

Current Concepts Review: Venous Thromboembolic Disease in Foot and Ankle Surgery

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INTRODUCTION

Venous thromboembolic disease (VTED) can be fatal, particularly in orthopaedic surgical patients.^{14,15} Clinicians and researchers continue to struggle to define, from a risk-benefit perspective, which subset of foot and ankle patients would benefit from prophylaxis and which treatment is appropriate for a given patient. Efforts have focused on preventing the most common and most dangerous sequelae of VTED: proximal and distal deep venous thrombosis (DVT), post-thrombotic syndrome, pulmonary hypertension, and particularly the potentially fatal pulmonary embolism (PE).⁵⁵ This current concepts review examines the pertinent literature that identifies the pathophysiology and treatment issues associated with venous thromboembolic disease in foot and ankle surgery.

PATHOPHYSIOLOGY

In 1860 Virchow attributed the development of DVT to the triad of stasis, vascular injury, and a hypercoagulable state.^{51,77} Stasis and vascular injury may occur after foot and ankle trauma or surgery, especially if the foot and ankle are immobilized. Hypercoagulable states may be hereditary or acquired. Hereditary conditions include factor V Leiden acquired protein C resistance (most common); prothrombin G20210A; antithrombin deficiency; protein C deficiency; protein S deficiency; anticoagulant, anticardiolipin antibody syndrome; and dysfibrinogenemia. Acquired risk factors include a history of VTE, recent surgery, recent trauma, airline travel, prolonged immobilization, older age, certain forms of cancer, congestive heart failure, recent myocardial

infarction, paralysis of a lower extremity, estrogen use, pregnancy or post-partum period, varicose veins, obesity, antiphospholipid syndrome, and hyperhomocysteinemia.⁶⁴

Thrombi in the lower extremity may form in the superficial or deep venous systems. Those of the deep system are classified as distal (confined to the calf region) or proximal. Superficial thrombi can be benign, but there is some evidence that they increase the chance of DVT. In a retrospective review of 40,013 patients of family physicians, Van Weert et al.⁷⁶ identified 185 patients with spontaneous superficial venous thrombophlebitis (SVT); within 6 months of their diagnosis of SVT, five (2.7%) of these patients developed DVT and one (0.5%) a pulmonary embolism. In an age and sex-matched cohort without SVT, only one (0.2%) of 370 patients developed DVT and two (0.5%) had pulmonary emboli.

FREQUENCY OF VTED IN PATIENTS WITH FOOT AND ANKLE SURGERY OR TRAUMA

Thromboprophylaxis of Lower Extremity Trauma

Lassen et al.,⁴⁵ in a prospective, double-blind, placebo-controlled trial (Level I), evaluated 440 patients who required immobilization in a plaster cast or brace for at least 5 weeks after a leg fracture or Achilles tendon rupture. DVT was diagnosed in 17 (9%) of 183 patients who received rivaroxan (low-molecular-weight heparin) and in 35 (19%) of 188 who received a placebo (odds ratio 0.45). The authors concluded that DVT is common with prolonged immobilization and that prophylaxis is warranted and effective.

In a randomized prospective study (Level I) of the effect of low-molecular-weight heparin (LMWH) on the occurrence of DVT in 339 patients with minor injuries (including ankle sprains and foot fractures) treated with plaster immobilization of the leg, Kock et al.⁴⁰ evaluated patients before casting with examination, leg circumference measurement, and ultrasound duplex scanning. Patients were then randomized to one of two groups: control (no treatment) or LMWH. The frequency of DVT was lower (0%) in the

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Table 1: Level of evidence and grades of recommendation

Level of Evidence
— Level I: high quality prospective randomized clinical trial
— Level II: prospective comparative study
— Level III: retrospective case control study
— Level IV: case series
— Level V: expert opinion
Grades of Recommendation (given to various treatment options based on Level of Evidence supporting that treatment)
— Grade A treatment options are supported by strong evidence (consistent with Level I or II studies)
— Grade B treatment options are supported by fair evidence (consistent with Level III or IV studies)
— Grade C treatment options are supported by either conflicting or poor quality evidence (Level IV studies)
— Grade I when insufficient evidence exists to make a recommendation

LMWH group than in the control group (4.3%) ($p < 0.006$). No side effects from LMWH were noted.

Spannagel et al.⁶⁸ showed in a randomized prospective trial (Level I) that LMWH was effective in decreasing the frequency of DVT in patients immobilized in a plaster cast. Using ultrasound, they identified DVT in 21 (16.5%) of 127 without LMWH prophylaxis and in six (4.8%) of 126 with LMWH ($p < 0.01$).

FREQUENCY OF VTED REPORTED IN THE FOOT AND ANKLE LITERATURE

Most of the data from which algorithms for preventing VTED and its complications are derived from patients with hip and knee arthroplasty. More Level 1 multi-center comparative studies involving patients with foot and ankle surgery or trauma are needed to create evidence-driven, specialty-based guidelines for managing VTED. This need is emphasized by the latest Cochrane Database meta-analysis,¹⁵ which included the 31 most recent comparative randomized trials evaluating the efficacy of physical and medical agents in preventing VTED: because of flaws in study designs, few valid conclusions could be made.

The 2004 American College of Chest Physicians (ACCP) consensus guidelines²⁹ include a meta-analysis of four randomized, prospective, controlled trials^{36,40,43,45} that included patients with foot and ankle injuries or procedures, including below-knee fractures, Achilles tendon ruptures, and leg injuries immobilized in casts who were routinely screened for VTED as an outcome measure. The authors concluded

that routine use of prophylactic anticoagulants is not indicated in patients with isolated below-knee injuries.

Of the four studies in the English literature that involve VTED and its complications in foot and ankle surgery,^{35,54,62,68} three have study design concerns. Mizel et al.⁵³ reported a 0.22% rate of clinically identifiable DVT after 2,733 foot and ankle procedures (Level V). High-risk multi-trauma patients were excluded, radiographic testing was not routinely done, and prophylaxis was relegated to surgeon preference without being standardized or recorded. Routine prophylaxis in foot and ankle surgery was not recommended, and non-weight bearing and immobilization were identified as risk factors for postoperative DVT.

In Solis and Saxby's study⁶⁸ (Level IV) of 201 patients who had foot and ankle surgery without DVT prophylaxis, routine postoperative duplex ultrasound screening identified DVT in seven (3.5%). This study also may have underestimated the frequency of DVT, because trauma patients were not included, patients with a history of DVT or PE were excluded, and duplex ultrasound screening was done at the first postoperative visit (average 10.5 days after surgery) but did not go proximal to the popliteal fossa, potentially missing all proximal or late occurring thrombi. They concluded that the infrequency of DVT in their patients suggested that routine prophylaxis is not warranted in patients who have elective foot and ankle surgery.

The study by Hanslow et al.³⁵ of VTED after foot and ankle surgery (Level IV) which included trauma patients reported a 4% occurrence of postoperative VTED in 602 patients. The investigation was retrospective, uncontrolled, and included patients as young as 7 years of age; all at-risk patients received DVT prophylaxis. The data are further compromised by the fact that only clinically evident (not silent) DVT was recorded and the patients who received prophylaxis were not studied separately. The most frequent co-morbidity of those who developed VTED was a connective tissue disorder such as rheumatoid arthritis, which, along with a history of DVT, showed a statistically significant correlation to the presence of postoperative VTED. These findings, however, are not corroborated by an earlier study.³ One unexplained and somewhat surprising finding by Hanslow et al.³⁵ was that univariate analysis actually identified prophylaxis as a risk factor for the development of VTE complications.

The one available Level I study⁴⁴ (prospective, randomized, placebo-controlled, single center, double-blinded) of DVT in foot and ankle patients included 105 patients who were surgically treated for Achilles tendon rupture and received either a placebo or LMWH (dalteparin, 5000U sc qd for 6 weeks). Each patient was screened with color duplex ultrasound at 3 and 6 weeks after surgery, and DVT was confirmed with phlebography. Ninety-one patients were followed to endpoint analysis (47 in the dalteparin group and 44 in the placebo group). Despite excluding some of the higher risk patients from this study (recent DVT, history of

malignancy, pregnancy, recent surgery), DVT rates were still high: 34% in the dalteparin group and 36% in the placebo group ($p = 0.8$). Proximal DVT was diagnosed in 2% of the dalteparin group and 6% of the placebo group ($p = 0.6$). The authors of this Level I study concluded that DVT is common after surgical treatment of Achilles ruptures and recommended thromboprophylaxis. They also concluded that dalteparin in the dosage used was statistically ineffective in decreasing the risk of DVT. Another Level I randomized, double-blind, placebo-controlled, comparative study of 440 patients immobilized for at least 5 weeks in a short-leg cast after operative or nonoperative treatment of a fracture or Achilles tendon rupture demonstrated a statistically significant difference in the rates of DVT (as identified by phlebography) between patients who received reviparin (9%) and those who received a placebo (19%).

Radl et al.⁶² reported the frequency of DVT after operative correction of hallux valgus in a single-center, prospective, phlebographically-controlled study of 100 patients (Level II). Unilateral ascending venography at an average of 29 days after surgery identified DVT in four patients (4%). A statistically significant ($p = 0.034$) correlation was demonstrated between DVT and patient age: the four patients with DVT had a mean age of 61.7 years, compared to 48.4 years in the 96 patients without DVT. The authors concluded that routine DVT prophylaxis might be justified for patients older than 60 years. This conclusion should not be taken as a general recommendation for all patients who have foot and ankle surgery. Independent Level I and Level II studies are necessary before this recommendation can be uniformly applied.

From these reports, it appears that VTED is much less frequent in patients who have foot and ankle surgery than in those who have hip or knee procedures. Because of the limited number of Level I and II studies currently available and the wide range of reported frequencies of DVT after foot and ankle trauma and surgery (0% to 37%), no definite conclusions can be made concerning the risk of DVT or the use of prophylactic anticoagulation.

DVT PROPHYLAXIS IN FOOT AND ANKLE SURGERY: WHO? AND HOW?

The uncertainty of the frequency of DVT after foot and ankle trauma or surgery is a major factor in the lack of consensus for the use of routine DVT prophylaxis in foot and ankle patients. Other factors include differences in methods of diagnosis and variability in treatment methods.³⁸ These differences were highlighted by Wolf and DiGiovanni,⁹⁰ who surveyed 1400 members of the American Orthopedic Foot Ankle Society (AOFAS) and the Orthopedic Trauma Association (OTA) members, with a response rate of 36% (508 of 1400). Fewer than half of respondents (44%, 223 of 508) reported ever using some type of postoperative DVT prophylaxis for foot and ankle patients, and the reported methods of treatment varied substantially: 6% (16) used

compressive stockings, 41% (91) used leg pumps, 15% (33) used warfarin, 7% (17) used subcutaneous heparin, 38% (85) used LMWH, 15% (33) used intrinsic foot exercises, 18% (40) used aspirin, 29% (50) used foot pumps, and 38% (86) used early mobilization. Even greater variation was noted in the tendencies of surgeons to rely on pre- or intra-operative prophylaxis, and there was a marked spread in the length of use of any post-operative prophylaxis: 33% (69) <1 week, 18% (37) 1 to 2 weeks, 11% (22) 2 to 3 weeks, 16% (32) 4 to 5 weeks, 15% (30) 6 weeks, and 6% (14) >6 weeks. While this study has some design concerns, it does emphasize the erratic application of VTED prophylaxis in foot and ankle surgery and highlights the need for studies of higher levels of evidence to determine appropriate use.

Numerous risk factors for the development of VTED in foot and ankle patients have been identified, and these risk factors are important in the decision to use VTED prophylaxis. Caprini¹² listed approximately 40 risk factors for VTED and created a grading system to determine a patient's risk for VTED.

The factors most often cited as increasing the risk of VTED are:

- *History of DVT or PE* (one of the most important risks for developing DVT)^{12,20}
- *Positive family history* (most often overlooked risk factor)^{6,12}
- *Obesity*^{1,33}
- *Smoking*³³
- *Immobilization*⁴³
- *Hereditary thrombophilias*^{65,80,87}
- *History of malignancy*⁴⁶
- *Oral contraceptive use*⁶⁰
- *Airline travel*²⁵

While such stratification might become useful as a rough guideline for assessing VTED risk, it is currently unclear how well each of these factors have truly been validated, and hence the categorization must be interpreted with caution.

The relative importance of factors identified as increasing the risk of DVT remains uncertain. Because of the variability of patient populations and surgical procedures reported, and conflicting conclusions of various authors, it is difficult to draw any firm conclusions from the literature. In a meta-analysis and literature review, Edmonds et al.²³ reported that there was evidence to support a significant association between increased risk of DVT and increased age, obesity, history of thromboembolism, varicose veins, oral contraceptive use, malignancy, Factor V Leiden gene mutation, general anesthesia, and orthopaedic surgery. They noted that there was insufficient evidence to support the suggested risk factors of hormone replacement therapy, gender, ethnicity or race, chemotherapy, other thrombophilias, cardiovascular factors, smoking, and blood type. Syed and Beeching,⁷⁰ however, in a study of lower-limb DVT in 232 patients, identified smoking, immobility, previous DVT, surgery in the last 3

months, malignancy, varicose veins, and intravenous drug use as important risk factors. DiMinno et al.²² reviewed 1536 surgeries done by general practitioners and noted that the prevalence of strong risk factors increased with age and that most risk factors were related to medical conditions, such as previous DVT, heart failure, and malignancy. They identified as moderate-to-weak risk factors smoking, history of miscarriage, estrogen therapy, obesity, and varicose veins. Kucher et al.⁴² prospectively analyzed 4,211 patients with an ultrasound-confirmed presence (639) or absence (3572) of DVT and identified proximal DVT, previous PE, obesity, chronic lung disease, and omission of prophylaxis as independent predictors of symptomatic PE. In another prospective study of 5,452 patients with ultrasound-confirmed DVT, Goldhaber et al.³² found the five most frequent comorbidities to be hypertension (50%), surgery within 3 months (38%), immobility within 30 days (34%), cancer (32%), and obesity (27%). In a recent review of the epidemiology of TVED, Cushman¹⁸ listed as major risk factors surgery, hospitalization, immobility, trauma, pregnancy, hormone use, cancer, obesity, and hypercoagulation disorders.

DIAGNOSIS

History and Physical Examination

Clinical detection of a DVT may be difficult because many patients do not demonstrate any signs or symptoms. Incomplete occlusion of the vein or collateral circulation may result in asymptomatic DVT.⁸⁶ Patients with DVT may have calf pain, swelling, venous distention, discoloration, warmth, a palpable cord, and a positive Homans' sign (pain in the calf after forceful dorsiflexion of the ankle with the knee flexed); however, this sign often is insensitive and nonspecific. It is positive in 8% to 56% of patients with proven DVT, but also may be positive in more than 50% of patients without DVT.⁷⁶ A review of pertinent risk factors should be included in the evaluation (Caprini¹²) to identify patients who are at an increased risk of VTE.

Imaging

Phlebography is considered the gold standard for diagnosing DVT in the lower extremity.⁵⁷ A contrast medium is injected into a dorsal superficial vein of the foot, and serial radiographs are taken to evaluate for a filling defect. Phlebography has a limited clinical application because of the expense and invasiveness of the procedure. Lack of adequate imaging of the pelvic vessels also is a disadvantage of this procedure.

Impendace plethysmography is used to assess the adequacy of venous outflow by measuring electrical impedance. Electrodes are placed around the calf and the electrical impedance between them is measured. With proximal venous occlusion, the venous vasculature is distended, thereby decreasing the electrical impedance.⁸⁶ This method is not effective, however, in diagnosing distal or non-obstructing venous

occlusions.⁶² Additionally, the sensitivity of this examination falls dramatically from 92% to 22% in asymptomatic patients.⁸⁶

Three types of *ultrasonography* are used for evaluation when DVT is suspected: compression ultrasound (CUS) in B-mode (brightness mode), echo-Doppler (duplex scanning), and color echo-Doppler (triplex scanning). In CUS, gentle external pressure on a vein is applied with the ultrasound transducer. Failure of the vein to collapse is the most sensitive finding for DVT.⁵⁹ A meta-analysis by Kearon et al.³⁹ demonstrated an overall sensitivity and specificity of 89% and 94%, respectively, with higher levels of sensitivity and specificity for detection of proximal DVT. Accuracy, ease of use, cost, and the noninvasive nature of the procedure make ultrasonography the first choice of imaging modalities to identify DVT.

Spiral computer assisted tomography is commonly used to evaluate patients for suspected pulmonary embolism; CT scans also can be used to evaluate for DVT. Sensitivity and specificity for the diagnosis of DVT are 89% to 100% and 94% to 100%, respectively. Advantages of CT include the ability to examine the pelvic vessels, which are not easily evaluated with ultrasonography, and to obtain simultaneous bilateral lower extremity images. Disadvantages include exposure to a large volume of renal toxic contrast, radiation exposure, and expense.

Magnetic resonance venography (MRV) allows evaluation of the pelvic vasculature without exposing the patient to contrast material. The sensitivity and specificity of MRI have been reported to be 94% to 96% and 90% to 92%, respectively.⁵⁹ Advantages include proximal (pelvic) screening, simultaneous bilateral evaluation, no requirement for contrast, and expanding use around implants and prosthetic devices.^{55,65} The significant disadvantage of MRV evaluation is the cost of the study.

COMPLICATIONS FOLLOWING DVT DEVELOPMENT

Complications following DVT include proximal extension of the thrombus, pulmonary embolus, recurrent DVT, and, most commonly, post-thrombotic syndrome.

Post-thrombotic syndrome (PTS) is characterized by chronic pain, swelling, a feeling of heaviness, pruritis, cramps, paresthesias, induration, hyperpigmentation, venous ectasia, redness, pain with calf compression, and ulceration.^{2,37,49,89} This is a chronic condition that develops, to some degree, in 20% to 80% of patients with DVT.^{49,89}

Pulmonary embolus (PE) is the most serious complication of DVT. PE occurs when a blood clot dislodges and migrates proximally into the pulmonary arterial vasculature. Pulmonary evaluation in a series of patients with known DVT documented the presence of a PE in 40%.³¹ Goldhaber et al.³² reported a 17.5% 3-month mortality rate in patients who had a PE. Symptoms and signs include dyspnea

(most common symptom), pleuritic pain, cough, hemoptysis, tachypnea (most common sign), syncope, and cyanosis.

Cushman¹⁸ noted that recurrent DVT has a 5% to 7% annual risk, which appears to be highest in the first 6 to 12 months after cessation of anticoagulation therapy, regardless of the duration of therapy. Residual thrombosis, proximal location of the original DVT, and PE at the initial event are risk factors for recurrence.

PROPHYLAXIS

Medical Prophylaxis

Medical prophylactic agents include warfarin, heparin, low-molecular-weight heparin, fondaparinux (a synthetic, selective factor Xa inhibitor), and aspirin.

Warfarin is a vitamin K antagonist that results in anticoagulation by interfering with the production of coagulation pathway clotting factors II, VII, IX, and X from vitamin K. Sulco et al.⁶⁷ found that fatal PE was reduced from 3.4% to 0.05% after total hip arthroplasty with the use of warfarin. Warfarin is administered in pill form and takes 3 to 5 days to reach therapeutic levels. The level of anticoagulation must be monitored with serial INR testing to ensure that the level of anticoagulation is appropriate. Side effects of warfarin use include prolonged bleeding time with cuts and easy bruising. A major complication is hemorrhage, which can be occur in the genitourinary, gastrointestinal, and pulmonary systems; hemorrhage also may be intracranial, intrathoracic, intraabdominal, or retroperitoneal. Hemorrhage in an extremity may cause compartment syndrome.

Low-molecular-weight heparin (LMWH) is a category of anticoagulants enzymatically derived from unfractionated heparin (UFH). LMWH exerts its antithrombotic effects through inhibition of thrombin (factor IIa) and factor Xa, enhances antithrombin activity, and promotes tissue factor pathway inhibitors. LMWH has better bioavailability than UFH and demonstrates consistent pharmacokinetics that allow it to be administered subcutaneously at fixed intervals.^{13,34,85,88}

Fondaparinux is an activated factor X inhibitor that does not require laboratory monitoring and can be administered once daily.^{71,73} Turpie et al.^{72,74} compared the efficacy of LMWH (enoxaparin) with that of fondaparinux in patients who had total knee arthroplasty and found fondaparinux to be more effective (6.8% VTE) than enoxaparin (13.7% VTE). However, another study¹¹ reported more frequent major bleeding complications with fondaparinux (2.1%) than with enoxaparin (0.2%). While several similar drugs currently are in Phase III clinical trials in Europe, at this time only fondaparinux is both commercially available and FDA approved for VTE prophylaxis in the USA. Its pre-operative role remains less clear, however, since it has an 18-hour half-life.^{11,73} Fondaparinux also is the only agent that received a Grade IA recommendation in the most

recent ACCP guidelines²⁹ for prevention of VTED in high-risk patients with hip fractures, based primarily on one large, randomized, double blinded study with enoxaparin.²⁶ It received only a Grade I recommendation for total hip arthroplasty patients in this same study, however, because of a lack of sufficient data. Relative risks were 45% to 63% lower with fondaparinux than with enoxaparin in four different Level I or II studies.^{8,29,72}

Aspirin is an antiplatelet agent that exerts its effect by permanently inactivating the cyclooxygenase activity of prostaglandin H.^{50,51,61} In the Pulmonary Embolism Prevention trial,⁵⁸ aspirin reduced the risk of symptomatic VTE by 36% and of fatal PE by 53%. Salvati et al.⁶⁶ summarized 30 years of clinical, basic, and applied research on the use of aspirin for VTE prophylaxis after hip arthroplasty. Adjuvant use of intra-operative heparin and hypotensive epidural anaesthesia for routine DVT prophylaxis demonstrated rates of symptomatic DVT and PE as low as 2.5% and 0.6% respectively, with an occurrence of asymptomatic (screened) DVT of 6.4%.^{21,66} A meta-analysis of the literature concerning anticoagulant therapy after total hip and knee arthroplasty found that the potent anticoagulants did not prevent PE and were associated with the highest mortality (0.47%), while aspirin demonstrated the lowest all-cause mortality (0.19%). However, LMWH was shown to decrease the risk of VTE 63% more than aspirin, and both LMWH and warfarin were more effective than aspirin in preventing VTE. The ACCP stated that the preponderance of current clinical data³¹ argues against the use (efficacy) of routine aspirin administration as a sole means of prophylaxis after orthopaedic surgery (Grade of Evidence 1A).^{29,31} Aspirin has not been studied in foot and ankle patients and cannot be recommended as a predictably effective isolated means of prophylaxis against DVT nor can it be labeled ineffective prophylaxis after foot and ankle surgery.

Mechanical Prophylaxis

The venous system is a low-pressure system comprised of veins that have thin walls and high compliance. To return blood from the periphery, the venous system must overcome vascular resistance and a pressure gradient that varies with position (standing versus recumbent). Muscle contraction in the calves compresses veins and encourages forward flow. Additionally, the compression of the venous plexus in the foot generates enough force to overcome the pressure gradient in the venous system of the calf.⁶⁷ Mechanical prophylaxis against DVT attempts to recreate the natural mechanisms of the body without the unwanted hemorrhagic side effects of LMWH, warfarin, and aspirin.

Intermittent compression pumps exert an antithrombotic effect through a reduction in venous stasis by increasing the velocity of venous return, enhancing fibrinolysis, and increasing the release of nitrous oxide (formerly known as endothelium-derived relaxing factor). Fibrinolysis is enhanced by increasing the amount of the plasma tissue

factor pathway inhibitor and reducing the amount of Factor FVIIa.^{17,24,41} In a meta-analysis, Urbankova et al.⁷⁵ found that the use of intermittent compression pumps reduced the risk of DVT by 60% ($p < 0.001$) when compared to no prophylaxis.

Graduated elastic compression stockings exert their effect by reducing the overall cross-sectional area of the limb, increasing linear velocity of venous flow, improving evacuation of incompetent or incompletely emptied valvular cusps, and decreasing venous distention.^{3,41} The Cochrane Peripheral Vascular Disease Group reviewed published data concerning the effectiveness of graduated elastic compression stockings for the prophylaxis of DVT. In seven randomized controlled trials, 15% of treated patients developed DVT compared to 29% of untreated patients.⁴

The use of mechanical prophylaxis is limited in foot and ankle patients because the device often cannot be applied to the operated extremity because of a cast or restrictive dressing.

COMPLICATIONS OF DVT PROPHYLAXIS

Hemorrhagic Events (hematoma, stroke, wound problems)

Unfortunately, the effectiveness of any pharmaceutical prophylaxis against VTE often parallels its bleeding risks. A randomized, double-blinded study^{8,72} involving 724 patients reported that fondaparinux was significantly ($p < 0.001$) more effective (12.5% rate of VTE) than enoxaparin (27.8% rate of VTE) in preventing VTE, but it also was associated with more frequent major bleeding episodes. Meta-analysis of four randomized, prospective clinical trials by Colwell and Spiro¹⁶ identified a major bleeding frequency of 4% in the placebo group and 6% in the heparin/heparin derivative treated group. These issues become increasingly important as 'new and improved' medications continue to be developed with theoretical advantages over more traditional medications. For example, idraparinux, a hypermethylated relative of fondaparinux, has an easy dosing schedule because of its extremely long (80-hour) half-life, but it also has been associated with several reports of fatal bleeding episodes and a somewhat linear dose-response curve for major bleeding.⁶⁰ Further, since neither fondaparinux or idraparinux interacts with protamine sulfate, overdosage can result in a major bleed, with no current medical remedy except perhaps recombinant Factor VIIa.^{9,10}

The reported frequency of severe ('major') wound or systemic hemorrhagic complications in postoperative orthopaedic patients who have received medical prophylaxis ranges from 1.5% to 5.1%.^{5,49,56} However, many of these studies excluded the highest risk patients (ie., elderly patients and those with a history of gastrointestinal bleeding or previous DVT) and their estimates of bleeding risk are likely to be low. A meta-analysis of 52 randomized controlled trials (10,929 patients) that used bilateral venography to compare methods of VTE prophylaxis after elective THA

found significantly ($p < 0.05$) more minor wound bleeding complications with either LDH or LMWH (7.6% to 8.9%) than in controls (2.2%).²⁸ A more recent Level I study of TKA patients found that clinically important operative site hemorrhage occurred in 3% to 7% of patients when anticoagulants were used.⁷⁷

The one Level I study (prospective, randomized, placebo-controlled, single center, double-blinded) of medical VTED prophylaxis (dalteparin) in foot and ankle patients⁴⁴ reported no bleeding complications in either group, but the authors expressed concern that the dosage of dalteparin they used (5,000U sc qd) was ineffective because of the similar VTED rates in the two groups. Another recent placebo-controlled, comparative study of 440 heterogenous cast-immobilized patients with lower extremity injuries, however, also noted no significant differences in hemorrhagic events between reviparin treatment (14 events) and placebo (12 events), despite a significant lowering of DVT rates (9% vs. 19%).⁴⁵

Heparin-Induced Thrombocytopenia (HIT)

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening adverse effect of heparin; it occurs more often after the use of UH than LMWH and is more common in postoperative patients than in medical patients. Girolami and Girolami³⁰ reported that HIT occurred in 6.5% of patients who were treated with UH after orthopaedic surgery, compared to 1% or fewer after other types of surgery. In up to 50% of patients, HIT leads to DVT, PE, myocardial infarction, stroke, organ hemorrhage, systemic and extremity ischemia, amputation, or death.^{7,47,52,81,82} Acute symptoms of HIT may include fever, chills, tachycardia, hypertension, pulselessness, diaphoresis, abdominal pain, chest pain, dyspnea, and, less commonly, rash or transient global amnesia.^{75,83,84} Once recognized, the hallmark of treatment remains immediate cessation of all forms of heparin or heparin derivative products, followed by the use of a rapidly acting anticoagulant other than heparin or any heparin-derived product to reduce thrombin generation and prevent platelet activation. The currently accepted anticoagulation options for treating HIT are heparinoids and direct thrombin inhibitors, with numerous complicated factors playing into this decision.

Ineffectiveness of Treatment (VTED, fatal PE)

Nonfatal PE has been reported in approximately 0.75% of the general orthopaedic postoperative population, regardless of prophylaxis.^{5,57} A meta-analysis of 52 randomized controlled trials comparing all methods of VTE prophylaxis after elective THA²⁸ (10,929 patients) identified the risk of venographically-proven breakthrough DVT (proximal and distal) as 17.7% to 31.1%, depending on the choice of agent. The risk of symptomatic PE ranged from 0.16% to 0.36%, again depending on the agent used ($p < 0.0001$). No significant difference was noted in mortality (including all causes) or fatal PE risk among the prophylactic agents.

These results compare favorably with more recent data in a similar Level I study of TKA patients screened by venography.²⁷ In these patients, the incidence of breakthrough VTE ranged from 25% to 45%, depending on the agent used, although only one symptomatic PE was reported in 349 patients.

While it is encouraging that most of these studies suggest that the fatality rates of patients who receive prophylaxis are significantly lower than those of untreated patients in the peri-operative period, not all fatal PE are prevented. The pooled database review¹⁹ of all available randomized and cohort studies that reported overall mortality statistics and fatal vascular events found that patients who had hip or knee replacement with DVT prophylaxis had a 0.44% (95% CI, 0.02-0.87%) overall mortality rate and a 0.43% (range 0.01-0.85%) fatal PE rate in the pooled autopsy studies. Despite prophylaxis, these numbers were substantially higher in the autopsy studies of patients who had hip fracture surgery than in those with THA or TKA, with a reported 8.5% (range 7.3% to 9.7%) overall mortality rate and a 1.0% (range 0.6% to 1.5%) fatal PE rate. Among cohort studies of patients who had THA or TKA, the pooled data suggested a 0.57% (range 0.51% to 0.62%) overall mortality rate and a 0.18% (range 0.14% to 0.30%) fatal PE rate. Again, even with prophylaxis, risks were higher in patients with hip fractures, who had a mortality rate of 3.2% (range 2.8% to 3.6%) and a fatal PE rate of 0.30% (range 0 to 0.61%).

SUMMARY

Venous thromboembolism is a potentially preventable cause of significant morbidity and mortality in orthopaedic surgery. Unfortunately, prophylaxis is not without a risk of complications. Proper identification of patients at risk for venous thromboembolism, particularly in foot and ankle surgery, will continue to be an essential aspect of the perioperative prophylaxis of venous thromboembolism. This process requires significantly more science than is currently available.

The incidence of fatal pulmonary embolism is not as well established in foot and ankle surgery as in arthroplasty or trauma, and the overall incidence of asymptomatic DVT also remains elusive. It does seem clear that the potential for VTED in foot and ankle patients exists and should be of particular concern in at-risk patients. Defining who needs prophylaxis and when and how this should be done is important, because it also seems clear that not all patients require treatment. A careful patient history is invaluable to identify potential risk factors, but only adequately powered, well-designed, properly screened Level I studies can answer this question, and these will likely require multi-center participation—perhaps through coordination with the AOFAS. Weighing the risks of any prophylaxis against its benefits for any chosen patient will continue to dominate discussion (and

should dominate the research) in our society over the next decade, since the levels of evidence guiding current treatment algorithms are mostly Level IV.

Two things seem clear today: 1) not all foot and ankle patients require VTED prophylaxis, and 2) the potential complications of VTED cannot be ignored. Concepts that appear to be important as part of our approach to avoiding and treating potential VTED today include:

1. Stasis is frequent after surgery of the foot and ankle, because patients often are immobilized with a splint or cast. According to Virchow's triad, stasis is one of three general risk factors that predispose to VTED, the other two being vascular injury and a hypercoagulable state..
2. DVT is more common after hip and knee arthroplasty surgery than after foot and ankle surgery. The exact rate of DVT after foot and ankle surgery is unclear.
3. Potentially severe complications that can follow DVT include proximal extension of the thrombus, pulmonary embolus, recurrent DVT, post-thrombotic syndrome, and death.
4. Patients who have foot and ankle surgery should have a basic screening for VTED risk to determine if some type of prophylaxis is warranted. High risk factors include a history of previous DVT or PE, a positive family history of a hypercoagulable state, and recent multiple trauma. Other risk factors include advancing age, relative immobility, obesity, recent airline travel, and a history of malignancy. Caprini published an outline of VTED risk factors and created a summary table of risk factors that may allow each patient's risk of VTED to be graded
5. Options for VTED prophylaxis include medical and mechanical methods. Medical prophylactic agents, including aspirin, warfarin, and LMWH (enoxaparin), and fondaparinux have different efficacy/safety profiles. Presently, aspirin is not recommended as an isolated prophylactic treatment for high-risk patients. Mechanical prophylaxis includes intermittent compression pumps, which work in part by increasing the velocity of venous return and thereby decreasing venous stasis. However, mechanical prophylaxis has been poorly studied in foot and ankle patients and often is not practical in patients with casts or restrictive dressings.
6. The use of DVT prophylaxis by practicing foot and ankle surgeons is widely variable because of the lack of conclusive evidence (Level I and II studies). No reasonable algorithm now exists to effectively guide treatment or avoid unnecessary complications.
7. Prophylaxis, even when properly administered, can result in complications in 1.5% to 5% of patients; complications most frequently are increased bleeding and more frequent wound problems, but heparin-induced thrombocytopenia (HIT), a potentially severe or fatal complication, also may occur.

REFERENCES

1. **Abdollahi, M; Cushman, M; Rosendaal, FR:** Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. *Thromb. Haemost.* **89**:493–498, 2003.
2. **Agno, W; Piantanida, E; Dentali, F; et al.:** Body mass index is associated with the development of the post-thrombotic syndrome. *Thromb. Haemost.* **89**:305–309, 2003.
3. **Agu, O; Hamilton, G; Baker, D:** Graduated compression stockings in the prevention of venous thromboembolism. *Br. J. Surg.* **86**:992–1004, 1999.
4. **Amaragiri, SV; Lees, TA:** Elastic compression stockings for prevention of deep vein thrombosis. *Cochrane Database Syst Rev* **3**:CD001484, 2000.
5. **Amstutz, HC; Friscia DA; Dorey, F; Carney, BT:** Warfarin prophylaxis to prevent mortality from pulmonary embolism after total hip replacement. *J. Bone Joint Surg.* **71A**:321–326, 1989.
6. **Appleby, RD; Olds, RJ:** The inherited basis of venous thrombosis. *Pathology* **29**:341–347, 1997.
7. **Arepally, G; Cines, DB:** Pathogenesis of heparin-induced thrombocytopenia and thrombosis. *Autoimmun. Rev.* **1**:125–132, 2002.
8. **Bauer, KA; Eriksson, BI; Lassen, MR; Turpie, AG; et al.:** Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N. Eng. J. Med.* **345**:1305–1310, 2001.
9. **Bijsterveld, NR; Moon, AH; Boekhodt, SM; et al.:** Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation* **106**:2550–2554, 2002.
10. **Bijsterveld, NR; Vink, R; van Aken, BE; et al.:** Recombinant factor VIIa reverses the anticoagulant effect of the long acting pentasaccharide idraparinux in healthy volunteers. *Br. J. Haematol.* **124**:653–658, 2004.
11. **Buller, H; Davidson, B; Decousus, H; et al.:** Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: A randomized trial. *Ann. Intern. Med.* **140**:867–873, 2004.
12. **Caprini, JA:** Thrombosis risk assessment as a guide to quality patient care. *Dis. Mon.* **51**:70–78, 2005.
13. **Cirlincione, AS; Mendicino, R; Catanzariti, R; Grossman, J:** Low-molecular-weight heparin for deep vein thrombosis prophylaxis in foot and ankle surgery: a review. *J. Foot Ankle Surg.* **40**:96–100, 2001.
14. **Clagett, GP; Anderson, Jr FA; Geerts, WH; et al.:** Prevention of venous thromboembolism. *Chest* **114**:531S–560S, 1998.
15. **Colwell, CW:** Evidence-based guidelines for venous thromboembolism prophylaxis in orthopedic surgery. *Orthopedics* **30**:129–135, 2007.
16. **Colwell, CW, Jr; Spiro, TE:** Efficacy and safety of enoxaparin to prevent deep vein thrombosis after hip arthroplasty. *Clin. Orthop.* **319**:215–222, 1995.
17. **Comerota, AJ; Chouhan, V; Harada, RN; et al.:** The fibrinolytic effects of intermittent pneumatic compression: mechanism of enhanced fibrinolysis. *Ann. Surg.* **226**:306–314, 1997.
18. **Cushman, M:** Epidemiology and risk factors for venous thrombosis. *Semin. Hematol.* **44**:62–69, 2007.
19. **Dahl, OE; Caprini, JA; Colwell, CW; et al.:** Fatal vascular outcomes following major orthopaedic surgery. *Thromb. Haemost.* **93**:860–866, 2005.
20. **Delis, KT; Hunt, N; Strachan, RK; Nicolaides, AN:** Incidence, natural history, and risk factors of deep vein thrombosis in elective knee arthroscopy. *Thromb. Haemost.* **86**:817–821, 2001.
21. **DiGiovanni, CW; Restrepo, A; Gonzalez Della Valle, AG; et al.:** The safety and efficacy of intraoperative heparin in total hip arthroplasty. *Clin. Orthop.* **379**:178–185, 2000.
22. **DiMinno, G; Mannucci, PM; Tufano, A; et al.:** The first ambulatory screening on thromboembolism: a multicentre, cross-sectional, observational study on risk factors for venous thromboembolism. *J. Thromb. Haemost.* **3**:1459–1466, 2005.
23. **Edmonds, MJ; Crichton, TJ; Runciman, WB; Pradhan, M:** Evidence-based risk factors for postoperative deep vein thrombosis. *ANZ J. Surg.* **74**:1082–1097, 2004.
24. **Eisele, R; Kinzl, L; Koelsch, T:** Rapid-inflation intermittent pneumatic compression for prevention of deep venous thrombus. *J. Bone Joint Surg.* **89-A**:1050–1056, 2007.
25. **Eklöf, B; Maksimovic, D; Caprini, JA; Glase, C:** Air travel-related venous thromboembolism. *Dis. Mon.* **51**:200–207, 2005.
26. **Eriksson, BI; Bauer, KA; Lassen MR; Turpie, ACG :** Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip fracture surgery. *N. Eng. J. Med.* **345**:1298–1304, 2001.
27. **Fitzgerald, RH; Spiro TE; Trowbridge AA; et al.:** Prevention of venous thromboembolic disease following primary total knee arthroplasty. A randomized, multicenter, open-label, parallel-group comparison of enoxaparin and warfarin. *J. Bone Joint Surg.* **83-A**:900–906, 2001.
28. **Freedman, KB; Brookenthal, KR; Fitzgerald, RH; Williams, S; Lonner, JH:** A meta-analysis of thromboembolic prophylaxis following elective total hip arthroplasty. *J. Bone Joint Surg.* **82A**:929–938, 2000.
29. **Geerts, WH; Pineo, GF; Heit, JA; et al.:** Prevention of venous thromboembolism: the seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest* **126(3 Suppl)**:338S–400S, 2004.
30. **Girolami, B; Girolami, A:** Heparin-induced thrombocytopenia: a review. *Semin. Thromb. Hemost.* **32**:803–809, 2006.
31. **Goldhaber, SZ:** Medical progress: Pulmonary embolism. *N. Eng. J. Med.* **339**:93–104, 1998.
32. **Goldhaber, SZ; Tapson, VF; DVT FREE Steering Committee:** A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am. J. Cardiol.* **93**:259–262, 2004.
33. **Gonzalez, R; Haines, K; Nelson, LG; Gallagher, SF; Murr, MM:** Predictive factors of thromboembolic events in patients undergoing Roux-en-Y gastric bypass. *Surg. Obes. Relat. Dis.* **2**:30–35, 2006.
34. **Handoll, HHG; Farrar, MJ; McBirnie, J; et al.:** Heparin, low-molecular-weight heparin and physical methods for preventing deep vein thrombosis and pulmonary embolism following surgery for hip fractures. *Cochrane Database Syst Rev* **4**:CD000305, 2002.
35. **Hanslow, SS; Grujic, L; Slater, HK; Chen, D:** Thromboembolic disease after foot and ankle surgery. *Foot Ankle Int.* **27**:693–695, 2006.
36. **Jorgensen, PS; Warming, T; Hansen, K; et al.:** Low-molecular-weight heparin (Innohep) as thromboprophylaxis in outpatients with a plaster cast: a venographic controlled study. *Thromb. Res.* **105**:477–80, 2002.
37. **Kakkos, SK; Daskalopoulou, SS; Daskalopoulos, ME; Nicolaides, AN; Geroulakos, G:** Review of the value of graduated elastic compression stockings after deep vein thrombosis. *Thromb. Haemost.* **96**:441–445, 2006.
38. **Kearon, C:** Duration of venous thromboembolism prophylaxis after surgery. *Chest* **124(6 Suppl)**:386S–392S, 2003.
39. **Kearon, C; Julian, JA; Math, M; Newman, TE; Ginsberg, JS:** Noninvasive diagnosis of deep venous thrombosis. *Ann. Int. Med.* **128**:663–667, 1998.
40. **Kock, HJ; Schmit-Neuerburg, KP; Hanke, J; Rudofsky, G; Hirche, H:** Thrombo-prophylaxis with low-molecular-weight heparin in outpatients with plaster-cast immobilisation of the leg. *Lancet* **346**:459–461, 1995.
41. **Kolbach, DN; Sandbrink, MW; Hamulyak, K; Neumann, HA; Prins, MH:** Non-pharmaceutical measures for prevention of post-thrombotic syndrome. *Cochrane Database Syst Rev* **1**:CD004174, 2004.
42. **Kucher, N; Tapson, VF; Goldhaber, SZ; DVT FREE Strengthening Committee:** Risk factors associated with symptomatic pulmonary embolism in a large cohort of deep vein thrombosis patients. *Thromb. Haemost.* **93**:494–498, 2005.
43. **Kujath, P; Spannagel, U; Habscheid, W:** Incidence and prophylaxis of deep venous thrombosis in outpatients with injuries of the lower limb. *Haemostasis* **23**[Suppl 1]:20–26, 1993.

44. **Lapidus, LJ; Rosfors, S; Ponzer, S; et al:** Prolonged thromboprophylaxis with dalteparin after surgical treatment of Achilles tendon rupture: a randomized, placebo-controlled study. *J. Orthop. Trauma* **21**:52–57, 2007.
45. **Lassen, RM; Borris, LC; Nakov, RL:** Use of low-molecular-weight heparin rivarparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N. Eng. J. Med.* **347**:726–730, 2002.
46. **Lin, PP; Graham, D; Hann, LE; Boland, PJ; Healey, JH:** Deep venous thrombosis after orthopedic surgery in adult cancer patients. *J. Surg. Oncol.* **68**:41–47, 1998.
47. **Lindhoff-Last, E; Wenning, B; Gerdson, MS; Bauersachs, R; Wagner, R:** Risk factors and long-term follow-up of patients with the immune type of heparin-induced thrombocytopenia. *Clin. Appl. Thromb. Hemost.* **8**:347–352, 2002.
48. **Lonner, JH; Frank, J; McGuire, K; Lotke, PA:** Postthrombotic syndrome after asymptomatic deep vein thrombosis following total knee and hip arthroplasty. *Am. J. Orthop.* **35**:469–472, 2006.
49. **Lotke, PA; Callaghan, JJ; Dorr, LD; Engh, GA; et al.:** Prophylaxis for thromboembolic disease. *J. Arthroplasty* **20**:273–274, 2005.
50. **Lotke, P; Lonner, J:** The benefit of aspirin chemoprophylaxis for thromboembolism after total knee arthroplasty. *Clin. Orthop.* **452**:175–180, 2006.
51. **Malone, PC; Agutter, PS:** Review: The aetiology of deep venous thrombosis. *QJM* **99**:581–593, 2006.
52. **Menajovsky, LB:** Heparin-induced thrombocytopenia: clinical manifestations and management strategies. *Am. J. Med.* **118**[Suppl 8A]:21S–30S, 2005.
53. **Mizel, MS; Temple, HT; Michelson JD; et al.:** Thromboembolism after foot and ankle surgery. *Clin. Orthop.* **348**:180–185, 1998.
54. **Montgomery, KD; Potter, HG; Helfet, DL:** The detection and management of proximal deep vein thrombosis in patients with acute acetabular fractures: a follow up report. *J. Orthop. Trauma* **11**:330–336; 1997.
55. **National Institutes of Health:** Prevention of venous thrombosis and pulmonary embolism. NIH Consensus Development. *J. Am. Med. Assoc.* **256**:744–749, 1986.
56. **Paiement, GD; Wessinger, SJ; Hughes, R; Harris, WH:** Routine use of adjusted low dose warfarin to prevent venous thromboembolism after total hip replacement. *J. Bone Joint Surg.* **75A**:893–898, 1993.
57. **Paiement, GD; Wessinger, SJ; Waltman, AC; Harris, WH:** Surveillance of deep vein thrombosis in asymptomatic total hip replacement patients. *Am. J. Surg.* **155**:400–404, 1988.
58. **Palareti, G; Cosmi, B; Lignani, C:** Diagnosis of deep vein thrombosis. *Semin. Thromb. Hemost.* **32**:659–672, 2006.
59. **Piegsa, K; Guillebaud, J:** Oral contraceptives and the risk of DVT. *Practitioner* **240**:544–551, 1996.
60. **PERSIST investigators:** A novel long-acting synthetic factor Xa inhibitor (SanOrg34006) to replace warfarin for secondary prevention in deep vein thrombosis. A Phase II evaluation. *J. Thromb. Haemost.* **2**:47–53, 2004.
61. **Pulmonary Embolism Prevention (PEP) Trial:** Prevention of pulmonary embolism and deep vein thrombosis with low-dose aspirin. *Lancet* **355**:1295–1302, 2000.
62. **Radl, R; Kastner, N; Aiger, C; et al.:** Venous thrombosis after hallux valgus surgery. *J. Bone Joint Surg.* **85-A**:1204–1208, 2003.
63. **Ramos, J; Perrotta, C; Badariotti, G; Berenstein, G:** Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy. *Cochrane Database Syst Rev* **18**:CD005259, April 18, 2007.
64. **Raskub, GE; Hull, RD; Pineo, GF:** Venous Thrombosis. In Lichtman, MA; Beutler, E; Kipps, TJ; et al. (eds.), *Williams Hematology*, 7th Edition. McGraw Hill Professional, New York, 2006.
65. **Salvati, EA; Gonzalez Della Valle, A; Westrich, GH; et al.:** The John Charnley Award. Heritable thrombophilia and development of thromboembolic disease after total hip arthroplasty. *Clin. Orthop.* **441**:40–55, 2005.
66. **Salvati, EA; Sharrock, NE; Westrich, G; et al.:** Three decades of clinical, basic, and applied research on thromboembolic disease after THA. *Clin. Orthop.* **459**:246–254, 2007.
67. **Sculco, TP; Colwell, CW Jr; Pellegrini, VD Jr; Westrich GH; Böttner F:** Prophylaxis against venous thromboembolic disease in patients having a total hip or knee arthroplasty. *J. Bone Joint Surg.* **84A**:466–477, 2002.
68. **Solis, G; Saxby, T:** Incidence of DVT following surgery of the foot and ankle. *Foot Ankle Int.* **23**:411–414, 2002.
69. **Spannagel, U; Kujath, P:** Low molecular weight heparin for the prevention of thromboembolism in outpatients immobilized by plaster cast. *Semin Thromb Hemost.* **19**[Suppl 1]:131–141, 1993.
70. **Syed, FF; Beeching, NJ:** Lower-limb deep-vein thrombosis in a general hospital: risk factors, outcomes and the contribution of intravenous drug use. *Q.J.M.* **98**:139–145, 2005.
71. **Turpie, A; Bauer, KA; Eriksson, BI; Lassen, MR:** Superiority of fondaparinux over enoxaparin in preventing venous thromboembolism in major orthopaedic surgery using different efficacy end points. *Chest* **126**:501–508, 2004.
72. **Turpie, AGG; Bauer, KA; Eriksson, BI; Lassen, MR; PENTATH-LON 2000 Study Steering Committee:** Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip replacement surgery: a randomized double blind trial. *Lancet* **359**:1721–1726, 2002.
73. **Turpie, AGG; Eriksson, BI; Bauer, KA; Lassen, MR:** Advances in therapeutics and diagnostics. Fondaparinux. *J. Am. Acad. Orthop. Surg.* **12**:371–375, 2004.
74. **Turpie, AG; Eriksson, BI; Lassen, MR; Bauer, KA:** A meta-analysis of fondaparinux versus enoxaparin in the prevention of venous thromboembolism after major orthopaedic surgery. *J. South. Orthop. Assoc.* **11**:182–188, 2002.
75. **United States Department of Health and Human Resources:** FDA Public Health Advisory: Reports of epidural or spinal hematomas with the concurrent use of low molecular weight heparin and spinal/epidural anesthesia or spinal puncture. Washington, DC, December 15, 1997.
76. **Urbankova, J; Quiroz, R; Kucher, N; Goldhaber, SZ:** Intermittent pneumatic compression and deep vein thrombosis prevention. A meta-analysis in post-operative patients. *Thromb. Haemost.* **94**:1181–1185, 2005.
77. **Urbano, F:** Homan's sign in the diagnosis of deep venous thrombosis. *Hospital Physician* **37**:22–24, 2001.
78. **van Weert, H; Dolan, G; Wichers, I; et al.:** Spontaneous superficial venous thrombophlebitis: does it increase risk for thromboembolism? A historic follow-up study in primary care. *J. Fam. Pract.* **55**:52–57, 2006.
79. **Virchow, R:** *Cellular Pathology as Based Upon Physiological and Pathological Histology.* London: Churchill; 1860
80. **Wahlander, K; Larson, G; Lindahl, TL; et al.:** Factor V Leiden (G1691A) and prothrombin gene G20210A mutations as potential risk factors for venous thromboembolism after total hip or total knee replacement surgery. *Thromb. Haemost.* **87**:580–585, 2002.
81. **Warkentin, TE:** Think of HIT. *Hematology: Am. Soc. Hematol. Educ. Program*, **2006**:408–414, 2006.
82. **Warkentin, TE:** Heparin-induced thrombocytopenia: a ten-year retrospective. *Ann. Rev. Med.* **50**:129–147, 1999.
83. **Warkentin, TE; Kelton, J:** A 14-year study of heparin-induced thrombocytopenia. *Am. J. Med.* **101**:502–507, 1996.
84. **Warkentin, TE; Roberts, RS; Hirsch, J; Kelton, JG:** An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. *Arch. Intern. Med.* **163**:2518–2524, 2003.
85. **Wein, L; Wein, S; Haas, SJ; Shaw, J; Krum, H:** Pharmacological venous thromboembolism prophylaxis in hospitalized medical patients: a meta-analysis of randomized controlled trials. *Arch. Intern. Med.* **167**:1476–1486, 2007.

86. **Weinmann, EE; Salzman, EW:** Deep-vein thrombosis. *N. Engl. J. Med.* **331**:1630–1641, 1994.
87. **Westrich, GH; Weksler, BB; Glueck, CJ; Blumenthal, BF; Salvati, EA:** Correlation of thrombophilia and hypofibrinolysis with pulmonary embolism following total hip arthroplasty: an analysis of genetic factors. *J. Bone Joint Surg.* **84-A**:2161–2167, 2002.
88. **Whang, P; Lieberman, J:** Low-molecular-weight heparin. *J. Am. Acad. Orthop. Surg.* **10**:299–302, 2002.
89. **Wille-Jørgensen, P; Jørgensen, LN; Crawford, M:** Asymptomatic post-operative deep vein thrombosis and the development of post-thrombotic syndrome. A systematic review and meta-analysis. *Thromb. Haemost.* **93**:236–241, 2005.
90. **Wolf, JM; DiGiovanni, CW:** A survey of orthopedics surgeons regarding DVT prophylaxis in foot and ankle trauma surgery. *Orthopedics* **27**:504–508, 2004.