association with VTE. Obesity appears to be associated with increased risk for first occurrence of VTE.\(^{66}\) In a meta-analysis of 8125 patients with VTE and 23,272 control patients indicated that the likelihood of first spontaneous VTE among obese patients was more than twice that of individuals with normal BMI (odds ratio (OR) = 2.33; 95% confidence interval (CI), 1.68 – 3.24).\(^{57}\)

Increase in BMI above normal values has been reported to be associated with rising risk of VTE. One study of 87,226 women in the Nurses’ Health Study showed that the relative risk of unprovoked PE is raised by 8% per 1 kg/m$^2$ increase in BMI and approaches nearly six fold greater risk in individuals with BMI $\geq 35$ (p < 0.001).\(^{68}\) In a large Danish study that enrolled 29,340 women and 26,674 men found that VTE was [HR: 1.45 ([1.03–2.05]), [HR: 1.81 (1.27–2.56)], [HR: 2.82, (1.96–4.04)] in females and [HR: 0.98, (0.73–1.31)], [HR:1.32 (0.98–1.79)] and [HR: 1.72 (1.27–2.33)] in men with BMIs of 23.7 – 26.3 (24.4 – 26.8), 26.3 – 29.9 (26.8 – 29.4), and > 29.9 (> 29.4) respectively after adjusting for age, physical activity, smoking, height, cholesterol, hypertension, diabetes mellitus, and use of hormone replacement therapy.\(^{69}\)

Several studies have indicated a relationship between obesity and VTE recurrence.\(^{66}\) In one study 1107 patients were followed for an average of 46 months after termination of anticoagulation therapy and they found the frequency of recurrent VTE was 9.3% (95% CI, 6.0% – 12.7%) among patients with a normal BMI and 17.5% (95% CI, 13.0% – 22.0%) among patients who were obese.\(^{70}\)

The association between VTE-related mortality and PE has yet to be explained. Unexpectedly, obesity appears to be protective and associated with lower mortality among patients with PE – the so called “obesity paradox”.\(^{71}\)

**History of VTE**

Individuals who have suffered a previous VTE event are at increased risk for developing another thrombosis including a fatal pulmonary embolus. This factor is particularly important in patients requiring surgery, subject to prolonged immobilization, or serious illness especially cancer. In an observational study of 1231 patients, Anderson and colleagues reported that 19% of these individuals had a prior history of thrombosis.\(^{72}\) In another case-controlled study, patients were eight times more likely to suffer a recurrent event during a high-risk period than those without a VTE history.\(^{73}\) Borow & Goldson many years ago reported in a large venographic-based study that 66% of patients with a prior history of VTE suffered a recurrent event postoperatively.\(^{74,75}\)
Family history of VTE

Family history of thrombosis has been the most neglected risk factor and is frequently not even asked preoperatively. Several widely used thrombosis risk assessment models in medical patients do not even include family history. Studies show that family history is a risk indicator for a first venous thrombosis regardless of the other risk factors identified in an individual patient. In clinical practice family history may be more useful for risk assessment than thrombophilia testing. Family history of VTE may reflect family genetic risk factors. We know that carriers of one or more genetic risk factors are at increased risk of the first venous thrombosis, particularly when exposed to environmental triggers. These triggers may include surgery, muscle ruptures or sprain, immobilization, plaster cast, extended bed rest, hospitalization, pregnancy or puerperium, use of oral contraceptives or hormonal therapy, diagnosis of malignancy, etc. The relative risk of thrombosis increases with the number of risk factors identified. The combination of a genetic and acquired risk factor can result in a risk 60-fold higher than for those with no known risk factors and a negative family history. One study showed a positive family history increased the risk of venous thrombosis more than twofold regardless of the risk factors precipitating the thrombosis. In that same study 29.7% of patients with a positive family history had a genetic risk factor when tested. In addition, the chance of finding a genetic risk factor was up to 36.1% for patients with several affected relatives. The authors also concluded that the relative risk associated with a positive family history was of similar magnitude as the risk associated with a genetic risk factor. The authors conclude that in clinical practice, family history may be more useful for risk assessment than thrombophilia testing.

One extremely important and valuable case-cohort study was done to determine the familial risk of VTE in first, second, and third-degree relatives of affected individuals. This was the Swedish Multi-Generation Register which was linked to Hospital Discharge Register data for the period 1987–2009, and involved 183,515 individuals. The authors found an increased VTE risk among not only first-degree relatives but also second and third degree relatives and non-biologic relatives. They concluded that the genetic component of the familial clustering of VTE is strong. We agree with the authors that the family history is potentially useful for clinical VTE risk assessment even in second and 3rd degree relatives.

Ambulation

This risk factor has been difficult to standardize but a practical working definition has been published a number of years ago when studies not only tracked symptomatic events but also used venography to identify asymptomatic DVT. The authors defined ambulation as the ability to independently walk a distance of > 10 m [30 feet]). The authors studied thrombosis prophylaxis in medical patients using two doses of low molecular weight heparin compared to a placebo group. They compared enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Another study published a few years ago sheds light on this issue. The authors examined the relationship between the use of prophylaxis, VTE risk, and ambulatory status. They found that despite becoming ambulatory, patients remained at risk and benefited from the use of low molecular weight heparin prophylaxis 40 mg daily. This makes sense since ambulation does not affect underlying risk factors but removes only the risks of bedrest. Furthermore, the mean duration of prophylaxis was 7.6 days. The authors comment that data are lacking to support the concept of stopping pharmacologic prophylaxis when the patient is ambulatory or discharged after a short hospitalization. The period of time demonstrating efficacy for thrombosis prophylaxis in hospitalized patients is at least one week. This agrees with more than one hundred-sixty studies done over the last 30 years establishing efficacy as 7–10 days. There is considerable data in over 1 million patients to suggest that a short course of one or two days of prophylactic anticoagulation is ineffective in reducing the incidence of venous thrombosis. These data will be dealt with more completely in another
section. The Caprini score defines bedrest as inability to ambulate 30 feet (10 M), and walking a short distance to the bathroom or sitting in the chair does not qualify as ambulation using the Caprini score.

![Fig. 1. Endothelial damage from venous distention due to slow blood flow.](image)

**Major vs. Minor surgery**

There are major and minor surgical procedures which are usually classified by the complexity or extent of the operative procedure. For example, a pancreatic or liver resection would be considered major surgery, whereas an inguinal hernia or interval appendectomy is considered minor surgery. The problem is that the definition of a major operation from the thrombosis standpoint is different and very specific. In order to better understand this concept, let us examine the work of Rudolf Virchow, a German doctor, pathologist and anthropologist well-known for his achievements including the pathophysiology involved in the development of venous thrombi. Virchow’s triad describes venous stasis, hypercoagulability and vessel wall injury as the three cornerstones that contribute to thrombosis formation. Anesthesia can affect the three components of the triad. It can lead to venous stasis due to calf muscle paralysis. Anesthesia also can cause venous over-distention due to slow blood flow causing endothelial cracks (Fig. 1).  

Major surgery from the thrombosis standpoint is related to the use of a general or regional anesthetic as an additional factor besides the patient’s type of surgery, underlying pathology, and any additional thrombosis risk factors. The effects of an anesthetic including the muscle paralysis secondary to the muscle relaxants given to facilitate intubation cause the veins of the lower extremity to dilate up to 3 times normal size. Muscle paralysis secondary to a regional anesthetic can have the same effect. This venous dilatation may cause over distention of the veins, cracking the endothelium which exposes subendothelial collagen allowing thrombi to form in these cracks. Pooling of the blood also occurs. This slow blood flow can affect the white blood cells, transforming them into adhesion molecules due to the stasis. These adhesion molecules release inflammatory cytokines creating a local inflammatory response. Eventually these molecules attach to and penetrate the capillary wall permanently damaging these tiny vessels. The attached adhesion molecule attracts other molecules that pile up and adhere to the damaged area. As a result, the exchange of vital nutrients to the tissues, and release of metabolic waste material into the bloodstream are badly impaired. These waste products can produce local hypercoagulability by activating the clotting system. Surgical stress and patient risk factors such as cancer or infection can increase the hypercoagulable state.
This hypercoagulability may be compounded by other risk factors most notably a past history or family history of thrombosis, the tendency to develop significant or fatal VTE may be quite likely. If the legs are in stirrups, or straps around the legs are tight, venous stasis may be increased. Complete extension of the knee may compress the popliteal vein, further promoting venous stasis; and this process is known as the popliteal entrapment syndrome.\(^{85}\) This phenomenon narrows or completely closes the popliteal vein which results in diverting the blood flow through the superficial veins of the leg bypassing the popliteal fossa resulting in slowing blood flow out of the leg. That is why it is important to put a pillow under the knees during the operation to prevent complete extension of the knee.

The reverse Trendelenburg (head up) position used for many laparoscopic procedures along with elevated intra-abdominal pressure due to distension of the abdominal cavity with gas intensifies venous stasis further distending the veins. These mechanisms represent Virchow’s triad of venous stasis, vascular injury, and hypercoagulability and have been shown many years ago to represent causative factors for venous thrombosis. Pneumatic compression during the procedure helps to minimize these changes. The longer the procedure, the more these changes can occur. Tourniquets during surgery can also have these effects. The clinical proof of these concepts starts with the work of Dr. Borow showing how the length of surgery affects the incidence of VTE. The longer the surgical procedure, the more these factors can intensify and lead to a venous thrombosis.\(^{7,32}\) The Caprini score assigns 2 points for any anesthetic over 45 minutes and this is considered major surgery from the thrombosis viewpoint despite the fact that the surgical procedure is considered minor. Some authors add an extra point for surgery longer than 2 hours, and the Boston Studies (Cassidy et al) score 5 points if the operation lasts 6 hours.\(^{86}\) A surgical procedure might be considered minor, but can pose major thrombotic risks if the anesthetic lasts more than one hour.\(^{74}\)

**Length of surgery**

Operations that lasted from 1–2 hours were associated with a 20% DVT incidence in the control group. The incidence rose to 46.7% for operations lasting between 2–3 hours, and the incidence rose to 62.5% for operations over 3 hours. One must remember that at that time in the early 1980’s fibrinogen scanning with venographic confirmation was the best method for determining the total incidence of DVT in a patient population. This included a large number of asymptomatic events. Furthermore, thrombosis prophylaxis was not the standard of care, so most patients were not receiving prophylaxis. Studies during this era looking at venographically documented thrombosis in patients not receiving prophylaxis were of immense value in justifying the administration of anticoagulants to surgical patients. The incidence of bleeding problems was minuscule compared to the results achieved reducing the incidence of postoperative thrombosis. Borow’s landmark study involved studying five methods of prophylaxis for the prevention of postoperative venous thrombosis. The groups were (1) control, (2) low-molecular weight dextran, (3) mini-dose heparin, (4) bilateral pneumatic compression devices, (5) and elastic compressive stockings. DVT was evaluated using fibrinogen scanning confirmed by venography. Overall, 36% of patients, in the control group suffered a DVT. All of the treatment groups lowered the incidence of DVT including aspirin.

**Laparoscopic surgery**

A great number of procedures are done with a more minimal approach including laparoscopically-assisted surgical procedures and arthroscopic surgery. Despite the advantages including earlier ambulation, decreased pain and discomfort, these procedures still represent a risk of thrombosis due to the anesthetic and length of surgery. Nguyen and his group from the Department of surgery, University of California Irvine published a very interesting study comparing the VTE incidence between open and laparoscopic approach for four common surgical pro-
procedures. These included appendectomy, cholecystectomy, anti-reflux surgery, and gastric bypass during the period of time between 2002 and 2006. He studied a total of 138,595 patients having one of these surgical procedures. Overall the thrombosis incidence was significantly higher in the open cases compared with the laparoscopic cases (P < 0.01). The incidence of VTE after laparoscopic surgery continues to be lower than that of open surgery even when the data are stratified according to the level of severity of illness. This study corrected an earlier opinion we had regarding adding 2 points to the score if the procedure was done laparoscopically, and we no longer add extra points for this minimally invasive approach. We do not reduce the score however since the score also reflects time of anesthesia. The approach is only one factor that determines thrombotic risk and careful overall risk assessment needs to be done to properly characterize risk.

We feel that this was an excellent study although these types of investigations where all the patients are grouped together without very careful individual risk assessment may not reflect the true nature of individual thrombotic risk.

Clinical vignette

A 75-year-old obese male having a laparoscopic cholecystectomy for acute cholecystitis requiring a two-hour anesthetic, may not reflect the thrombotic risk of the average younger, laparoscopic cholecystectomy patient in this series. If this patient had a past history or family history of VTE, that would increase the risk even further (Caprini score = 9). Therefore, although this series showed a lower overall risk of VTE for the average laparoscopic cholecystectomy patient compared to the equivalent open cholecystectomy patient, that may not hold true when individual risk assessment is employed since a much higher level of risk may exist in individual patients such as this example. The concept of evaluating thrombotic risk according to type of procedure may be important but only when taken in the context of the individual risk factors of a given patient. We have seen many examples where the overall low incidence of thrombosis for an individual procedure changes drastically when individual risk assessment is applied. This patient would benefit from 30 days of LMWH prophylaxis postoperatively.

Reza Fazl Alizadeh and his colleagues, again from the University of California Irvine Department of Surgery continue to do pioneering research in this area and have published a subsequent study involving 750,159 patients from the period of 2005 to 2014. They used the National Surgical Quality Improvement Program database and looked at the overall incidence of VTE within 30 days of operation. Overall incidence of VTE was 0.32% in patients with benign disease who underwent laparoscopic abdominal operations including colorectal surgery, bariatric surgery, cholecystectomy, esophageal surgery, abdominal wall hernia repair, and appendectomy. Colorectal surgery had the highest incidence of VTE (1.12%) and was associated with significantly the longest length of stay and operative times. Those patients who develop thrombosis had a higher mortality and worse outcomes compared to those who did not suffer a thrombotic event. They concluded that laparoscopic colorectal procedures for benign disease represent a higher risk for the development of thrombosis compared with other laparoscopic abdominal operations. This study had some limitations since the National Surgical Quality Improvement Program database does not include details about past history of thrombosis, family history of thrombosis, type of prophylaxis postoperatively, dose of any anticoagulants used, and does not record the length of any of these prophylactic treatments. We know that all of these variables affect the VTE incidence for an individual.

Another individual patient factor is conversion from the laparoscopic approach to an open operation. This factor needs to be considered when assessing the patient risk. Excessive operative time that may be associated with certain laparoscopic robotic procedures also may increase the level of risk. The Boston group has assigned a higher score to patients who have operative procedures lasting 5 hours or more. Their impressive results using the score tied to a mandatory prophylaxis protocol will be discussed later in this chapter.
Previous major surgery

Landmark studies of Borow, 18% of patients developing a postoperative thrombosis had a past history of a major surgical procedure at some previous time. When the Caprini score was designed, we considered those procedures done within one month to be a minor risk factor (1).

Cancer

Cancer is a major risk factor leading to the development of VTE and approximately 20% of patients with cancer will develop this complication. The score does not stratify between different types of cancer thus there is expected variation in rate as some cancers have higher associated risk for developing VTE. VTE is also recognized as one of the leading causes of death in cancer patients. Rates of thrombosis vary widely depending upon the type of cancer, with the highest rates observed in brain, pancreatic, gastric cancer, and a variety of hematologic malignancies. Patients with cancer have an increased level of thrombotic risk especially when additional risk factors are present. The Khorana and Vienna scores are two additional scores that try to predict risk of VTE in cancer patients, but neither of them is validated for perioperative risk. Khorana score aims to identify ambulatory patients with cancer at increased risk of VTE by using two clinical variables (tumor site and body mass index) and three laboratory measurements (platelet, hemoglobin and leukocytes). Vienna score is a modification of the Khorana score (addition of biomarkers D-dimer and soluble P-selectin).

Chemotherapy

The prothrombotic state associated with malignant tumors has been shown to be further increased by chemotherapy. This is a complex issue since frequently central lines are necessary for the continued administration of these drugs which also increases the thrombotic risk. Many times, chemotherapy is used for patients with metastasis which in itself is also a risk factor for thrombosis. The type of chemotherapy also influences the risk of incidental VTE which appears more frequent in patients receiving platin-based drugs. However, with the multiple changes in the agents it is hard to individualize the expected risk with each agent.

Thrombophilia

Thrombophilia is a congenital or acquired condition that is characterized by an imbalance in the hemostasis producing a hypercoagulable state. It is often diagnosed by a first episode of VTE associated with increased risk of recurrence. It is recognized in about 50% of subjects who had experienced a VTE.

Hereditary thrombophilia

The most common entities of hereditary thrombophilia include antithrombin deficiency, protein C deficiency, protein S deficiency, resistance to activated protein C due to the mutation of Factor V Leiden, and G20210A mutation in the prothrombin gene (FII G20210A). These defects increase the chance of a VTE. Hereditary causes of VTE should be suspected in recurrent or life-threatening thromboembolism, young age (< 45 years old), multiple abortions or stillbirths, family history of VTE, or where there are no obvious acquired risk factors. In a prospective cohort study of 202 patients with colorectal cancer were stratified in those with thrombotic mutations (PTM +) and without thrombotic mutations (PTM-). These patients were screened for
factor V Leiden and prothrombin G20210A mutations which are the 2 most common defects in the western population. Coagulation markers including platelet counts, fibrinogen and D-dimer levels were measured and symptomatic VTE was observed. In the post-prophylactic period 2–12 months after surgery symptomatic VTE was observed. In the prophylactic period VTE incidence in PTM+ and PTM– was 0% and 1.6% respectively (p = 0.73). Levels of coagulation markers were comparable in both patient cohort within 28 days postoperatively. In the post-prophylactic period, VTE incidence in PTM+ and PTM– was 15% and 5.5% respectively. There was significantly increased incidence of lower extremity DVT in patients with factor V Leiden (17.6%).

Antithrombin deficiency was initially described by Egeberg in 1965. Protein C and S deficiency were found to be a cause of hereditary thrombophilia as reported in the early 80s. Factor V Leiden mutation related to activated protein C resistance and the mutation G20210A on the prothrombin gene were identified as causes of hereditary thrombophilias in the early 90’s. These are the 2 most common defects. Unprovoked VTE occurs more frequently in patients with hereditary thrombophilia than patients without thrombophilia HR 22.3 (P = 0.003) and the presence of hereditary thrombophilia increases the risk of VTE approximately 7-fold.

Other causes of thrombophilia are elevated concentration of coagulation factors (FVIII, FIX, FXI), deficiency of FXII or hyperhomocysteinemia.

Acquired thrombophilia

The most common causes of acquired thrombophilia are antiphospholipid syndrome (APS), acquired deficiency of natural inhibitors of coagulation, myeloproliferative syndromes and the presence of the mutation JAK2V617F, and nocturnal paroxysmal hemoglobinuria.

APS is a condition that increases the risk of vascular occlusion and is frequently seen in patients with pregnancy complications. It is an autoimmune disorder characterized by the presence of antibodies directed against proteins and phospholipids such as antiphospholipid antibodies (aPL) or anticardiolipid antibodies (aCL) or antibodies against the β2 glycoprotein I (anti-β2GPI) of IgG or IgM class.

The acquired deficiency of natural coagulation inhibitors (AT, PC or PS) are also independent risk factors for VTE (Table 1).

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, potentially life-threatening hematologic disorder characterized by chronic intravascular hemolysis caused by uncontrolled activa-

Table 1
Thrombophilia testing recommendations.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not test with concomitant VTE event</td>
<td>Test at completion of anticoagulant therapy for provoked VTE Test after treatment for acute event for unprovoked VTE, if cessation of anticoagulant therapy is considered and test results might change management.</td>
</tr>
<tr>
<td>Do not test when receiving anticoagulation therapy</td>
<td>Test when warfarin has been stopped for a minimum of 2 weeks, DOAC has been stopped for 2 days or longer and UFH or LMWH for antithrombin levels has been stopped for more than 24 hours</td>
</tr>
<tr>
<td>Do not test if VTE is provoked by strong risk factors</td>
<td>Risk factors are trauma, surgery, immobility, severe illness</td>
</tr>
<tr>
<td>Consider testing</td>
<td>VTE episodes at a young age in association with no clear provoking factors Strong family history of VTE</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td></td>
</tr>
</tbody>
</table>

Modified from: Connors et al.98
tion of the terminal complement pathway. Complement systems and coagulation systems are closely integrated with each influencing the activity of the other.\textsuperscript{[99]} Clinical manifestations may include involvement of unusual sites of thrombosis especially (hepatic (Budd-Chiari being one of the most common sites), mesenteric, cerebral (superior sagittal sinus thrombosis, dural veins). Thrombophilia is a major cause of morbidity and mortality in PNH. When thrombosis occurs, indefinite anticoagulation is recommended. This disease is also associated with breakthrough and recurrent thrombosis. The physician should have a high index of suspicion in cases of thrombosis at unusual sites, breakthrough thrombosis on adequate therapy, and excessive abdominal pain associated with well-treated visceral thrombosis such as portal vein or mesenteric thrombosis.

Eculizumab is a new available drug that controls intravascular hemolysis in PNH and inhibits the complement system. This drug needs to be given life-long.\textsuperscript{[99]} It enables patients who may die in their 30’s to have a normal life span. In a study including 195 patients that were followed for 66 months 3-year survival was estimated to be 97.6% with patients showing reduction in lactate dehydrogenase levels reflecting inhibition of chronic hemolysis. Thromboembolic events decreased by 818%, with 96.4% of patients remaining thromboembolic event free. Transfusion independence increased by 90.0% from baseline, with the number of red blood cell units transfused decreasing by 54.7%.\textsuperscript{[100]} Eculizumab was well tolerated, with no evidence of cumulative toxicity and a decreasing occurrence of adverse events over time.\textsuperscript{[100]}

**History of superficial venous thrombosis**

The incidence of superficial venous thrombosis (SVT) varies in different populations from 3% to 11\textperthousand.\textsuperscript{[101–103]}

The prevalence during the third decade of life is 0.05/1000 per year and 0.31/1000 per year in men and women respectively. It increases during the eighth decade of life to 1.8/1000 per year and 2.2/1000 in men and women respectively. SVT is more common in women (50–70\textperthousand).\textsuperscript{[101,104,105]}

The development of SVT in patients who concomitantly have varicose veins ranges from 4–59\textperthousand,\textsuperscript{[101,105–107]} whereas SVT in patients without varicose veins is found in approximately 5–10\textperthousand of all cases.\textsuperscript{[105,108,109]} SVT is a risk factor for the development and recurrence of DVT and it may even coexist with DVT in 6–53\textperthousand of patients and the most common presentation is extension from the great saphenous vein into the femoral vein.\textsuperscript{[75,103,105,106,110–121]} SVT above knee is associated with 17–19\textperthousand incidence of DVT versus SVT located below the knee segment has an incidence of DVT in 4–5\textperthousand of patients.\textsuperscript{[112,122,123]} SVT is a risk factor for DVT and recurrent PE. PE has been seen in a wide range from 1.5 to 33\textperthousand of patients with SVT. It has been reported in 18\textperthousand of patients when the SVT was involved in the great saphenous vein above the knee and 4\textperthousand when in the small saphenous vein.\textsuperscript{[103,105,108,117,124]}

The diagnosis of SVT should include a complete duplex scan with full evaluation of the entire deep venous system of the leg.

**Varicose veins**

Varicose veins are an entity within the spectrum of chronic venous disease (CVD); the presentation may vary from spider telangiectasias to reticular veins, and true varicosities. It affects approximately 23\textperthousand of adults in the US and it is more commonly seen in women and older adults. Varicose veins affect approximately 22 million women and 11 million men between the ages of 40 to 80 years.\textsuperscript{[125]} The prevalence increases to 80\textperthousand in men and 85\textperthousand in women if all forms of varicose veins are included (spider telangiectasias, reticular veins and true varicosities).\textsuperscript{[126]}

Risk factors for varicose veins include estrogen exposure (female), lifestyle (prolonged sitting or standing, smoking), acquired (obesity, pregnancy, DVT, age) and inherited (family history, tall height, congenital syndromes that affect venous pressure, valvular incompetence and venous ob-
The major mechanisms resulting in varicose veins include venous valvular incompetence, venous hypertension, inflammation, structural changes in the vein wall and shear stress.

Varicose veins may advance in severity and extent if causative factors are not corrected and treatment is not initiated. Advanced forms of chronic venous insufficiency may develop including lower extremity edema and venous ulceration. Varicose veins were associated with a 7-fold increased risk of DVT in a large observational cohort study.\textsuperscript{127}

Management options include lifestyle modifications, compression therapy, local/endovascular ablative therapies and surgical interventions. The majority of patients with varicose veins will require a multisystemic approach.

A retrospective evaluation of prospectively collected data undergoing procedures for varicose veins from March 2008 until June 2014 was completed. Patient clinical severity scores pre- and post-procedure, treatment choice and perioperative complications were collected. Venous clinical severity scores improved more with radiofrequency ablation + trans illuminated powered phlebotomy as compared to radiofrequency ablation alone. $(3.8 \pm 3.4 \text{ vs. } 3.2 \pm 3.1, p = 0.018)$. Regarding deep venous thrombosis, there was no significant difference between radiofrequency ablation + trans illuminated powered phlebotomy in patients vs. radiofrequency ablation alone. This study demonstrated that ablation of axial reflux plus trans illuminated powered phlebotomy produces improved outcomes as measured by venous clinical severity score, with slight increases in minor post-operative complications and should be strongly considered as initial therapy when patients present with significant symptomatic varicose veins and superficial venous insufficiency. Implementation of a standardized thromboprophylaxis protocol with individual risk assessment results in few significant thrombotic complications among high-risk patients, thus potentially obviating the need for routine post-operative duplex.\textsuperscript{128}

Königsbrügge et al demonstrated that the presence of varicose veins is associated with an elevated risk of VTE in cancer patients. In a prospective cohort study 1270 cancer patients were recruited and followed for 590 days. Sixty-six patients (5.2%) had a history of VTE, superficial thrombophlebitis was seen in 79 patients (6.2%), and varicose veins seen in 160 patients (12.6%). Ninety-eight patients (7.7%) developed VTE during follow-up. The hazard ratios for the risk of VTE in patients with a history of VTE or superficial thrombophlebitis were 1.44 (95% confidence interval: 0.67–3.07) and 1.94 (1.04–3.61), respectively, and 2.01 (1.26–3.21) in those with varicose veins. In multivariate analysis including history of VTE, history of superficial thrombophlebitis, presence of varicose veins, and other patient-related factors, the presence of varicose veins (2.10 [1.29–3.41]) remained significantly associated with an increased risk of VTE.\textsuperscript{129}

**Chronic Venous Disease (CVD)**

CVD is a very common problem affecting more than 25 million adults in the United States and more than 6 million with more advanced venous disease.\textsuperscript{130}

The most common manifestations of CVD are telangiectasias, reticular veins, and varicose veins. Chronic venous insufficiency (CVI) is a condition in which the venous system of the lower extremities is affected. It is associated with persistent ambulatory venous hypertension causing pain, edema, skin changes, and ulcerations. The edema seen in CVI is dependent and pitting. The forefoot is often spared to help distinguish it from other causes of edema such as lymphedema. Due to the obstruction of lymphatic drainage, lymphedema leads to accumulation of fluid that extends into the foot and toes.

Lipedema is characterized by accumulation of fatty tissues instead of fluid, therefore it is not pitting and often spares involvement of the feet, usually with a cuff of tissue at the ankle.

Post thrombotic syndrome (PTS) is characterized by lower extremity pain upon standing, dependent edema, and development of tender induration of the subcutaneous tissues (lipodermatosclerosis). The clinical picture of PTS is nonspecific, as clinical conditions other than DVT may result in a similar constellation of signs and symptoms of the lower extremity, including superficial venous insufficiency, trauma and obesity. Pruritus and eczematous skin changes are commonly seen. Ulceration of the affected area arises in a considerable number of patients.
some patients these changes may result in permanent disability. PTS is often triggered by minor trauma, and is mostly chronic and indolent with a high recurrence rate. Rarely, patients with persistent obstruction may experience venous claudication, which mimics arterial claudication.\textsuperscript{131}

It is known that venous hypertension may be a precursor of PTS. Patients with extensive thrombosis including major involvement of the iliofemoral segment, frequently have venous hypertension. Venous hypertension can be modified by appropriate compression garments including stockings and Velcro devices.\textsuperscript{132} Appropriate compression modalities including GEC stockings are a necessity to control pain and edema, frequently on a permanent basis.\textsuperscript{133}

**Leg swelling and Lymphedema**

Swelling of distal leg characterized by loss of definition of the normal bony prominences about the ankle. This can be seen with PTS, venous insufficiency, or lymphedema.

Chronic venous insufficiency which does not involve the foot so the veins of the foot are visible. Lymphedema presents with a hump over the dorsum of the foot which obliterates the venous pattern, along with a positive Stemmer's sign (inability to pinch the tissue at the base of the toes). When considering this risk factor, we score one point for either one or both legs affected with swelling from any cause.

**Stroke**

Stroke remains the third leading cause of death in the United States.\textsuperscript{134} DVT commonly develops in patients admitted to hospital with acute stroke, and may then lead to PE.\textsuperscript{135} It is associated with increased mortality and long-term morbidity.\textsuperscript{136}

The estimated rate of DVT in hospitalized patients who have a stroke is 20%–50% and two thirds of these are calf DVTs.\textsuperscript{62,137} The risk of fatal PE is estimated to be 4.9-fold higher in immobilized patients with a neurological disease.\textsuperscript{138} In a 19-year study period that analyzed deaths from the United States Bureau of the Census Compressed Mortality File, demonstrated that the corrected rate of fatal PE among patients with ischemic stroke ranges from 1.5% to 2.1%.\textsuperscript{139} Recurrent venous thromboembolism (VTE) is also more common in patients with limb paresis following stroke.\textsuperscript{140} The risk is even higher in patients with brain tumors presenting as stroke.\textsuperscript{141}

**Inflammatory bowel disease**

Data suggest that most patients with inflammatory bowel disease (IBD) have active disease at the time of the diagnosis of VTE.\textsuperscript{142,143}

It has been shown that patients with active IBD have a three-fold increase in risk of VTE and that has led to the use of thromboprophylaxis as the standard of care for patients in the hospital.\textsuperscript{144} Approximately 50% of VTE episodes developing concomitantly with IBD occur in patients who have been hospitalized within the past 3 months.\textsuperscript{145}

In a cohort study from the General Practice Research Database, 13,756 patients with inflammatory bowel disease and 71,672 matched controls were included in the analysis. Patients with IBD had a higher risk of VTE versus control group (HR 3\textsuperscript{-}4, 95% CI 2\textsuperscript{-}7–4\textsuperscript{-}3; p < 0\textsuperscript{-}0001; AR 2\textsuperscript{-}6 per 1000 person-years). It was seen that at the time of a flare, this increase in risk was much higher (8\textsuperscript{-}4, 5\textsuperscript{-}5–12\textsuperscript{-}8; p < 0\textsuperscript{-}0001; 9\textsuperscript{-}0 per 1000 person-years). Interestingly, the relative risk at the time of a flare was higher in non-hospitalized patients (15\textsuperscript{-}8, 9\textsuperscript{-}8–25\textsuperscript{-}5; p < 0\textsuperscript{-}0001; 6\textsuperscript{-}4 per 1000 person-years) compared to hospitalized patients (3\textsuperscript{-}2, 1\textsuperscript{-}7–6\textsuperscript{-}3; p = 0\textsuperscript{-}0006; 37\textsuperscript{-}5 per 1000 person-years).\textsuperscript{146}
**Figure 2** is an illustration of advanced inflammatory bowel disease in a surgical specimen from a diseased colon.

**Sepsis- Infection requiring IV antibiotics**

The association between acute infection and VTE is of paramount clinical importance due to the high rates of both entities. Acute infection it is associated with systemic inflammation which may increase the risk of VTE causing at least one or even more of the three components of Virchow triad: venous stasis, hypercoagulability and vessel wall injury.\(^{146–148}\)

In a population-based case–control study conducted in Denmark, of approximately 15,000 patients diagnosed with a first VTE episode in the hospital during the period 1999–2009 among all cases of hospital-diagnosed infections and community prescriptions for antibiotics 1 year preceding the VTE were evaluated. Schmidt, et al, found that, skin, intra-abdominal, respiratory tract, urinary tract and bacteremic infections diagnosed in hospital or treated as outpatient were associated with twofold increased VTE risk. The authors observed that this association was strongest within the first 2 weeks after the onset of the infection, and gradually lessening subsequently.\(^{149}\)

**Acute Myocardial Infarction**

Acute myocardial infarction is associated with a transient increased VTE risk independently of traditional atherosclerotic risk factors. The estimate was particularly high for PE. Rinde et al recruited 29,506 participants with a median follow up of 15.7 years. This Study concluded that highest risk of PE was observed in the first 6 months after the MI (HR 8.49; 95% CI 4.00–18.77). MI explained 6.2% of the PEs in the population (population attributable risk) and 78.5% of the
PE risk in MI patients (attributional risk). In an older study 89 patients were followed after an acute MI and 27% of patients developed VTE. These patients were more likely to be over 60 years old and had a previous history of angina and developed congestive heart failure with significant dysrhythmias. In a large population-based case controlled Danish study, inpatient diagnosis of heart disease was associated with a markedly increased risk factor for venous thromboembolism. The relative risk was particularly high for isolated pulmonary embolism without a concurrent diagnosis of primary deep venous thrombosis. There was an increased risk with myocardial infarction especially if MI occurred less than three months after VTE. The risk extended beyond 3 months past the initial hospitalization for heart disease; however, the association got weaker.

In 41,259 patients with VTE from the RIETE registry 22,633(55.6%) experienced a provoked VTE. Those with provoked events were more likely to have diabetes (OR 1.04; 95%; CI: 1.02 - 1.07), history of coronary artery disease (OR: 1.03; CI: 0.9–1.2), or prior stroke (OR 1.09; CI:106–1.1). During follow-up, patients with provoked VTE were 32% more likely to develop major adverse cardiac events (MACE) and major adverse limb events (MALE) than patients with non-provoked VTE (hazard ratio [HR]: 1.32; 95% CI: 1.1–1.5). The association was strong with recent immobility (HR: 1.37; 95% CI: 1.5–12.1), and cancer (HR: 1.7; 95% CI: 1.4–1.9), but not for other risk factors for VTE. After adjusting for multiple conventional cardiovascular risk factors, provoked VTE was independently associated with an increased risk for MACE (HR Adj: 1.39; 95% CI: 1.1–1.7). Cancer remained an adjusted predictor for both MACE (HR Adj: 1.7, 95% CI: 1.4–2.1) and MALE (HR Adj: 2.1; 95% CI: 1.01–4.6) outcomes.

**Serious lung disease**

Several lung conditions have been associated with VTE. Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and morbidity worldwide that is characterized by systemic inflammation. COPD patients are at increased risk of VTE because of immobilization, heightened systemic inflammation, cigarette smoking and venous stasis. The overall reported prevalence of VTE during COPD exacerbation ranges from 5% to 29%. VTE remains undiagnosed in this population because it can present similarly to COPD exacerbation. Post mortem studies of COPD patients have found pulmonary embolism (PE) in 28%–51% of cases. Furthermore, increased COPD severity is associated with VTE severity when measured in terms of lung function impairment [OR]moderate: mild = 1.16; 95% confidence intervals [CIs] = 1.03, 1.32) or medication usage (ORsevere: mild/moderate = 1.17; 95% CIs = 1.06, 1.26). However, there is no evidence that frequent exacerbation is associated with greater risk of VTE OR = 1.06; 95% CIs = 0.97, 1.15).

Idiopathic Pulmonary fibrosis (IPH) poses a higher risk for VTE. Sprunger et al used data from National Center for Health Statistics from 1988–2007 and identified 218,991 patients with pulmonary fibrosis. Risk of VTE in pulmonary fibrosis was 34% higher than in the background population and 44% and 54% greater for patients with COPD and lung cancer respectively. Patients with VTE died at a younger age than patients with IPH alone (females: 74.3 versus 77.4 years (p < 0.0001); males: 72.0 versus 74.4 years (p < 0.0001). Pneumonia is also associated with an increase in VTE. Pneumococcal infection specifically has been associated with host coagulation/anticoagulation stimulated by components of the bacterial cell wall. The cell wall also stimulates an inflammatory response including recruitment of leukocytes, cytokine production such as TNFα, IL-1 and IL-05 reducing barrier function and exposing extracellular matrix. This leads to exposure of subendothelial tissue factor which in combination with circulating factor VII induces coagulation. Platelet activating factor (PAF) has also been implicated in pneumococcus-associated VTE. In a large multicenter database of surgical patients it was shown that preoperative pneumonia may increase risk of developing venous thrombosis DVT, OR:8.20 (95% CI 6.75–9.96) and PE, OR: 5.07 (95% CI 3.63–7.07). A prospective population-based ARIC cohort concluded that obstructive spirometry patterns (COPD pattern, low FEV1 and low FEV1/FVC) are associated with elevated risk of VTE (HR 1.35,
95% CI 1.08–1.68). Patients with respiratory symptoms and normal spirometric results also had significantly increased risk of VTE (HR 1.40, 95% CI 1.12–1.73).

Restrictive lung disease pattern was not significantly related with increased risk of VTE (HR 1.52, 95% CI 0.93–2.49).\textsuperscript{165}

\textit{Congestive heart failure}

Patients with reduced cardiac function are thought to have a higher risk of venous thromboembolism (VTE). Thromboembolic events in hospitalized patients with heart failure (HF) seem to be under-recognized and can contribute to increased mortality and morbidity.\textsuperscript{166} More severe HF as defined by high NT-proBNP was associated with increased risk of VTE.\textsuperscript{167} Congestive heart failure has been described as a significant risk factor for VTE in bariatric surgery.\textsuperscript{168} In a retrospective analysis of the National Inpatient Sample database from 2005–2014 patients with VTE and heart failure had higher length of hospitalization. There was also an upward trend of VTE related hospitalization among patients with HF.\textsuperscript{169}

\textit{Sleep apnea}

Sleep apnea can also be associated with VTE. In a systematic review of 15 studies obstructive sleep apnea was found to be an independent factor of VTE with risk of DVT or PE being two-three-fold higher in patients with obstructive sleep apnea than those without.\textsuperscript{170}

\textit{Diabetes}

VTE incidence appears to be 2 times higher among diabetic patients < 65YO vs no diabetes.\textsuperscript{171} In a population-based study patients with diabetes who develop venous thromboembolism are more likely to suffer a complicated course and diabetes was an independent predictor for recurrent vein thrombosis.\textsuperscript{172} A Taiwanese study with 56,158 patients concluded that the incidence of VTE was higher in Type 2 diabetes mellitus (T2DM) patients than in controls [adj HR: 1.44 95% CI 1.27–1.63]. The risks of DVT (aHR = 1.43, 95% CI = 1.23–1.65) and PE (adjHR = 1.52, 95% CI = 1.22–1.90).\textsuperscript{173} In one study that included 358 patients undergoing total knee arthroplasty the incidence of DVT 14 days after TKA was significantly higher with than without diabetes OR: 2.71 (95% CI 1.183–6.212, p = 0.018).\textsuperscript{174}

Metabolic syndrome is associated with increased plasma levels of fibrinogen, factor VII and factor VIII potentially leading to a hypercoagulable state.\textsuperscript{175} In a case control study a total of 200 patients, metabolic syndrome was independently associated with idiopathic DVT (OR 1.94; 95% CI 1.04, 3.63).\textsuperscript{176} Prevalence of metabolic syndrome in recurrent venous thromboembolism was higher than in controls in a study of 116 patients with confirmed recurrent venous thromboembolism [OR:2.1 (95% CI 1.2, 3.7)].\textsuperscript{177} In another case control study in Korean population metabolic syndrome was associated with VTE (OR: 1.56; 95% CI: 1.07 to 2.27, $P = 0.020$) and especially with idiopathic VTE (OR: 1.71; 95% CI: 1.04 to 2.81, $P = 0.033$).\textsuperscript{178}

\textit{Hypertension}

Hypertension can also be a risk factor for DVT. In a metanalysis of 16 articles regarding hypertension, including 68,955 males and 53,057 females, this factor was associated with DVT after orthopedic surgery (OR 2.89, 95% CI 2.18–3.83, $Z = 7.38$, $P < 0.05$). Hypertension was also associated with an increase of VTE patients in newly diagnosed lung cancer OR 1.8; 95% CI 1.0–3.3).\textsuperscript{179}
Central Venous Access

Catheter-related thrombosis is a common complication of all anatomical sites and especially smaller veins. Presence of catheter within the lumen of a vein decreases flow and can created stasis leading to thrombosis. Nifong et al used fluid mechanics to calculate relative flow rates as a function of the ratio of the catheter to vein diameters. They determined that there is a decrease in fluid flow rate with catheter size (<0.001). PICCs in particular may contribute to substantial decrease in venous flow as much as 93%.180

Several studies have indicated that catheters are associated with increased risk of thrombosis. The MITH study included 299 patients with catheter-related thrombosis. Upper extremity DVT constituted 51% of all deep vein thrombosis. The use of central venous catheters (CVC) was associated with a 14.0-fold increased risk of upper extremity DVT (95% CI, 5.9–33.2).181 Post mortem examination of catheterized veins vs controls in 72 autopsied patients showed that in the catheters sheath fibril and staph can adhere to fibrin producing enzymes that promote thrombogenesis.182 In an 18-month long study, 208 central venous catheters including jugular and subclavian were analyzed with duplex sonography less than 24 hours after catheter removal. Mean duration of catheterization was 9 days. In these patients, catheter-related thrombosis was 33% with 42% localized in the internal jugular vein and 10% in subclavian veins.183 In patients with catheter associated staph aureus bacteremia, 48 patients had venous duplex US and outcomes were assessed at 12 weeks. Thrombosis by US was present in 71% of patients.184 In a prospective study of 105 patients undergoing chemotherapy having ≥2 positive cultures was associated with thrombosis (71% vs 3% in patients with negative or single positive culture).185 In a case study CVC related thrombosis was associated with paradoxical embolism through a patent foramen ovale.186 Thrombosis of a CVC can also lead to a superior venacava syndrome.187

Peripheral Inserted Central Catheters (PICC) lines can cause trauma to the vein wall and predispose patients to upper extremity venous thrombosis.188 PICC lines complications versus central venous catheters were analyzed in surgical patients. PICC lines did not differ from infectious complications with central venous catheters and thrombotic complications appeared more significant in PICC lines, also appearing earlier after catheterization.189

Hip, Leg, or pelvic fracture

The incidence of DVT is higher in patients with proximal extremity fractures than distal extremity fractures. In one study 102 patients underwent lower extremity venography 9 days after operative fixation and followed for 6 weeks. The overall incidence of clinically occult DVT was 28% with 40% in the femoral shaft, 43% in the tibial plateau, 22% in the tibial shaft and 12.5% in the tibial plateau.190 Multiple injured patients with pelvic fracture are at an increased risk of venous thrombosis. The incidence of pulmonary emboli in these patients has been reported to be from 0.5 to 8.3%. In a prospective study 198 patients with pelvic trauma were followed for 3 years. The incidence of pulmonary embolism was related to the Injury Severity Score ISS (ISS < 15 = 0% vs ISS > 15 = 4%, P < 0.05).191 In a Canadian study of 349 patients with major trauma, DVT occurred in 58% of the single cohort with major trauma who did not receive prophylaxis. Patients with highest risk were those with injuries of the lower extremities and spinal cord that were followed over 2 years. DVT was associated with spinal cord injury, fracture of the femur or tibia.192 Britt et al. reviewed the incidence of lower extremity DVT in 1093 patients with pelvic and lower extremity fractures. They found an incidence of 13% DVT and patients with DVT (1.3% PE), 15% in patients with both pelvic and lower extremity fractures (0.99% PE), and 9% in patients with lower extremity fractures only (0.63% PE).193

Lower extremity DVT can occur in patients with lower extremity trauma not undergoing surgery. The lower extremity DVT in patients with brace or immobilization can be from 0–17%.194,195 Use of prophylaxis in these patients significantly reduces the incidence of VTE but there is wide variation between physicians using anticoagulants.195,196
Patients treated with surgery following lower extremity trauma have a reported risk of 2.1% of DVT despite being anticoagulated with LMWH in the first 24 hours of admission.\textsuperscript{197,198} A retrospective review of 57,000 ankle traumas revealed a rate of 0.05% due to VTE.\textsuperscript{199} In patients undergoing surgery for hip or femur fracture DVT presence was 10%.\textsuperscript{200}

Upper extremity trauma is also related to a higher risk of VTE. Incidence of VTE reported in these patients is 1–5%.\textsuperscript{197} In a recent study between trauma patients, rate of VTE in patients with upper extremity trauma was reported to be 4.95% similar to the rate of VTE of all trauma patients.\textsuperscript{201}

**Multiple trauma with involvement of different organ systems**

Trauma is also a risk factor for VTE. The incidence of VTE after injuries depends on the population being described, nature of their injuries and prophylactic measures used.\textsuperscript{202} Patients at risk have an incidence of DVT that ranges from 10–20% and PE 1–2%, but mortality can be as high as 20–50%.\textsuperscript{202} Geerts et al performed a prospective study in 349 patients and 58% of them had clots.\textsuperscript{192} The occurrence of VTE during post-traumatic hospitalization is associated with morbidity and mortality. In a study from the German Trauma Surgery registry, 7937 were included and from them 146 developed clinically relevant VTE events with an overall incidence of 1.8%. Two-thirds of the VTE events occurred in the first 3 weeks of admission while patients were either receiving mechanical or chemical prophylaxis. Multivariate analysis identifies injury severity score, number of operative procedures, pelvic injury and concomitant disease as independent risk factors for VTE. Presence of VTE was also associated with higher frequency of sepsis, multiple organ failure and prolonged hospital stay. Mortality in the VTE group was 13.7% vs 7.4% in the non VTE group (P=0.004). Presence of PE was associated with mortality of 25.7%.\textsuperscript{203} Knudson et al used the American College of Surgeons national trauma data bank and found that age ≥40, pelvic fracture, LE fracture, spinal cord injury with paralysis, ventilator days, venous injury, shock on admission and major surgery were associated with VTE.\textsuperscript{202} Ratan et al analyzed 5,151,617 patients in Nationwide Readmission Database from 2010–2014 and 1.2% of these patients were readmitted within one year with VTE. The yearly cost of one-year readmission for VTE was $256.9 million accounting for one-third of the cost.\textsuperscript{204} The risk assessment profile score (RAP) identifies trauma patients at risk for DVT. In the prospective study there were 102 high-risk (64%) and 58 low-risk (36%) individuals studied. Eleven of the high-risk group (10.8%) experienced the development of DVT (asymptomatic, 64%). None of the low-risk group was diagnosed with DVT. Five of the 16 RAP factors were statistically significant for DVT. Eliminating prophylaxis and Doppler scans in low-risk patients resulted in a total savings of $18,908 in hospital charges. The RAP score correctly identified trauma patients at increased risk for development of DVT, and despite prophylaxis the high-risk group warranted surveillance scans.\textsuperscript{205}

A recent study using hospital discharge data in a pediatric population from 19 states indicated that DVT occurred at a rate of 0.77 per 1000 discharged among injured patients.\textsuperscript{206,207} In a pediatric trauma population risk factors included older age, injuries to the head, thorax, abdomen, lower extremity, spinal cord injury and use of central catheters.\textsuperscript{202}

**Acute spinal cord injury (paralysis)**

VTE remains a cause of significant mortality in patients with spinal cord injuries. Venous stasis is a major concern in these patients as well as DVT. These patients exhibit all 3 components of Virchow’s triad and the incidence of DVT is reported to be greater than 50% with incidence of final PE as high as 5%.\textsuperscript{208} Prevalence of DVT has been described to range from 14–100%.\textsuperscript{205} In a retrospective chart review of 151 patients with spinal cord injury (SCI) 17 (11%) had symptomatic VTE (9 PEs, 6 lower extremity DVT, 1 upper extremity DVT, and 1 with DVT and PE). In the univariable analyses, male sex and having other sites of injuries along with SCI were significant risk factors. In stepwise Cox modeling, independent risk factors were other sites of injuries.
(hazard ratio [HR] 6.07, 95% confidence interval [CI] 1.89–19.47, p = 0.002), age (HR 1.05 per year, 95% CI 1.02–1.08, p = 0.002) and the presence of leg paresis (HR 2.7, 95% CI 0.72–10.54, p = 0.14), whereas hypertension appeared to reduce the risk (HR 0.18, 95% CI 0.04–0.78, p = 0.02).²¹⁰ In a metaanalysis of 23 studies, there was strong evidence to support use of LMWH for thrombophylaxis.²⁰⁸

VTE remains a common complication following spinal cord injury. Because patients with SCI might not report the initial symptoms that are associated with VTE oftentimes the initial presentation includes extensive DVT and PE including sudden death. Furthermore, DVT in patients with spinal cord injury resolves more slowly and can lead to chronic venous occlusion. Early thromboprophylaxis is the most effective way to reduce the burden of this complication in the spinal cord injury patient population. Clinical practice guidelines are in place to guide clinicians in management of VTE in this patient population.²¹¹

**Risk factors affecting female patients**

VTE is a specific reproductive health risk for women. There is a synergistic effect between thrombophilia and various reproductive risk factors. VTE in women occurs during pregnancy, with the use of reproductive hormones and as a consequence of ovarian stimulation. In pregnancy, the risk of VTE is increased ~5 fold while the use of combined hormonal contraception (CHC) doubles the risk including contraceptive pills containing desogestrel, gestodene and drospirenone when compared with levonorgestrel. Hormone replacement therapy (HRT) increases the VTE risk 2–4 fold. In women who are at high risk, CHC and HRT should be avoided.

Pregnancy increases the risk of VTE 4-5-fold over that in the non-pregnancy state.²¹²,²¹³ VTE can occur at any trimester in pregnancy but is more common during the first half of pregnancy.²¹⁴ DVT during pregnancy is more common in the left leg compared to the right. This might be a consequence of May-Thurner syndrome in which the left iliac vein is compressed by the right iliac artery.²¹⁵ Also 12% of DVT’s are in pelvic veins and VTE remains common in the post-partum period.²¹⁶ In a 30-year-population-based study, Heit et al concluded the risk of VTE and pulmonary embolism was 5-fold to 15-fold respectively in the postpartum period compared to during pregnancy.²¹³

In a large primary care database containing 376,154 pregnancies ending in live birth or stillbirth, pregnancy ending in stillbirth was associated with a 6-fold increase in the rate of VTE compared with a live-birth outcome. In the postpartum phase still birth was the strongest risk factor with VTE (AR, 2444/100 000 person-years; IRR, 6.2/100,000 person-years).²¹⁷

Recurrent miscarriages affect 2–5% of women.²¹⁸,²¹⁹ The cause of recurrent miscarriage is only identified in 50% of patients.²²⁰ Thrombophilic disorders nowadays are thought to play a part in the cause of recurrent miscarriages, particularly the antiphospholipid antibody syndrome (ACA) syndrome.²²¹ Women who are thought to have higher risk of thrombophilia prior to pregnancy show an increased risk of thrombotic events during pregnancy and/or abortion.²²²

Estrogen influences hemostasis by increasing the levels of clotting factors (VII, VIII, X, fibrinogen) and plasminogen and lowering antithrombin III and protein S levels and altering activated protein C (ACP) resistance which decreases factor V activity.²²³ In a large case control study that compared VTE risk associated with levonorgestrel containing pills (2nd generation) and 3rd generation pills (desogestrel, gestodene) included 1524 cases and 1750 controls. Overall OCPs were associated with a fivefold increased risk of VTE. The risk was lower with levonorgestrel-containing pills (odds ratio [OR] 3.6; 95% CI 2.9–4.6) when compared with pills containing desogestrel (OR 7.3; 95% CI 5.3–10), gestodene (OR 5.6; 95% CI 3.7–8.4), drospirenone (OR 6.3; 95% CI 2.9–13.7), or cyproterone acetate (OR 6.8; 95% CI 4.7–10). The risk for VTE was highest in the first 3 months of use (OR 12.6; 95% CI 7.1–22.4), but even at 1 year a fivefold increased risk was detected. Among those who used the pill for at least 2 years, the risk was still elevated with desogestrel- (OR 1.9; 95% CI 1.3–2.9) and gestodene- (OR 1.5; 95% CI 0.9–2.6) containing pills when compared with levonorgestrel-containing pills.²²⁴
In a systematic review of progesterone only contraception (POCs) did not suggest an increase in odds of venous or arterial events with use of most POCs. Limited evidence suggested increased odds of VTE with use of injectables and use of POCs for therapeutic indications.225

Hormonal therapy is also a risk factor for VTE in women. Route of hormonal therapy is also important in risk for VTE. Oral but not transdermal estrogens are associated with a higher risk of recurrent VTE in postmenopausal women [HR, 1.0; 95% CI, 0.4–2.4], transdermal and [HR 6.4; 95% CI, 1.5–27.3, oral therapy].226 Treatment with tamoxifen has also been associated with increased risk of VTE. In a Danish population study of 16,289 women found that patients taking tamoxifen have a higher risk of VTE. The 5-year risk of DVT/PE was 1.2% for women receiving tamoxifen and 0.50% for women not receiving tamoxifen. Women treated with tamoxifen were at a higher risk for DVT/PE during the first 2 years after exposure (RR, 3.5; 95% confidence interval [95% CI], 2.1–6.0). Subsequently, their risk was not found to be substantially increased (RR, 1.5; 95% CI, 0.88–2.5). Older women taking tamoxifen appeared to be at higher risk than younger women during the first 2 years of exposure.227

END OF PART ONE

PART TWO: RISK ASSESSMENT USING THE CAPRINI SCORE

Risk assessment models (RAM's)

A variety of RAM's have been proposed ranging from those looking at a few major factors to very detailed models designed to capture all of the important factors that could lead to a thrombotic event. Most of these models attempted to simplify the assessment process by including only the most frequently associated factors known to increase the incidence of VTE. The problem with this approach is many patients with risk factors not included in the model may be denied prophylaxis but remain at high risk. Scores such as the Padua score and Improve score that do not include family history of thrombosis, or obstetrical-related complications, are good examples. These scores do identify most of the patients that are “at risk” for VTE but anytime a patient with family history of thrombosis, or history of an obstetrical complication is encountered, the patient may be misclassified. We began development of a RAM designed for surgical patients in 1986 inspired by the work of Professor Maxwell Borow who demonstrated that the more risk factors, the more likely the patient would suffer a thrombosis. He further observed that there was a linear relationship between the age of the patient and the length of surgery and development of a postoperative thrombosis.7,32 He also reported that 25–40% of patients having an operative procedure lasting over one hour developed a postoperative thrombosis. The rate was even higher when additional risk factors were present. He further documented that a physical method of compression when combined with an anticoagulant resulted in a very low rate of postoperative thrombosis.

Caprini risk model

Risk assessment is the first step in preventing death and disability from VTE. A multidisciplinary team put together a list of common risk factors and weighted these factors assigning a point score to each factor based on the literature of the day. The points were totaled, and the score correlated with the 30 and 60 days clinically evident VTE events (Fig. 1). This system accounted for most of the risk factors known at the time to be associated with VTE. The underutilization of VTE prophylaxis seems to be a global problem. In a large international cross-sectional study across 32 countries, 39.5% only of at-risk medical patients received VTE prophylaxis.228 On a national level, in 2011 around 2000 VTE events and 940 deaths have been avoided in England by implementing a compulsory VTE risk assessment tool developed by British investigators.229 That tool like the Caprini score includes family history of VTE as a risk factor.

The Caprini RAM was first published in 1991. This model was subsequently modified and updated to its most widely used version in 2005 to reflect new evidence and improved
understanding of VTE predictors as seen in Fig. 3. The value of the Caprini risk model resides on the ability to divide patients into four categories based on the VTE risk instead of assigning patients into a sole pool. The Caprini RAM uses individual risk factors such as age, weight, personal history of VTE and also surgery-related variables such as type and length of the procedure. Thirty-nine factors are included in the original score plus a box for additional risk factors. It is important to remember that additional risk factors not specifically listed but known in the literature to be associated with the development of VTE can be included in this OTHER box. Some of the well-known risk factors since the appearance of the original score are discussed in a subsequent section. Point values are assigned to risk factors to derive an aggregate score, which places patients into low, moderate, high and highest risk for VTE.

**Caprini risk scoring method**

This scoring tool involves assigning a point value to each risk factor according to the power of that risk factor based on the available literature. Next the point totals are calculated to obtain an overall score. This score has been validated in more than 100 publications comparing the score result to the 30-day real venous thromboembolism event rates. Based on a number of studies the scores are placed in one of three categories.
Low-risk patients are spared anticoagulant prophylaxis postoperatively since the incidence of 30-day clinically evident venous thromboembolism events is less or equal to the risk of bleeding from anticoagulation. Different set points for this low-risk group have been established depending upon the population studied. In general, those patients with a score of less than five fall into this category. As many as 50% of patients fall into this category although a recent meta-analysis suggests this number may even be higher.\(^{231}\)

Standard-risk patients are those that have a risk score reflecting a VTE incidence that exceeds the incidence of bleeding events using anticoagulation. Point totals in this group average between five and eight although those numbers may shift slightly depending on the population tested. We feel that there is strong evidence that patients in this group require 7 to 10 days of anticoagulant prophylaxis postoperatively. This opinion is based on the premise that patients who are at risk to develop venous thromboembolic events need to be protected for the period of time that has been shown in the literature to effectively prevent thrombosis. This large body of evidence will be discussed in a subsequent section. The results of all of these trials indicate the appropriate period is at least 7–10 days.

High-risk patients are those whose point totals indicate that they are at great risk to develop venous thromboembolism postoperatively, and merit anticoagulant protection for 30 days. There is strong evidence in the literature that 30 days of prophylaxis are more effective than shorter time periods in patients who are at very high risk for thrombosis which would include people in this group. Point totals for these patients are ≥ 8 for general surgery, 10 or greater for total joint replacement, and 12 or more following hip fracture.

The process of collecting these data has evolved over time, and we now feel that the most appropriate method is to have the patient fill out a patient friendly questionnaire prior to the operative day. Patients are encouraged to complete the document in the presence of their family so that thorough historical perspectives including family history of thrombosis can be uncovered. The patient should then submit this form ahead of time especially using the electronic medical record portal or other means so that at the time of the admitting history and physical, the appropriate healthcare provider can double check the form and ask a few final questions.

Some of the critiques of the Caprini RAM are its complexity and its time-consuming process. However, a patient-completed form of the Caprini RAM was recently devised and tested.\(^{232}\) The authors demonstrated an almost perfect correlation between patient and physician-completed scores. Having the patient fill out the form with their family removes the onus of extensive patient questioning and simplifies the face-to face encounter with the admitting physician. Collecting all of these data using the EMR and linking the score to a treatment plan is ideal (Fig. 4).

Fuentes and colleagues in a multistep process developed and validated this patient friendly form that is highly accurate compared to the same form being filled out by a trained physician. Their studies have shown that the average patient can complete a form in about five minutes, and the physician or healthcare provider completing and checking the document can accomplish that task in another five minutes. The authors have found that patients often fail to answer family history questions correctly, and do not understand how to calculate the BMI. Female patients often do not understand the questions regarding obstetrical complications and their importance in the risk assessment process. The examiner can quickly correct these simple problems as well as look for certain physical findings. These include leg edema and clinically significant varicose veins. Finally, the most important objection to collecting the Caprini score list of 39 variables has been resolved and this system is now published in four languages, with translations into Thai, Turkish, and at least one Chinese dialect on the way. Paz et al validated the Caprini score in Spanish, Arabic and Polish speaker languages and reported excellent agreement comparing physician and patient results (\(\kappa = 0.93\)) and high correlation 0.97 (\(P < 0.01\)) for the overall score.\(^{232}\)

One of the unique features of the scoring system is the dynamic nature of data collection possible. During hospitalization the score can be revised depending upon the appearance of certain clinical problems including infection, central lines for administration of antibiotics or chemotherapy, unexpected diagnosis of cancer, or emergent reoperation for anastomotic leaks, or infection.
A final score can be calculated upon hospital discharge, but revisions are still possible if events occur in the post hospitalization period due to the appearance of infection, or unexpected immobility. In these cases, the 7 to 10 day course of anticoagulants may be prolonged, and in some cases significantly extended depending upon the nature of the complication (Fig. 4).

We strongly discourage chart review for obtaining these data since one never knows if all the questions were asked and during what time frame. The dynamic nature of the tool is lost and if the score was obtained just prior to the operation many inaccuracies are possible.

We feel the preoperative holding area is the wrong place to try to determine the score except for emergency surgery. The nurses in the preoperative holding area are not trained to take detailed history and physical examinations, and the patient’s mind is focused on the planned operative procedure. The concerns of most patients at that time include—will the operation be

![Caprini Patient Friendly Score](image-url)

Fig. 4. Continued

successful? will the surgeon find something abnormal including cancer? will the surgeon have a bad day? how much pain will I be in after surgery? and finally how long will I be out of work?

Trying to have a preoperative patient focus on detailed historical items including family history and obstetrical complications while waiting preoperatively is not appropriate.

The National Surgical Quality Improvement Program (NSQIP) developed by the American College of Surgeons is a fantastic data pool of approximately 5 million surgical patients and growing all the time. Unfortunately, history of venous thromboembolism in the patient, family history of venous thromboembolism, the use, type, and duration of prophylaxis are not data points in this program. As a result, it is very difficult to analyze these data to determine the actual risk of individual patients as well as the effects of thrombosis prophylaxis including the anticoagulants modifying the venous thromboembolism event rate.

Pannucci and colleagues presented some very compelling data to indicate how venous thromboembolism risk is underestimated when chart reviews are compared to live patient interviews. Key questions regarding obstetrical complications, and family history of thrombosis including relatives of different degrees are much more likely to be discovered with face-to-face patient physician interactions.

We have observed that VTE related studies involving large groups of patients in a certain specialty, type of operative procedure, or following a traumatic injury do not accurately represent the group studied unless specific and detailed risk assessment is done. The purpose of this analysis is to separate out those very high-risk patients who may require a lot of prophylaxis to those low-risk individuals that may not even need any anticoagulation.

**Individual risk factor criteria interpretation for the healthcare provider**

**Age**

Patients aged 41–60 score = 1 point; 61–74 years = 2 points; age 75 + = 3 points.
Minor surgery

Patients having surgery with an anesthesia time of less than 45 minutes = 1 point.

Past major surgery

Individuals having surgery with an anesthesia time of greater than 45 minutes during the past month = 1 point.

Major surgery

Planned major surgery with an anesthesia time lasting longer than 45 minutes (including laparoscopic and arthroscopic procedures) = 2 points.

Total hip or knee replacement

These operations are scored as 5 points each due to their high-risk nature. It should be understood if additional risk factors are present, that further increases the level of risk. It is a misnomer to conclude that since all of these procedures are high risk, there is no need to risk assess. It is important to understand as the level of risk escalates above what is seen in the average patient, the type, duration, and intensity of the thrombosis prophylaxis must be adjusted. Patients with scores at the highest level may want to postpone or not have one of these elective quality-of-life improving procedures.

Visible Varicose Veins

Patients with visible bulging veins would receive a score of 1. This risk factor does not refer to a patient with spider veins or a patient with a history of surgically removed varicose veins. = 1 point.

Inflammatory Bowel Disease

History of Inflammatory Bowel Disease (IBD) and includes Crohn’s disease or ulcerative colitis. This risk factor includes both active and inactive inflammatory bowel diseases such as ulcerative colitis or regional ileitis. This would not include irritable bowel syndrome or diverticulosis. = 1 point.

Swollen legs (current)

Swollen legs include pitting edema of any level, loss of definition of the bony prominences, obscured surface foot veins, or indentation of the leg when a stocking is removed. This factor refers to either one or 2 legs affected. = 1 point.
Overweight or obese (Body mass index above 25 kg/m²)

This weight level was associated with patients developing symptomatic thrombosis readmitted following total hip replacement and women developing thrombosis. The combination of BMI 25 kg/m² and oral contraceptives increased the thrombotic risk 10-fold. = 1 point.

Heart attack

This refers to an acute myocardial infarction during the past 30 days. = 1 point.

Congestive Heart Failure

This risk factor includes patients who have had an episode within the last month. Additionally, patients who are currently being treated with medication for CHF are included, even if they have not had an acute episode within the past month. An ejection fraction alone should not be used when determining if a patient qualifies for this risk factor. = 1 point.

Serious infection (e.g. Pneumonia)

A “serious infection” is defined as a patient who requires hospitalization and intravenous antibiotics for treatment. For example, if a patient has a cellulitis requiring hospitalization with IV antibiotics they would receive one point for this risk factor. Treatments that are less severe and are managed on an outpatient basis with oral antibiotics are not included. Serious infections would include diverticulitis, bacterial infection of the bladder and lungs, and septicemia. = 1 point.

Lung disease (e.g. Emphysema or COPD)

In addition to emphysema or COPD these criteria also include any interstitial lung disease or patients with abnormal pulmonary function tests. This would include, but not limited to, any patient with sarcoidosis, pulmonary fibrosis, pulmonary hypertension, and bronchiectasis. Patients who present with more than one diagnosis meeting the criteria for lung disease will receive a point for each diagnosis. For example, if the patient has a diagnosis of sarcoidosis and COPD they would receive a total of 2 points for this risk assessment. Asthma is not considered a “lung disease” for the purpose of the risk assessment score. Additionally, patients with restrictive pulmonary disease related to obesity would not be included in these criteria. = 1 each point.

Bed rest (Restricted Mobility) [1 or 2 points depending on duration]

We define restricted mobility (bedrest) as any individual who is unable to ambulate continuously more than 30 feet. We have chosen this definition based on the prospective randomised, double-blind, placebo-controlled trial in MEDical patients with ENOXaparin (MEDE-NOX), which was a large prospective study where this definition was used. The rate of VTE in
non-ambulatory medical patients without prophylaxis was 19.7% compared to 10.6%; (p = 0.03) in those that were ambulatory without prophylaxis. Furthermore, the incidence of VTE in non-ambulatory patients in the LMWH group was reduced to 9.0% compared with 19.7% seen in the placebo group (RR = 0.46; 95% CI, 0.23 – 0.91; p = 0.02) (10.7% absolute risk reduction). In the ambulatory group, VTE incidence was 3.3% with enoxaparin 40 mg compared with 10.6% in the placebo group (RR = 0.31; 95% CI, 0.13 – 0.78; p = 0.008. The absolute risk reduction was 7.3%.

We assign one point to those fitting the definition of bedrest < 72 hrs. We realize that there are other definitions regarding ambulation but we feel the above data are the most robust.

Critics ask why isn’t everyone who spends a night in bed sleeping also at risk? We would answer that the bedrest in hospitalized patients is associated with their underlying disease process. For example, a person who has congestive failure, severe pain, infection, stroke, etc. is at bedrest because of their disease process. A normal person goes to bed to get necessary rest, not because of a specific illness. Patients moving short distances to the bathroom or sitting in a chair are not ambulatory according to this definition. Although we use the term medical patients at bedrest, these scores apply to all patients.

Patients who are using a cane or walker for stability are not considered as having restricted mobility if they are using their calf muscles for ambulation.

Patients who are unable to ambulate 30 feet continuously for > 72 hrs. receive 2 points total for restricted mobility. (We do not add an additional point for the first 24 hrs.)

A patient who requires crutches and is non-weight bearing would pass the restricted mobility criteria but would receive 2 points if they are not using calf muscles in one leg due to a brace, boot, or cast even though they can ambulate 30 feet.

Non-Removable Plaster Cast Or Mold (Worn For >72 Hours) That Prevents Leg Movement Within The Last Month (2 points)

The intent of this criterion is to capture any limitation in leg mobility which would interfere with calf muscle pumping action such as a leg brace or cast. Remember that patients using crutches who are non weight bearing on one leg would also be included. The use of an assistive device for stability, such as a walker, would not meet the criteria if the patient is using their calf muscles. = 2 points.

Confined to bed for 72 hours or more (unable to ambulate continuously 30 feet)

“Confined to bed” is confusing terminology and should be referred to as impaired mobility. The patient is unable to ambulate continuously 30 feet. This would also apply to any patient who is unable to ambulate using both leg muscles. For example, a patient who requires crutches and is non-weight bearing would be considered as restricted mobility even though they can ambulate 30 feet. Patients who are using a cane or walker for stability are not included in this group if they are using their calf muscles for ambulation. Patients moving a short distance to the bathroom or sitting in a chair are not ambulatory according to this definition. = 2 points.

Central Venous Lines

Tube in blood vessel in the neck or chest that delivers blood or medicine directly to the heart within the last month (e.g. central venous access, PICC line, port). = 2 points.

Current Or Past Malignancies (Excluding Skin Cancer But Including Melanoma)

Whether the cancer diagnosis is remote or recent the patient will receive a score of 2. This is because patients with a remote history of cancer are always at risk for occult metastasis which would increase their risk for thrombosis. Every incidence of cancer is considered separately and scored accordingly. For example, a patient who has a remote history of breast cancer and is recently diagnosed with uterine cancer would receive a score of 4 (2 points for each episode of cancer). For the purpose of this document Ductal Carcinoma in situ (DCIS) would also receive a score of 2 as there is always the potential of an invasive cancer. Myelodysplastic Syndrome (MDS) would be scored as 2 points only if the disease requires chemother-
apy treatment. The patient would also receive an additional point for the chemotherapy treatment.

**History of Blood Clots, Either DVT or PE. This Also Includes History of Superficial Venous Thrombosis (SVT) = 3 points**

Arterial blood clots are not included in the scoring. A CVA due to a paradoxical embolus would be given 3 points; however, a DVT must be documented by an objective measure in this case. Each episode of a DVT or PE is captured as a separate event for scoring. For example, a patient with a medical history of DVT in 2014 and PE in 2015 would be given a cumulative score of 6. However, PE and DVT events that occur simultaneously would be scored as 3 points. SVT must be captured and scored a 3 here as well.238

**Family History VTE = 3 points**

Family history of VTE should include first-degree relatives (sibling, son/daughter, parent), second-degree relatives (maternal half-sibling, paternal half-sibling, niece/nephew), and third-degree relatives (cousin). Younger age of first VTE and male relative increase the risk.77

**Personal or family history Of positive blood test indicating an increased risk Of blood clotting (e.g. Genetic Or Acquired Thrombophilia)**

A patient will receive a score of 3 points for each genetic thrombophilia marker. If a family member has a proven genetic marker the patient will receive a score of 3 unless it has been confirmed that the patient does not have this genetic marker. Genetic (inherited) factors: Factor V Leiden/Activated protein C resistance, Antithrombin III deficiency, Protein C & S deficiency, Dysfibrinogenemia, homozygous MTHFR, 20210A prothrombin mutation. Acquired factors: Lupus anticoagulant, antiphospholipid antibodies, myeloproliferative disorders (including thrombocytosis), disorders of plasminogen and plasmin activation, Heparin-induced thrombocytopenia, hyperviscosity syndromes, homocysteinemia. Human immunodeficiency virus (HIV) infection is an acquired thrombophilia.239

**Fracture of the Hip, Pelvis, Or Leg**

Fractures requiring surgical repair would receive 5 points for the fracture and will also be assessed additional points depending on the type of surgery. Patients undergoing an open reduction and internal fixation (ORIF) would be given 2 points for “surgery over 45 minutes”. Patients requiring a hemi-arthroplasty would receive 5 points “for elective hip replacement surgery”. For example, a patient with a fractured ankle undergoing an ORIF would receive a score of 7; 5 points for the fracture and 2 points for the surgical repair. An additional 2 points would be added if a cast or brace is applied or the patient is non-weight bearing.

**Serious trauma (E.G. Multiple Broken Bones Due To A Fall Or Car Accident) = 5 points**

Now or within the past month. There is some overlap between this category and the previous one and only one of these categories should be chosen.

**Spinal Cord Paralysis or Stroke = 5 points**

Now or within the last month.

**Women Only**

**Current use of birth control or Hormone Replacement Therapy (HRT)**

This includes estrogen contraceptives of any type. This also includes estrogen-like drugs, including raloxifene, tamoxifen, anastrozole, and letrozole. Exemestane has not been shown to increase the risk for DVT. Additionally, estrogen plus progestin, and progestin with or without estrogen are independent VTE risk factors.240 Recent publications have shown that there is no increased risk of DVT in men who are on long term testosterone therapy, therefore, testosterone is excluded. = 1 point.
Pregnancy or postpartum In The Last Month = 1 point

History of unexplained stillborn infant, recurrent spontaneous abortion (more than 3), premature birth with toxemia or growth restricted infant = 1 point

Recurrent fetal loss is associated with antiphospholipid antibody syndrome, procoagulant platelet microparticles and some inherited thrombophilias such as Factor V Leiden. There have been reports of both heritable and acquired thrombophilias being associated with pre-eclampsia, intrauterine growth restriction (IUGR) and abortion. However, these associations are not consistently reported with hereditary thrombophilias.241

Additional risk factors not specifically validated in the original Caprini model

A number of additional risk factors that have been associated with the development of VTE although not specifically listed in the 2005 score should be considered as additional risks. Note that there is a category for others in the original 2005 document and no audit has been done to indicate what additional risk factors have been scored over the past 13 years. Each one may be scored as one point.

Smoking242 Smoking is defined as the inhalation of anything that burns, including tobacco, marijuana, or vaping = 1 point.

BMI > 40243244 Individuals who are physically fit or athletes but very large are not exempt from this risk factor. The increased body mass is associated with stress on the cardiovascular and respiratory systems and thrombotic risk = 2 points.

Diabetes requiring insulin173,173,172 Only insulin products are included in the risk assessment score. This does not include any other oral or parenteral medications used for the treatment of diabetes = 1 point.

Chemotherapy90,245 Chemotherapy treatments used for any medical condition are included in the scoring. For example, a patient receiving Methotrexate for Rheumatoid Arthritis, regardless of the dose given, would receive a point for this risk assessment. Patients diagnosed with essential thrombocytosis taking hydroxyurea would also receive a point here, in addition to 3 points for “personal history of positive blood test indicating increased risk for blood clotting”.

Blood Transfusions246 Add one point for one or more blood transfusions

Length Of Surgery Over 2 Hours7 Actual current surgery time exceeding 2 hours, including anesthesia time. Do not add to the “5” for total hip or knee replacement surgery (add 1 point).

Meta-analysis involving selected studies using the Caprini score

One of the most valuable features of the Caprini Score is the ability to protect low-risk patients from receiving anticoagulant prophylaxis. Multiple studies have shown that the incidence of clinical thrombotic events in patients with a score of 4 or less is below 1%,247 and Panucci has published a meta-analysis involving 13 studies (14,776 patients) showed that 75% of patients had a score of 6 or less, and could be spared anticoagulant prophylaxis.231 They also found that these patients did not have a significant VTE risk reduction with chemoprophylaxis. On the other hand, those individuals not receiving prophylaxis had a 14-fold variation in clinical VTE risk depending upon their score (0.7% to 10.7%). These findings underscore the importance of knowing the type, dose, and extent of thrombosis prophylaxis in a surgical population for proper overall evaluation of VTE incidence.

One must remember that meta-analysis only analyzed 13 of over 100 studies as of this date. CHEST 2012 guidelines suggest that a Caprini score of 5 or more is associated with up to a 6% incidence of clinical VTE, and these individuals benefit from anticoagulant prophylaxis.249

Leonard has shown that the bleeding complications associated with anticoagulants are not trivial. He found that the incidence of wound hematoma, mucosal bleeding, and those having
prophylaxis ranges from 2.0 to 5.5%. These data emphasize the importance of using the score to target truly at-risk individuals.

This meta-analysis is an excellent example of how the Caprini score works. The low risk category comprises people who are spared of anticoagulation since the risk of bleeding exceeds the risk of anticoagulants to prevent VTE. The second group of patients that have risks factors for VTE and prophylaxis is clearly warranted. The high and highest risk subgroups comprise patients at high risk of thrombosis in whom extended thromboprophylaxis should be given after leaving the hospital up to 30 days post discharge.

General and vascular surgery

Bahl and associates from the University of Michigan published a landmark study to validate the Caprini score in a retrospective analysis. A total of 8,216 surgical patients from the National Surgical Quality Improvement Program were included (general, urology, and vascular surgery), the majority (52.1%) of the patients were classified to the highest risk level; 36.5% were high-risk, 10.4% as moderate risk, and 0.9% as low risk. The overall incidence of acquired VTE within 30 days post procedure was 1.44%. The incidence of DVT was associated with an increased risk according to the level of the patient’s risk (highest risk level 1.94%); (high-risk patients 0.97%); (moderate risk patients 0.70%); and (low-risk patients 0%). The difference between high and highest risk levels was statistically significant (p: 0.001). The University of Michigan hospitals have used this risk assessment tool along with mandatory care pathways since 2008. Physicians must opt-out of the standard algorithm for using thrombosis prophylaxis during hospitalization. Without enforcing care pathways, they are often ignored.

Benchmark study for reducing the VTE rate

Cassidy, et al, from the Boston Medical Center, the largest safety-net urban hospital in New England, developed a strategy to reduce VTE complications using the Caprini RAM. The scores obtained indicated the nature and length of thromboprophylaxis including an outpatient setting. The investigators used mechanical (pneumatic compression boots) and pharmacologic (unfractionated or low molecular weight heparin) as dictated by the risk stratification tool comparing the National Surgical Quality Improvement Program VTE outcomes (DVT, PE) before and after applying the standardized risk-stratified protocol in conjunction with a postoperative mobilization program.

The study resulted in decreasing the incidence of DVT observed by 84%, from 1.9% to 0.3% (p < 0.01), with implementation of VTE prevention efforts.

The PE incidence decreased 55%, from 1.1% to 0.5% (p < 0.01). Risk-adjusted VTE outcomes steadily declined from an OR of 3.41 to 0.94 (p < 0.05). The authors concluded with the following statement “A patient care program, emphasizing early postoperative mobilization along with mandatory VTE risk stratification and commensurate electronic prophylaxis recommendations, significantly reduced the likelihood of VTE complications among our patients”. Key elements in this program centered on mandatory compliance with an opt-out clause for the physician combined with providing prophylaxis according to risk for the period of time shown in the literature to be efficacious. The highest risk patients (score 9+) received 30 days of LMWH and there was 77% compliance in these patients. Patients with a score of 5–8 received 7–10 days of LMWH prophylaxis with a compliance rate of 89%.

Plastic and reconstructive surgery

In a retrospective analysis from the Venous Thromboembolism Prevention Study Network, Pannucci et al. investigated the validity of the Caprini RAM in plastic and reconstructive surgery
patients. A total of 1126 patients were included. The overall incidence of VTE was 1.69%. Patients with a Caprini score 8 were significantly more likely to develop VTE when compared with patients with Caprini score of 3 to 4 (OR: 20.9, p 0.001), 5 to 6 (OR: 9.9, p 0.001), or 7 to 8 (OR: 4.6, p 0.015). Approximately 1 in 9 patients (11.3%) with Caprini score 8 had a VTE event. It was noted that VTE risk was not limited to the immediate postoperative period (days 1–14) among patients with Caprini score 7 to 8 or Caprini score 8. Among these high-risk patients, more than 50% of VTE events were diagnosed in the late postoperative period (days 15–60).\textsuperscript{248}

**Trauma surgery**

A single center, retrospective case-control study of 78 patients with VTE versus 156 non-VTE patients who were randomly selected in a 2:1 ratio and admitted to the intensive care unit due to their critically ill status was done. The Caprini RAM was used to obtain the VTE risk score and VTE risk classification in critically ill VTE patients and non-VTE patients in order to prove the validity of the Caprini RAM. Zhang et al., found that patients with VTE had a higher Caprini score compared to the control group (\( p < 0.001 \)). Critically ill VTE patients classified at high risk and very high accounted for 88.4% according to the Caprini RAM. Compared to low-risk patients, the incidence risk of VTE patients at high-risk and very high-risk was significantly higher (OR: 2.042 in high-risk; OR: 11.681 in very high-risk patients). The logistic regression model identified eight risk factors in the Caprini RAM as predictors of VTE: bed-bound in internal medicine wards, severe lung disease (< 1 month), sepsis (< 1 month), large operation (< 1 month), malignant tumor, VTE personal history, VTE family history, and thrombosis with multiple trauma (< 1 month). The authors concluded that the Caprini RAM was applicable for critically ill patients, and had good predictive value for risk of VTE.\textsuperscript{251}

**Otolaryngology**

One of the Boston University studies involved patients from the Otolaryngology Service. Seven hundred and four patients were included in this study and the average score was 9.87 for those patients suffering a VTE event. The score for those without thrombosis was 5.62. Patients with a score of six and below did not suffer any thrombotic events. The incidence of thrombosis with a score of 7 to 8 was 3.01% percent while those with a score of greater than nine was 13.16%. The authors concluded that a score of over eight predicts a high risk of thrombosis despite chemoprophylaxis during the hospitalization. This is a good example of how the score threshold should be derived in individual surgical specialties to target the use of prophylaxis with anticoagulation to those at or above the threshold rather than a shotgun approach giving anticoagulants to all postoperative patients.\textsuperscript{252}

Another study in 2016 otolaryngology patients from the University of Michigan demonstrated the use of the Caprini Score to risk stratify this patient population. Those with the score of six or less had a DVT incidence of 0.5% while those with a score of seven or eight the incidence rose to 2.4%. Finally, in those with a score of > 8, the incidence of thrombosis was 18.3%. These statistics were based on 30-day follow-up of the patients and in this study these patients did not receive prophylactic anticoagulation.\textsuperscript{253}

**Chest surgery**

The Caprini score was evaluated in a retrospective study of 232 patients operated for lung cancer from 2005–2013 at Boston University. All of the patients received inpatient prophylaxis with UFH 5000 units TID, and were followed for 60 days. The overall incidence of VTE at 60 days was 5.2%, and 33% of the events occurred post-discharge. No VTE events were seen with
patients scores of < 5, while 1.7% of patients had a VTE event with a score of 5–8. The very high-risk group with a score of 9+ had a 10.3% incidence of VTE events. The authors suggested that these data should result in establishing a policy for outpatient anticoagulant prophylaxis for those with high scores.254

In another study from Boston University thromboembolism rates were compared using a preintervention group of thoracic surgery patients retrospectively analyzed from 2005–2013 including some patients in the previous study. The patients included both those having lung surgery as well as a group of esophagectomy patients. These patients all received inpatient prophylaxis with UFH only (302 patients). This patient group was compared to a post-intervention group (64 patients) starting in 2014 which divided patients into 3 categories according to a previously established protocol in general surgery described elsewhere. The most important element of this protocol was continuing prophylaxis with LMWH beyond discharge for a total of 30 days. In addition, those with a BMI > 40 received 40 mg injections twice daily instead of once daily in the lower weight patients. Provider adherence to the protocol was 100% and the patient adherence was 97.4%. The preintervention group had an incidence of VTE events of 7.3% (22/302), and the post intervention group had a VTE incidence of 3.2% 2/64. There were no bleeding complications and although these results are not statistically significantly different, the positive trend and high patient acceptance of extended prophylaxis, the authors felt, supports this approach.255

**Orthopedic surgery**

A prospective study involving 92 fracture patients was done to evaluate clinical predictors for preoperative DVT. Specifically, clinical signs, p-dimer, DVT risk assessment score both with Wells and Caprini scores and Doppler ultrasononography were done preoperatively. The incidence of preoperative DVT was 16.3% and in these patients the Wells and Caprini scores were statistically significantly higher than those not suffering a thrombosis (p < 0.05 all).256 The authors concluded that patients with a Caprini score of 12 or more should be screened with a preoperative ultrasound examination to rule out DVT.

A very recent publication involving 1078 patients has appeared comparing the results of a prospective department-based protocol in patients undergoing total joint replacement to the Caprini risk assessment model retrospectively in the same patient group.257 The investigators’ goal was to determine if the department protocol or the Caprini score would better identify VTE events after total joint replacement. All therapeutic decisions regarding thrombosis prophylaxis were based on the department protocol not the Caprini score. The department protocol divided patients into low or high risk based on the presence or absence of one or more of the following criteria. Patients were considered high risk if they had a VTE within the prior year, morbid obesity with a BMI greater than 40 with additional comorbidities, active malignancy, bilateral staged total joint replacement, and inherited or acquired thrombophilia. If none of these criteria were present the patient was considered low risk. Total hip and knee replacement patients who were considered low risk received aspirin 325 mg twice daily for six weeks. Those patients considered high risk received 12 days of DOAC anticoagulant followed by twice daily aspirin for an additional four weeks. At the conclusion of the study a retrospective chart review of every patient was conducted and a Caprini score determined for each of these individuals. Statistical analysis indicated that the high-risk cutoff for the Caprini score was 10 or above.

Eight patients in this study suffered a symptomatic venous thromboembolic event and according to the department protocol, 7 of these individuals were considered low risk receiving only aspirin prophylaxis. On the other hand, seven of the eight patients with the thrombotic event were correctly placed in the high-risk group with a Caprini score of 10 or more. Once the results of this study became available, the department protocol was abandoned in the Caprini score is now used prospectively to classify these total joint replacement patients and provide appropriate prophylaxis. A large multicenter trial is being proposed to verify these preliminary results. We feel it is possible in the future, based on additional studies, to define the population
where aspirin is the most appropriate choice and selectively use the more powerful anticoagu-
lants where the risk is clearly greater.

Medical patients

A number of studies have addressed the Caprini score in medical patients over the past few
years.258–265 These studies in many cases have compared the Caprini Score to the Padua Score
which has been recommended by CHEST 2012 for use in medical patients. CHEST consensus
leaders did not look at the Caprini score at that time despite several reports indicating the util-
ity of this score in medical patients. Since that time a number of reports have documented the
Caprini score as being more valuable in identifying patients at high risk for VTE. Several impor-
tant factors are recorded in the Caprini score that are missing in the Padua score and other more
recent scores proposed for use in medical patients. The most important missing factor in these
other scores is family history of thrombosis. This factor is discussed in detail elsewhere, and
represents a powerful predictor of VTE. Obstetrical complications are another important missing
question not addressed in other scores. These obstetrical complications may be associated with
the Antiphospholipid Antibody Syndrome which may be associated with an increased risk for
thrombosis. Another simple fact is no other risk scores look at as many variables, and we know
the more thorough a history and physical, the more comprehensive analysis of risk is possible.
Unfortunately life is not simple and just looking at some common risk factors often results
in missing important variables.266 The latest guidelines for thrombosis prophylaxis in medical
patients have just been published. They discuss the use of the Padua or IMPROVE scores but
acknowledge that “Although optimal strategies for VTE risk assessment and decision making
on prophylaxis are yet to be identified, when clinicians and health care systems use these ASH
VTE guidelines, they should integrate VTE and bleeding risk assessments into clinical decision
making processes.” We assume that despite the number of publications addressing the Caprini
Score in medical patients none of that data was considered relevant for their review.267 We look
forward to more studies using the Caprini score in this patient population. A number of large
hospitals have suggested that using a hospital-wide risk assessment tool is preferred for a num-
ber of practical reasons.

Bleeding Vs. Thrombosis

It is important to understand that skilled surgeons are rightfully concerned about postopera-
tive bleeding that may result from prophylactic anticoagulants. Certain bleeding events may be
associated with significant postoperative complications including infection, reoperation, or de-
creased functional outcomes in the case of total joint replacement procedures. While that’s a
major concern it is important to realize that bleeding deaths are very rare using prophylaxis.
Withholding anticoagulation and in surgical patients who are at significant risk may be associ-
ated with an increased incidence of fatal pulmonary embolism.

Kakkar and associates published a randomized prospective multicenter trial involving pro-
phylaxis against fatal pulmonary emboli using low-dose unfractionated heparin.268 They en-
rolled 4121 patients undergoing major surgery in this trial. Anticoagulant prophylaxis was used
for one week, and objective endpoints including venography were employed. In the 24 centers
involved, 16 fatal pulmonary emboli occurred in the control group versus two patients in the
group treated with heparin prophylaxis for one week. The authors concluded that low-dose un-
fractionated heparin saved 7 lives for every 1,000 operated patients. The overall incidence of
deep vein thrombosis was reduced from approximately 30% in the controls to 10% in the treated
patients. No deaths from bleeding were observed in the patients receiving heparin prophylaxis.

Many surgeons were skeptical of these results since at that time (1975) it was unheard of to
give surgical patients anticoagulants which might result in postoperative bleeding. Public opin-
ion changed when Rory Collins published the results from the analysis of 70 evenly randomized trials of perioperative unfractionated heparin compared to controls in general, orthopedic, and urological surgery.\textsuperscript{269} There were over 12,000 patients in this study and the results were remarkably similar to the original Kakkar trial 15 years earlier. The risk of fatal pulmonary embolism was reduced from 0.9% to 0.3% representing a 66% relative risk reduction in the treated patients. The overall incidence of pulmonary emboli was 3% in the control group and 1.7% in the treated subjects. There was no difference in bleeding deaths between controls and treated patients. In 1988 one could conclude that in 94 centers around the world over a 15-year period highly statistically significant reduction of venous thromboembolism including deaths resulted from administering unfractionated heparin in small doses to postoperative patients. Of great significance was the fact that there was no difference in bleeding deaths between the controls and the treated patients. THE TREATMENT PERIOD FOR ALL OF THESE STUDIES WAS 7–10 DAYS.

A randomized double-blind comparison of LMWH with unfractionated heparin involving 23,078 surgical patients given prophylaxis for 5 to 20 days was carried out in 67 worldwide centers and the results reported in 2005.\textsuperscript{270} Autopsy adjudicated fatal pulmonary emboli represented the primary endpoint in the trial and occurred in 0.15% of patients in either group. There were no deaths from anticoagulant related bleeding in the 23,078 patients. One may conclude from these results that administration of one of these anticoagulants for at least five days practically eliminated the possibility of a fatal pulmonary embolus despite many patients at significant risk for venous thromboembolism. The combined results of the above three trials involved 43,000 patients, 160 centers worldwide given anticoagulant prophylaxis for ONE WEEK establishing efficacy with objective diagnostic endpoints. Remember these studies were conducted over a 30-year period.

The CHEST 2012 guidelines reported on the results of a meta-analysis of 51 randomized controlled trials comparing low molecular weight heparin to low-dose unfractionated heparin in 48,000 general and abdominal surgical patients who were treated for at least SEVEN days, and the thrombotic risk was 30% lower in the low molecular weight heparin groups.\textsuperscript{271} Unfortunately, the CHEST 2012 consensus guidelines did not emphasize providing prophylaxis for one week despite the fact that this period was shown to be efficacious in these 51 trials they analyzed.

Length of prophylaxis

The Surgical Care Improvement Program (SCIP) was a nationwide program established in 2006 to improve surgical care. One of the initiatives involved the administration of a single dose of anticoagulant medication within 24 hours of surgery to patients who were judged to be at risk for venous thromboembolism and did not have a contraindication from bleeding (SCIP-VTE measure). It was a required Joint Commission measure for all hospitalized surgical patients.\textsuperscript{272} Altom and associates published a large trial involving 30,531 patients having surgery from 2006 to 2009 in a database linked with the Veterans Administration surgical quality improvement program data.\textsuperscript{80} Compliance with the measure was documented in 89.9% of the patients and the incidence of venous thromboembolism in these patients was 1.4%. Noncompliance was documented in 10.1% of the patients, and the incidence of venous thromboembolism in these individuals was 1.3%. The authors concluded that there was no association between SCIP-VTE adherence and the incidence of postoperative venous thromboembolism. Although those results were published in 2012 this practice continues in many hospitals to this day despite the fact that this measure has been discontinued by the centers for Medicare and Medicaid services.

A study involving 500,000 US venous thromboembolism events annually was reported by John Heit from the Mayo Clinic in 2017.\textsuperscript{75} Half of these events were related to hospitalization in patients where universal in-hospital VTE prophylaxis was provided. The mean duration of hospital stay was 70 hours. The authors concluded that a short course of anticoagulant is ineffective in lowering the VTE rate.
Another study, this time focusing on total joint replacement, found that the rate of pulmonary emboli increased from 0.87% prior to the SCIP-VTE measure to 1.3% following implementation of the measure.\textsuperscript{273} The authors concluded that this measure was not successful in reducing complications in total joint replacement patients. The largest study demonstrating the discordance between SCIP-VTE adherence and postoperative outcomes involves 779,922 patients followed for 30 days over a five-year period and reported in 2017.\textsuperscript{81} During that time adherence to the measure improved from 14.6% to 20%. The postoperative DVT rate increased by 7.1% and the postoperative PE rate increased by 3.7%. The authors concluded that short-term anticoagulant prophylaxis postoperatively does not lower the VTE rate. Lowering the VTE rate after surgery requires at least one week as previously shown in more than 160 centers over the past 40 years.

Extended prophylaxis

The RIETE worldwide database was queried in 2008 by Arcelus and colleagues and they reported on the time course in clinical presentation of postoperative VTE using these registry data. They observed that 77% of patients developed their thrombotic event after leaving the hospital and 55% of these thrombotic events were diagnosed after prophylaxis was discontinued.\textsuperscript{274} These data emphasize the need for continued prophylaxis after hospitalization for at least a week or in cases of very high risk up to 30 days postoperatively.

CHEST 2004 guidelines considered history of thromboembolism in the highest risk group of patients along with cancer and indicated that the risk of thrombosis was as high as 40 to 80% with a 1% to 5% chance of a fatality.\textsuperscript{60} These data were based on objective endpoints including asymptomatic thrombotic events. They recommended continuing thrombosis prophylaxis for 28 days on the basis of these event rates. The 2008 CHEST guidelines emphasized that patients who have undergone major cancer surgery or have previously had VTE should be considered to receive LMWH prophylaxis for 28 days.\textsuperscript{275}

The CHEST 2012 guidelines suggested that risk of VTE remains elevated for at least 12 weeks following surgery.\textsuperscript{249} This edition of the guidelines included three excellent studies including one meta-analysis in patients having surgery for benign and malignant disease. All three studies concluded that extended duration prophylaxis reduces the risk of symptomatic or asymptomatic DVT by at least 50% and two of them reported that proximal DVT was reduced by 75%. The CHEST authors reiterated their suggestion that for patients undergoing major cancer surgery 28 days of prophylaxis should be considered, but failed to include a past history of DVT in these recommendations despite the fact that the prior two editions of the guidelines made that recommendation. We find that conclusion odd considering that the data in the 2012 guidelines regarding extended prophylaxis was much more robust than in the previous editions. This included the meta-analysis involving patients with both cancer and benign diseases.\textsuperscript{276} We would suggest based on all of these data as well as the excellent study from Boston University that patients considered to be very high risk using the Caprini score should receive 30 days of anticoagulant prophylaxis with LMWH. The very high-risk group in that study and related studies in the Boston Hospital system was defined as a score of \( > 8 \).\textsuperscript{61} We also suggest that in an individual population the very high-risk score be determined prospectively. Several orthopedic groups performing joint replacement use a score of \( 10 + \) as the very high-risk category,\textsuperscript{257} and one study uses \( 12 + \) in hip fracture patients.\textsuperscript{256}

Conclusions

1. Avoid chart reviews since they depend on the accuracy of the data collection including did the examiner ask all of the questions. Face-to-face encounters are critical as well as using the patient-friendly form. Patients welcome the invitation to participate in their care.
2. Mandatory compliance must be enforced for prophylaxis protocols based on risk score to have a lasting effect lowering the VTE rate. The physician should be given the opt-out option based on individual clinical circumstances; otherwise, the protocol should be automatic.

3. Use of clinical judgment to select a prophylaxis option in the face of patients with a history or family history of VTE, or increased risk of bleeding, instead of relying on guidelines is critical and may be lifesaving. The guidelines commonly exclude patients at high risk for VTE as well as those with a past history or family history of VTE.

4. Understanding that bleeding deaths from the use of prophylaxis are very rare, while withholding anticoagulation in surgical patients “at risk” is associated with an increased risk of fatal pulmonary emboli.

5. Administering anticoagulant prophylaxis to high risk patients for one week as shown in 160 trials involving 43,000 patients should be followed since that is the time period shown to be efficacious for thrombosis prevention. It is important to avoid the temptation of short courses of anticoagulants during brief hospital stays, or outpatients in high-risk individuals.

6. Prescribe anticoagulant prophylaxis for at least 30 days in very high-risk individuals. It is important to remember that most patients develop thrombosis after leaving the hospital, and when short courses of anticoagulants are discontinued.

7. Ambulation has no effect on existing risk factors such as cancer or history of venous thromboembolism and only decreases the risk associated with immobility.

8. Remember that 66% of patients having surgery, who had a history of venous thrombosis suffered a postoperative thrombosis when prophylaxis with anticoagulants was omitted.

9. Understand the value of family history as a risk indicator for venous thrombosis and pulmonary emboli. Note that this is the most frequently missed or ignored risk factor which can result in a serious postoperative thrombotic event. This history should include all 3 degrees of relatives.

10. Continue appropriate anticoagulant prophylaxis long-term in patients with ongoing risks such as immobilization, infection, casts, rigid leg braces, or metastatic cancer.

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