

# PRACTICE INSIGHTS

## Key Articles and Guidelines in the Treatment of Venous Thromboembolism

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Venous thromboembolism (VTE) is a significant medical diagnosis that affects millions of patients each year. Appropriate management of VTE can help treat the initial event as well as reduce the frequency of complications such as postthrombotic syndrome, pulmonary hypertension, and death. Due to increasing regulatory requirements, hospitals nationwide are developing necessary documentation of appropriate and safe use of anticoagulants for the management of VTE. It is essential that a wide range of clinicians have an understanding of what constitutes appropriate VTE treatment in various patient populations. With the existence of numerous pharmacologic agents, abundance of major clinical trials, and nationally recognized clinical guidelines, compiling the needed reference material to make evidence-based decisions on appropriate VTE treatment can be difficult for clinicians. Therefore we have provided bibliographies of key articles and guidelines related to the treatment of VTE with a number of different strategies in a variety of special patient populations. It is our hope that this compilation will serve as a resource for pharmacists, physicians, nurses, residents, and students responsible for the care of patients with VTE.

**Key Words:** anticoagulation, cardiology, evidence-based medicine, pharmacoeconomics, pharmacy practice, warfarin, unfractionated heparin, low-molecular-weight heparin, LMWH, fibrinolytics, venous thromboembolism.

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Venous thromboembolism (VTE), which encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant health-care problem, producing considerable morbidity, mortality, and resource utilization.<sup>1</sup> In the United States (US) alone, there are well over a million DVT events and more than 100,000 deaths per year from PE. Even after the initial event, approximately 30% of patients will develop a recurrent DVT, approximately 30% will develop post-thrombotic syndrome, and thousands of patients will develop pulmonary hypertension over the next several years.<sup>2</sup> Concerns about the lack of safe use of anticoagulants, and the insufficient management of VTE, has led to the recent involvement of government and other regulatory agencies in an attempt to improve appropriate and safe anticoagulant use and treatment of VTE in US hospitals. Hospitals attempting to be compliant with the Joint Commission National Patient Safety Goals and the newly approved Joint Commission/National Quality Forum VTE Performance Measures need to have thorough knowledge of the literature surrounding the

treatment of VTE.

The Cardiology Practice and Research Network (PRN) of the American College of Clinical Pharmacy has taken the initiative to compile lists of key articles and guidelines in major focus areas of cardiology. From 2004 to 2006, five collections of annotative bibliographies were published on the topics of acute coronary syndrome, arrhythmias, hypertension, systolic heart failure, and dyslipidemias.<sup>3-7</sup> These documents are currently in the process of being updated and published in *Pharmacotherapy*.<sup>8-10</sup> Since VTE is not only a cardiology issue, the Cardiology PRN has joined with the Internal Medicine PRN and the Ambulatory Care PRN to compile two documents that focuses on key articles and guidelines on the topic of VTE. The first document focused on prevention of VTE and was published in *Pharmacotherapy* in April 2009.<sup>11</sup> This document completes the topic of VTE by covering the key articles and guidelines in the treatment of VTE. The authors collected guidelines and significant manuscripts published in the area of VTE treatment and have provided a summary of the results of the clinical trials and their insights on the implications on clinical practice and research. This document will serve as an excellent review and resource for pharmacists, physicians, nurses, residents, and students, especially in this time of increased attention on safe anticoagulant use and new quality measures for the treatment of VTE.

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## Guidelines

**Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ.** Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines (8<sup>th</sup> edition). *Chest* 2008;133(suppl 6):454S-545S.

The 8<sup>th</sup> edition of the ACCP (American College of Chest Physicians) guidelines was published in June of 2008. They represent the most comprehensive and widely accepted evidence-based guidelines for the management of thromboembolic disease, and use an internationally-accepted method to grade both strength of recommendation and level of evidence. The chapter on the treatment of VTE begins with a summary of recommendations before getting into the justification for each recommendation. This provides a quick method for finding a specific recommendation if the more detailed discussion behind the recommendation

is not needed. While much of the text focuses on the rationale for different anticoagulation strategies for management of VTE, there are also extensive reviews of topics such as the use of fibrinolytic therapy for DVT and PE, vena cava filters, embolectomy, treatment of upper extremity DVT, as well as prevention of secondary complications of VTE. The chapter initiates the discussion on the treatment of DVT and then moves into recommendations for the treatment of PE.

General recommendations for the treatment of DVT include the use of an injectable anticoagulant over warfarin alone (Grade 1A), both started on day 1 (Grade 1A), with at least a five day overlap of injectable therapy with warfarin and until the international normalized ratio (INR) is greater than or equal to 2 for 24 hours (Grade 1C). Monitoring of unfractionated heparin (UFH) with an activated thromboplastin time (aPTT) that correlates to plasma heparin levels of 0.3 to 0.7 IU/mL anti-Xa activity is recommended (Grade 1C). There is also an option for the use of unmonitored subcutaneous (SC) UFH (Grade 1C). The use of low molecular weight heparin (LMWH) is recommended over UFH for treatment of DVT (Grade 1A), outpatient treatment is favored over inpatient treatment if possible (Grade 1C), but UFH is recommended over LMWH if the patient has severe renal failure (Grade 2C). These recommendations are consistent with the recommendations for the treatment of non-massive PE as well. This chapter is over 90 pages long with extensive discussion and tables on the major literature (393 references) used to support the recommendations. Knowledge of the information in this chapter is a must for any clinician responsible for acute or chronic management of VTE, as well as for institutions attempting to be in compliance with the Joint Commission National Patient Safety Goals and the newly approved Joint Commission/National Quality Forum VTE Performance Measures.

**Ansell, J, Hirsh, J, Hylek E, Jacobson A, Crowther M, Palareti G.** Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133(suppl 6):160S–198S.

This chapter of the 8<sup>th</sup> edition of the ACCP guidelines provides extensive information about the use of vitamin K antagonists, which is warfarin in the US. While most patients with

VTE end up on warfarin for some period of time, this chapter does cover the use of warfarin in several different clinical situations besides the treatment of VTE. As with the chapter on the treatment of VTE, the chapter begins with a summary of the recommendations before getting into the justification for each recommendation. This provides a quick method for finding a specific recommendation if the rationale behind the recommendation is not needed. Most of the general recommendations on the use of warfarin apply to its use in the treatment of VTE. Recommendations are provided on the initiation and maintenance dosing of warfarin, frequency of monitoring, management of non-therapeutic INRs, and optimal management of warfarin therapy. The chapter also includes a detailed discussion on the pharmacology of warfarin and role of genetics, drug and food interactions, and monitoring concepts. This chapter is almost 40 pages long with detailed discussion on the major issues and literature (419 references) surrounding the use of warfarin. Any clinician that manages patients on warfarin for acute or chronic therapy should review this chapter.

**Snow V, Qaseem A, Barry P, et al, for the Joint American College of Physicians/American Academy of Family Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism.** Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med.* 2007;146:204–10.

The American Academy of Family Physicians and American College of Physicians formulated a number of questions relative to the management of VTE. The authors conducted a systematic review of the evidence needed to answer each question and then developed a number of recommendations based on the literature review. There were eight questions identified, which resulted in six recommendations. While these guidelines are not as extensive as the ACCP guidelines, the question and answer method for developing the guidelines is unique. The questions the authors set out to answer are similar to many of the clinically relevant questions that clinicians have to consider every day in the management of patients with VTE. These organizations also published a similar guideline on the diagnosis of VTE, which may be of interest to clinicians specializing in this topic area. Many of the recommendations in this

guideline are similar to those in the ACCP guidelines. This guideline provides an additional reference in the development of an evidence-based medicine approach to the management of patients with VTE.

### Detection and Diagnosis

**Wells PS, Hirsch J, Anderson DR, et al.** Accuracy of clinical assessment of deep-venous thrombosis. *Lancet* 1995;345:1326–30.

The identification of DVT can be challenging due to the non-specific nature of symptoms, and objective testing plays an important role in the establishment of a firm diagnosis. When this article was published, venography was considered the “gold standard” for objective diagnosis of DVT, but with many drawbacks due to its invasive nature. Venous ultrasound of the lower extremities had begun to emerge, but use was limited by the need for serial testing and the occurrence of false positive results.

The investigators postulated that the use of a clinical probability score would improve and streamline the diagnosis of DVT. They prospectively assessed the accuracy of a clinical model, known as the Wells Criteria, at improving and simplifying the diagnostic process for DVT. The clinical model incorporated items that could be placed into three groups: (1) signs and symptoms of DVT; (2) risk factors for DVT; and (3) the likelihood of a potential alternative diagnosis. Based on the presence or absence of items in the Wells clinical model, patients could be categorized as either having a high, moderate, or low probability for DVT. Clinical probability scores were combined with ultrasound and selected use of venography in a comprehensive diagnostic approach. Important components included patients at low probability for DVT and having a normal ultrasound were ruled out for DVT, and no further diagnosis or treatment was implemented. Similarly, in patients at high probability and with an abnormal ultrasound, DVT were confirmed and treatment initiated. Importantly, in patients where pre-test probability and ultrasound results were discordant (low probability — abnormal ultrasound, high probability — normal ultrasound), venography was selectively employed to confirm the diagnosis.

Five hundred and twenty-nine patients with suspected DVT were enrolled and evaluated using the proposed diagnostic approach. Seventy-two of 85 patients (85%) in the high

probability group had a confirmed DVT, as compared to 47 of 143 in the moderate probability (33%) and 16 of 301 patients (5%) in the low probability groups. The differences between groups were statistically significant and demonstrated the value of the clinical probability score. In addition, invasive tests such as venography could be reserved for select patients where the risks of an invasive procedure are balanced against the need for a firm diagnosis. Post-test probability for DVT in patients with a low probability clinical score and normal ultrasound was less than 1%. Coupled with good results across the spectrum of patients, this analysis was the first to establish the vital role of clinical probability scoring in the overall diagnostic approach to DVT. In addition, this paper laid the groundwork for additional investigations, some of which are discussed below, that refined clinical probability scoring systems and incorporated emerging diagnostic technologies.

**Wells PS, Anderson DR, Bormanis J, et al.** Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997;350:1795–8.

In this follow-up from the authors of the original Wells Criteria, a revised clinical probability score was evaluated using the same diagnostic approach as in the 1995 paper by Wells and colleagues. In addition, the authors sought to confirm that the use of pre-test probability scoring could eliminate the need for serial ultrasound testing in many patients. As ultrasound had emerged as a significant diagnostic strategy for DVT in the mid-1990s, a major limitation was the need for repeat testing 1 week after an initial negative test to identify patients with calf vein thrombosis (which cannot be reliably detected with ultrasound) that had extended into the proximal veins. Approximately 20–30% of patients with isolated calf-vein thrombosis will have extension and potentially be at risk for PE. The revised clinical probability score was simplified into a point scoring system that could more easily be completed by the treating physician.

When evaluated in 593 eligible patients with suspected DVT, the diagnostic approach that incorporated the revised probability score performed well. In patients with a negative ultrasound and a low or moderate pre-test probability, the rate of DVT in the following 3 months was 0.6%. Serial ultrasound testing was

limited to only those patients at moderate risk for DVT who had an initial normal ultrasound. This manuscript provided further support for the use of clinical probability scoring systems in the diagnosis of DVT, and demonstrated that by using such systems the use of objective diagnostic tests such as ultrasound and venography can be streamlined and applied to the most appropriate patients.

**Wells PS, Ginsberg JS, Anderson DR, et al.** Use of a clinical model for safe management of patients with suspected pulmonary embolism. *Ann Intern Med* 1998;129:997–1005.

The diagnosis of PE can often be challenging due to non-specific signs and symptoms encountered in patients. As such, objective testing is needed to confirm the diagnosis. Pulmonary angiography, although at the time considered the “gold standard”, is limited by expense, availability, and risks. Additionally, results can be difficult to interpret with a significant false negative rate. Non-invasive V/Q scanning was therefore the first test typically employed in the late 1990’s to circumvent these limitations. While a normal V/Q scan effectively rules out PE, and a high-probability scan has a high positive predicative value, more than 50% of patients will have an intermediate probability result and require further testing such as ultrasound of the lower limbs or angiography.

In this analysis, the investigators sought to mimic their success with incorporating clinical probability testing in the diagnosis of DVT by developing a similar strategy for the diagnosis of PE. A clinical probability score was developed for PE, and incorporated into an overall diagnostic strategy similar to the previous approach for DVT. The diagnostic approach utilized V/Q scanning in all patients and selectively targeted patients to receive ultrasound of the lower extremities or angiography when there was discordance between clinical probability estimates and the results of V/Q scanning. In 1239 evaluable patients, 25 of 734 low probability (3.4%), 112 of 403 moderate probability patients (27.8%), and 80 of 102 high probability (78.4%) patients had a confirmed PE. Importantly, through the use of pre-test probability scoring, as well as ultrasound and V/Q scanning, 96% of patients with PE were diagnosed. The results of this study extended the importance of incorporating clinical probability scoring to PE.

**Wells PS, Anderson DR, Rodger M, et al.** Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost* 2000;83:416–20.

In this manuscript the authors describe further enhancement to the Wells Criteria for assessing clinical probability of PE by incorporating the results of D-dimer testing into the pre-test probability assessment and overall diagnostic strategy for PE. D-dimer results from the breakdown of fibrin and elevated levels can manifest from active clot formation. However, the D-dimer is sensitive, but not specific for the presence of VTE and therefore the value of the test is in excluding DVT or PE when D-dimer levels are normal. In this current analysis of an existing dataset from a previous trial looking at the diagnosis of PE, the investigators assessed whether patients could be safely categorized as not having PE without any further diagnostic testing. In patients with a low clinical probability score (PE unlikely) and a negative D-dimer, the rate of subsequent PE was 1.7%. Overall the importance of this paper is in highlighting the central role that D-dimer testing would eventually take in the overall diagnostic approach to both DVT and PE. Most contemporary diagnostic approaches utilize the D-dimer test to successfully rule out DVT or PE in patients prior to the use of invasive and non-invasive diagnostic modalities.

**Wicki J, Perneger TV, Junod A, Bounameaux H, Perrier A.** Assessing clinical probability of pulmonary embolism in the emergency ward. *Arch Intern Med* 2001;161:92–97.

While the Wells Criteria is well known and a useful tool in the overall diagnostic approach to DVT and PE, limitations may exist for some healthcare practitioners based on ease of use. A key component is the assessment for the likelihood of other disease states that may be responsible for the presenting signs and symptoms. This assessment is by nature subjective and may limit the utility of the Wells criteria in a broad array of clinicians. As such, the authors of the current analysis sought to develop a clinical pre-test probability score that was based on objectively obtainable clinical data. This clinical score, known as the Geneva criteria, incorporates age, previous VTE, recent surgery, heart rate, arterial blood gas information, and well as chest x-ray data into a point score and

subsequent categorization of the likelihood for PE. When validated against a known population of patients in whom the presence of PE was assessed via a standard diagnostic algorithm, the clinical probability score accurately predicted who developed a PE to a similar degree as the Wells criteria. Low probability patients had a 10% incidence of confirmed PE, while moderate and high probability patient had an incidence of 38% and 81% respectively. These results suggest that the Geneva score would be a useful component of an overall diagnostic strategy for PE similar to what has been demonstrated by the Wells Criteria.

**Le Gal G, Righini M, Roy PM, et al.** Prediction of PE in the emergency department: the revised Geneva Score. *Ann Intern Med* 2006;144:165–171.

By 2006, the central role of clinical probability assessment in the overall diagnosis of VTE was well recognized. While the Wells criteria and Geneva score had been successfully developed, both scores had some limitations that prevented widespread use in variable environments (outpatient, emergency department, acute care). In particular, the Geneva score developed in 2001 required arterial blood gas information which may not be easily obtained. Given their importance, standardization of clinical probability scores to improve utility and increase their use was desirable. Therefore the investigators developed a revised Geneva score, based on easily obtainable objective variables, and then validated the score in a cohort of patients presenting to the emergency department with suspected PE.

The new prediction rule was obtained from a multicenter prospective outcome study which used a standard diagnostic algorithm for PE utilizing clinical probability assessment, plasma D-dimer results, lower-limb ultrasound, and helical computed tomographic (CT) scanning. Multivariate regression identified age, history of VTE, recent surgery, active malignancy, the presence of unilateral lower limb pain, hemoptysis, elevated heart rate, and pain on lower limb palpation as significant factors to be incorporated into the revised Geneva score. As with the previous scoring system, each item is assigned a point score and the total points indicates the clinical probability of PE. The revised score performed well in the validation analysis, indicating that the revised Geneva score may offer the same utility within a diagnostic

approach as the previous Geneva score or the Wells criteria.

**Becattini C, Vedovati M, Agnelli G.** Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation* 2007;116:427–433.

Accurate estimation of prognosis in patients with PE is vital as aggressive therapies such as fibrinolysis with tissue plasminogen activator (t-PA) are best applied to patients at the highest risk of death. Risk stratification focuses on assessment of hemodynamic status, with patients presenting with hypotension or cardiogenic shock at the highest risk for short-term death. This is typically also the patient population where fibrinolysis is considered appropriate. In patients with normal blood pressure, there is some data which suggest that right ventricular dysfunction, as seen on echocardiography, also identifies a high-risk subgroup. However, echocardiography may not be universally available and may be subject to variable interpretation.

Serum troponin levels are readily available and may identify patients with PE who are at significant risk for short-term mortality. As such, the authors conducted a meta-analysis of currently available studies to assess the relationship between elevated troponin levels and PE prognosis. Twenty studies met inclusion criteria for the analysis, with both troponin T and troponin I utilized in various studies. Patients with elevated troponin levels had a significantly higher risk of death [19.7%; 95% confidence interval (CI) 16.6 to 22.8 vs. 3.7%; 95% CI 2.7 to 4.7] as compared to patients with normal troponin levels. Additionally, patients with an elevated troponin had an increased risk of adverse outcome events, defined as either death, shock, need for fibrinolysis, intubation, hypotension, cardiopulmonary resuscitation, or recurrent PE. Overall this meta-analysis clearly establishes the role of serum troponin values in determining the prognosis of patients with PE. It remains to be determined whether serum troponin testing can serve as an appropriate trigger for aggressive treatment such as fibrinolysis.

**Anderson DR, Kahn SR, Rodger MA, et al.** Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. *JAMA* 2007;298:2743–53.

The timely and accurate diagnosis of PE is essential to targeting therapy such as anticoagulation to appropriate patients. The use of V/Q scanning has been a preferred non-invasive testing modality over the last several decades. While a normal V/Q scan reliably excludes PE, and a high probability result has a high positive predictive value, many patients will have a low or intermediate probability result, and 10–40% of them will have PE. The inability to arrive at diagnostic certainty in a large number of patients limits the utility of V/Q scanning. In the past 10 years, computed tomography pulmonary angiography (CTPA) has been introduced as a potential diagnostic test for PE. Although the test has relatively low sensitivity, adoption of the test has been widespread due to the clear results provided (either positive or negative), as well as the potential to identify other causes (such as pulmonary infection or malignancy) for symptoms. This study is the first to directly compare V/Q scanning and CTPA in the diagnosis of PE. The investigators randomized 1417 patients to either a V/Q scan-based diagnostic strategy, or a CTPA diagnostic strategy. All patients were first evaluated with the Wells Criteria and received D-dimer testing. Subsequent use of lower leg ultrasonography was also incorporated into the overall diagnostic approach similar to previous studies. Patients unlikely to have PE using the Wells Criteria and a negative D-dimer were excluded as the diagnosis of PE was ruled out. Remaining patients were enrolled and randomized in the study. The primary outcome, defined as the subsequent development of VTE in patients initially deemed to not have PE was no different between the V/Q group and the CTPA group (0.4% vs. 1.0%;  $p = 0.29$ ). These results support CTPA as a viable non-invasive testing modality that can be incorporated into an overall diagnostic approach for PE. Additional significant results include a higher incidence of PE being diagnosed in the CTPA group compared to the V/Q group (19.2% vs. 14.2%). Given the equivalent outcomes overall between the two groups, CTPA may identify clots which may not require long-term anticoagulation. Further research in this area is warranted in order to optimize CTPA in the overall diagnosis of PE.

### Initial (Short-Term/Acute Phase) Therapy

#### Unfractionated Heparin

**Barritt DW, Jordan SC.** Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial. *Lancet* 1960;1:1309–1312.

This landmark publication, released almost 50 years ago, was the first randomized trial to demonstrate that the use of UFH in the acute treatment of PE reduced the risk of recurrent PE and death. Prior to these results, evidence supporting the use of UFH to improve outcome in PE stemmed mainly from large case studies that had been published in the preceding 20 years. However, despite the favorable results the authors note that oral anticoagulants alone were the typical treatment strategy employed at the time, partially due to the high cost of UFH. Additionally, the investigators recognized the trial design limitations of the available case series and elected to conduct a randomized trial to assess the safety and efficacy of UFH in the treatment of PE.

Patients who met diagnostic criteria for PE were confined to bed for 10 days and randomized to UFH 10,000 units intravenous (IV) every 6 hours plus nicoumalone (acenocoumarol), or placebo for 14 days. Randomization was halted after 35 patients. In 19 patients receiving no anticoagulant therapy, 5 patients had recurrent PE, and 5 died from PE. Conversely, in 16 patients treated with UFH plus oral anticoagulation, there were no recurrences and no patient died from PE. Comparisons between groups for recurrent PE and death both reached statistical significance. One patient experienced bleeding in the anticoagulation group and died with a duodenal ulcer being a contributing factor. This study supplied the groundwork for investigations in the coming decades seeking to identify the optimal dosing strategy for UFH in the treatment of PE, and VTE in general.

**Hull RD, Raskob GE, Rosenbloom D, et al.** Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. *N Engl J Med* 1990;322:1260–1264.

Jumping ahead 3 decades from the previous landmark trial, clinical research had begun to identify an optimal treatment strategy for UFH in the setting of both DVT and PE. It had been clearly established that reaching a threshold level of anticoagulation was essential at improving outcomes, and that monitoring UFH therapy could help clinicians achieve the necessary level

of anticoagulation in a given patient. However, the duration of UFH therapy needed during initial treatment was unclear. The standard of practice at the time of this publication typically called for 10 days of UFH therapy, with oral anticoagulation being started on day 5 to allow for 5 days of overlap prior to discontinuing UFH, provided the INR was within the designated therapeutic range. However, this approach was costly, requiring 10 days of hospitalization. If initial heparin therapy could be shortened, significant savings could be realized in healthcare utilization and costs.

Patients in whom DVT was confirmed by venography were randomized to either a short course of UFH therapy (5 days, with warfarin starting day 1), or a long course of UFH therapy (10 days, with warfarin starting day 5). The UFH was initiated in all patients as a 5000 unit bolus, followed by a continuous infusion of 40,000 units over 24 hours and titrated to an aPTT of 1.8–2.8 times the mean normal control of 30 seconds. Patients deemed at high-risk for bleeding received a lower initial infusion of 30,000 units over 24 hours. The initial dose of warfarin was 10 mg and therapy was titrated to an INR of 2.0–3.0. The UFH therapy could only be discontinued when the INR reached a threshold of 2.0. The risk of recurrent symptomatic VTE was no different in the short and long course groups (7.1% vs. 7.0%, respectively). Hemorrhagic complications occurred more frequently in the long course group (12%) compared to the short course group (9.1%), although these results were not statistically significant. Overall the results of this study provided the basis for the current practice of VTE treatment where both an acute anticoagulant (UFH, LMWH, fondaparinux) and warfarin are started on day 1, with transition to warfarin after a 4–5 day overlap and a therapeutic INR.

**Brandjes DPM, Heijboer H, Buller HR, et al.** Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1992;327:1485–1489.

Although UFH was the standard of care for initial treatment of VTE there was little evidence supporting UFH as the preferred anticoagulant strategy. In fact, the investigators note that at the time of publication the standard practice in several countries was to treat patients with new onset VTE with oral anticoagulants alone on an

outpatient basis. This strategy, if proven effective, would eliminate the need for hospitalization for VTE treatment in many patients. Therefore, the authors conducted a randomized, double-blind study in which patients with proximal DVT identified by venography were randomized to UFH (5000 unit bolus, 1250 unit/hour infusion, titrated to goal aPTT of 60–90 seconds) plus acenocoumarol (6 mg initial dose, titrated to an INR of 2.0–3.0), or acenocoumarol alone. The UFH was given for a minimum of 7 days, with acenocoumarol to be continued for 12 weeks. The primary endpoint was a composite of symptomatic extension of VTE, symptomatic pulmonary embolism, or symptomatic recurrence of VTE during the follow-up period of 6 months.

The trial was stopped early after enrollment of 120 patients due to a higher incidence of the primary endpoint in the acenocoumarol alone group, as compared to the combined UFH/acenocoumarol group (20% vs. 6.7%;  $p=0.058$ ). Additionally, asymptomatic extension of DVT or silent PE as determined through non-invasive testing occurred at a much higher frequency in the acenocoumarol alone group (39.6% vs. 8.2%). There was no difference in major bleeding between the two groups. While a majority of the symptomatic recurrences of VTE occurred after the first month of therapy, the results highlight the importance of achieving therapeutic anticoagulation within the initial 24 hours in order to improve outcomes in patients with DVT and PE. As current oral anticoagulant options have a delayed onset of action, treatment of VTE should always include a rapid acting injectable anticoagulant to quickly achieve therapeutic anticoagulation.

**Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S.** The weight-based heparin dosing nomogram compared with a “standard care” nomogram. *Ann Intern Med* 1993;119:874–881.

This landmark publication greatly enhanced the understanding of how UFH should be optimally dosed. The authors succinctly reviewed the current literature regarding UFH in the treatment of VTE, including the importance of rapidly exceeding a therapeutic threshold (1.5 times the control aPTT value) to improve outcomes. The optimal UFH dose to achieve this goal had yet to be determined, and available literature suggested that clinicians often underdosed UFH in the early treatment of VTE leading to delays in achieving therapeutic

anticoagulation. Based on an internal audit of patients on UFH and the dose required to produce a therapeutic aPTT, the investigators developed a dosing and titration nomogram for UFH. Initial weight-based dosing consisted of an 80 unit/kg bolus followed by an 18 unit/kg/hour infusion. Therapy was titrated to a goal aPTT (1.5 – 2.3 times control) using a weight-based (units/kg/hr) titration scheme. This weight-based dosing nomogram was compared to a standard empiric dosing strategy (5000 unit bolus, 1000 unit/hour infusion, non-weight based adjustments for titrating to a therapeutic aPTT). One hundred fifteen patients were randomized, 85 of whom were being treated for VTE. The weight-based dosing strategy was more successful at both rapidly achieving a therapeutic level of anticoagulation, as well as achieving a therapeutic aPTT, as compared to an empiric dosing strategy. The risk of recurrent VTE was also reduced in patients receiving weight-based UFH (5% vs. 25%;  $p=0.02$ ). This publication confirmed the importance of rapidly achieving therapeutic anticoagulation in the treatment of VTE, as well as establishing weight-based dosing as the standard of care for UFH for VTE, and eventually acute coronary syndrome.

**Hull RD, Raskob G, Brant RF, et al.** The importance of initial heparin treatment on long-term clinical outcomes of antithrombotic therapy. *Arch Intern Med* 1997;157:2317–2321.

This pooled analysis of three previous studies investigating the use of UFH in the treatment of VTE by the same investigators provided important insight into the effects of failing to achieve rapid therapeutic anticoagulation. While the three studies investigated different aspects of UFH use (one study compared IV to SC UFH, one compared 10 days of UFH to 5 days, and the third compared UFH to LMWH), all were able to provide adequate information to assess whether inadequate anticoagulation in the short-term had long-term consequences. The investigators indeed found that subtherapeutic anticoagulation during the initial treatment of VTE not only increased the risk of recurrence in the short-term, but also in the long-term (2–3 months after initiation of therapy). These results further emphasize the need to achieve rapid therapeutic anticoagulation within 24 hours during the initial treatment of VTE.

#### Low Molecular Weight Heparin

**Hull RD, Raskob GE, Pineo GF, et al.** Subcutaneous low-molecular-weight-heparin compared with continuous intravenous heparin in the treatment of proximal vein thrombosis. *N Engl J Med* 1992;326:975-982.

This is one of the first double-blind clinical trials to demonstrate the efficacy of LMWH (tinzaparin) in the treatment of DVT in hospitalized patients. Patients with acute proximal DVT ( $n=432$ ) were randomized to weight-based fixed-dose SC tinzaparin given once daily or to adjusted-dose IV UFH for the initial acute phase treatment of DVT. Recurrent VTE occurred in 2.8% of patients assigned to LMWH and 6.9% of patients treated with UFH ( $p=0.07$ ; 95% CI, 0.02% to 8.1%). Major bleeding associated with initial therapy occurred in 0.5% of patients receiving LMWH and in 5% receiving IV UFH, a RR reduction of 91% ( $p=0.006$ ). Ten patients (4.7%) on LMWH died, as compared with 21 patients (9.6%) receiving IV UFH, a RR reduction of 51% ( $p=0.049$ ). This is one of the early landmark studies to demonstrate that LMWH has a favorable efficacy and safety profile compared to IV UFH in the treatment of acute DVT and one of the few studies that shows a mortality benefit in favor of LMWH.

**The Columbus Investigators.** Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;337:657–662.

Initial studies that evaluated the efficacy of LMWHs in the treatment of acute uncomplicated VTE excluded patients with PE and some excluded patients with a history of VTE. This large prospective, open label, randomized study is one of the first to report the efficacy of LMWH (reviparin) in the treatment of patients with acute VTE, including DVT and/or PE. A total of 1021 patients were randomly assigned to a fixed dose of SC reviparin (determined based on a weight range) or adjusted dose IV UFH. Oral anticoagulation was started concurrently and given for 12 weeks. One third of enrolled patients also had an associated PE. The primary outcome was objectively confirmed symptomatic recurrent VTE and major bleeding within 12 weeks of randomization. Recurrent VTE occurred in 5.3% of patients who received LMWH compared to 4.9% of patients who received UFH, thus showing equivalency of the two treatment regimens based on a

predetermined criterion for equivalence of an absolute increase in recurrent VTE of no more than 3% with LMWH. Major bleeding was reported in 3.1% on LMWH and 2.3% on UFH ( $p=0.63$ ), whereas the mortality rate was 7.1% in the LMWH group and 7.6% in the UFH group ( $p=0.89$ ). This is one of the first studies to show that LMWH is at least as effective as UFH in the initial treatment of VTE that also included patients with PE expanding the clinical role of LMWH therapy.

**Simonneau G, Sors H, Charbonnier B, et al.** A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. *N Engl J Med* 1997;337:663-669.

The next step in the evaluation of LMWH in the treatment of VTE was to evaluate its role in the treatment of acute symptomatic PE. A total of 612 patients with symptomatic PE who did not require embolectomy or fibrinolytic therapy were randomized to SC LMWH (tinzaparin) once daily (175 units/kg) or weight adjusted IV UFH. Patients were initiated on oral anticoagulation therapy between days 1 and 3 and therapy was given for at least 3 months. The combined primary end point was recurrent VTE, major bleeding and death was evaluated at day 8 and day 90. By day 8 of therapy, 2.9% patients in the UFH group reached at least one of the end points and compared to 3% in the LMWH group ( $p=0.05$ ; 95% CI, -2.7 to 2.6). At 90 days, 7.1% of UFH and 5.9% of LMWH patients had reached at least one end point ( $p=0.54$ ; 95% CI, -2.7 to 5.1). Major bleeding and mortality were not different between the groups. This study is significant in that is one of largest studies establishing the potential role of LMWH in patients with nonmassive PE.

**Gould MK, Dembitzer AD, Doyle RL, et al.** Low-molecular weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. *Ann Intern Med* 1999;130:800-809.

Although several individual studies had established the role of LMWHs in the treatment of DVT, some previous reviews and meta-analyses had reached mixed conclusions. This paper is one of the largest meta-analyses of randomized controlled trials comparing the

safety and efficacy of LMWH with UFH for treatment of acute DVT and was undertaken in an attempt to resolve discrepancies reported among previous smaller reviews. A total of eleven studies were included through September 1997. Recurrent VTE was slightly less common in LMWH patients but this difference was not statistically significant, [odds ratio (OR), 0.85 CI 0.63 to 1.14; number needed to treat (NNT) =114]. For major bleeding complications, the OR favored LMWH (0.57, CI 0.33 to 0.99;  $p=0.047$ ), but the absolute risk reduction was small and not statistically significant (0.61%, CI -0.04% to 1.26%;  $p=0.07$ ; NNT=164). Compared to UFH, LMWHs were found to reduce mortality at 3 to 6 months (OR 0.71, 95% CI 0.53 to 0.94;  $p=0.02$ ; NNT, 61). In a small subgroup of cancer patients ( $n = 279$ ), the mortality advantage of LMWH was even larger (OR 0.57, CI 0.31 to 1.03;  $p=0.06$ ; NNT, 10). This was the first meta-analysis to report a mortality benefit and similar efficacy and safety of LMWH compared to UFH in the treatment of acute DVT. The findings of this meta-analysis have contributed in establishing LMWHs as mainstay therapy for the treatment of acute DVT.

**Dolovich LR, Ginsberg JS, Douketis JD, et al.** A metaanalysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. *Arch Intern Med* 2000;160:181-188.

This is the second in a series of meta-analyses that sought to further clarify the question of relative efficacy of LMWHs compared to UFH in the treatment of VTE. This paper also attempted to address controversies in treatment such as efficacy of outpatient LMWH therapy, efficacy of once daily LMWH, and differences in efficacy and safety among the various LMWH preparations. A total of 13 randomized controlled trials of patients diagnosed with acute VTE that compared LMWHs with UFH were included. There was no statistically significant difference in risk between UFH and LMWHs for recurrent VTE (RR, 0.85, 95% CI 0.65-1.12), pulmonary embolism (RR, 1.02, 95% CI, 0.64-1.62), and major bleeding (RR, 0.63, 95% CI 0.37-1.05). However, there was a statistically significant difference for risk of total mortality (RR 0.76, 95% CI 0.59-0.98) in favor of LMWHs. Inpatient treatment may reduce the risk of major bleeding compared to outpatient therapy. Once-

daily therapy is as safe and effective as twice-daily therapy when compared indirectly. Different products could not be statistically compared, but qualitative analysis shows that there are no apparent differences in efficacy and safety. Like the previous paper, this meta-analysis confirmed that LMWHs are at least as effective as UFH but are unlikely to be superior in preventing recurrent VTE. Treatment setting, once daily versus twice daily regimens, or the specific LMWH product had no effect on the reported outcomes.

**van Dongen CJ, van den Belt AGM, Prins MH, Lensing AWA.** Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev* 2004;(4):CD001100.

The purpose of this systematic review was to evaluate the efficacy and safety of LMWH compared to UFH for the initial treatment of acute VTE. A total of 22 randomized controlled studies (published between 1988 and the end of 2003) with prospective follow-up of patients with acute VTE treated with fixed dose SC LMWH or weight adjusted UFH (IV or SC) were included ( $n = 8867$ ). Thirteen of the 22 studies included patients with DVT without symptoms of PE. In 7 studies patients were included if they had DVT with or without PE, and in 2 studies patients with PE only were included. The use of 8 different LMWHs was identified. The primary outcome measure was incidence of symptomatic recurrent VTE during the initial treatment and during follow-up. Frequency of major bleeding during initial treatment or within 48 hours after treatment cessation and overall mortality at the end of follow-up were part of the secondary outcome measures. Venous thrombosis occurred in 3.6% of patients treated with LMWH, compared with 5.4% of patients treated with UFH (OR 0.68, 95% CI 0.55 to 0.84). Major bleeding occurred in 1.2% of patients treated with LMWH, compared to 2.0% of patients treated with UFH (OR 0.57, 95% CI 0.39 to 0.83). Death was reported in 4.5% of patients treated with LMWH, compared to 6.0% of patients treated with UFH (OR 0.76, 95% CI 0.62 to 0.92). In this systematic review, LMWH was found to be more effective than UFH for the initial treatment of VTE. In addition, LMWH resulted in lower major bleeding and mortality rates compared to UFH. Based on these data, LMWHs can be advocated as the preferred initial

therapy for patients with confirmed acute VTE. However, as only approximately 25% of the participants had a diagnosis of primary PE, the investigators caution that more data are required before LMWHs can be recommended as the standard first-line treatment for primary PE.

**Quinlan DJ, McQuillan A, Eikelboom JW.** Low-molecular weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a metaanalysis of randomized, controlled trials. *Ann Intern Med* 2004;140:175–183.

This meta-analysis was undertaken to further elucidate the efficacy and safety of LMWH for the initial treatment of PE. Randomized trials comparing fixed-dose SC LMWH with dose-adjusted IV UFH for the treatment of nonmassive symptomatic PE or asymptomatic PE in the context of symptomatic DVT were included in the analysis. A total of 1951 patients with PE from 12 trials up to August 2003 were included. Six LMWH preparations were evaluated. Recurrent symptomatic VTE was similar in the LMWH and UFH groups at the end of treatment (1.4% vs. 2.4%; OR 0.63, 95% CI 0.33 to 1.18) and at 3 months (3.0% vs. 4.4%; OR 0.68, CI 0.42 to 1.09). Similar estimates were obtained for patients who presented with symptomatic PE (1.7% vs. 2.3%; OR 0.72, CI 0.35 to 1.48) or asymptomatic PE (1.2% vs. 3.2%; OR 0.53, CI 0.15 to 1.88). Major bleeding complications were not different between the LMWH and UFH groups (1.3% vs. 2.1%; OR 0.67, CI, 0.36 to 1.27). There was no evidence of any advantages or disadvantages between LMWH preparations in terms of efficacy or safety outcomes. As reported by previous studies, this meta-analysis re-confirmed that fixed-dose LMWH is as effective and safe as dose-adjusted IV UFH for the initial acute treatment phase of patients with nonmassive PE.

**Partsch H, Kechavarz B, Mostbeck A, et al.** Frequency of pulmonary embolism in patients who have iliofemoral deep vein thrombosis and are treated with once- or twice-daily low-molecular-weight heparin. *J Vasc Surg* 1996;24:774–782.

Controversy surrounds the appropriate dosing frequency of LMWH in the treatment of VTE. This study was one of the first to evaluate a once daily and twice daily LMWH (dalteparin) in the treatment of DVT. A total of 140 consecutive patients with iliofemoral DVT were randomized

to SC dalteparin either 200 IU/kg once daily (group 1; n=76) or 100 IU/kg twice daily (group 2; n=64). The primary end point was reduction in frequency of PE on a second lung scan at 10 days. The incidence of symptomatic PE was reduced from 14.5% to 5.3% in group 1 and from 12.5% to 1.6% in group 2 ( $p < 0.05$ ). There was one single fatal PE, one serious PE and three minor bleeding episodes in group 1, and one minor bleeding episode in group 2 (95% CI -3.6% to 8.1%). In this study of patients with iliofemoral DVT, twice daily dalteparin appeared to be more safe and effective than once daily dalteparin. Although a small study, it questions the efficacy of once daily LMWH in high risk DVT patients. Based on these findings, high risk DVT patients (iliofemoral thrombosis) may benefit from using the twice daily dalteparin regimen.

**Merli G, Spiro TE, Olsson CG, et al.** Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001;134:191–202.

This randomized, controlled, partially blinded equivalency study sought to determine whether SC enoxaparin could be administered once or twice daily to be as effective as IV UFH in the treatment of acute symptomatic VTE. A total of 900 patients with symptomatic lower-extremity DVT, including 287 (32%) with PE were randomized to initial therapy with dose-adjusted IV UFH (n=290), once daily SC enoxaparin (1.5 mg/kg; n=298), or twice daily SC enoxaparin (1 mg/kg; n=312). Efficacy was similar in the 3 groups. Symptomatic VTE recurred in 4.1% of UFH patients, 4.4% of the once daily enoxaparin group, and 2.9% of the twice daily enoxaparin group ( $p = \text{NS}$ ). The incidence of major bleeding did not differ among the 3 groups. Prespecified subgroup analysis showed that patients with obesity or malignancy had a trend towards higher VTE recurrence with once daily enoxaparin, suggesting that the once daily regimen should be avoided in these patients. In this study, once or twice daily SC enoxaparin was as effective as IV UFH in the prevention of recurrent symptomatic VTE, however in high-risk patients (cancer, obesity, etc) the twice daily dosing regimen maybe preferred.

**van Dongen CJ, MacGillavry MR, Prins MH.** Once versus twice daily LMWH for the initial treatment of venous thromboembolism.

Cochrane Database Syst Rev. 2005;(3):CD003074.

Although a once daily LMWH regimen maybe more convenient to use in the treatment of patients with VTE, it is not clear if a once daily treatment regimen is as safe and effective as a twice daily treatment regimen. The objective of this analysis was to compare the efficacy and safety of once daily compared to twice daily administration of LMWH. Randomized clinical trials in which LMWH given once daily was compared with LMWH given twice daily for the initial treatment of VTE were included through April 2005. A total of 1508 patients and 5 studies were included. The pooled data showed a non-significant difference in recurrent VTE between the twice and once daily regimens (OR 0.82, 95% CI 0.49 to 1.39). A comparison of major bleeding events (OR 0.77, 95% CI 0.40 to 1.45) and mortality (OR 1.14, 95% CI 0.62 to 2.08) also showed no difference between the two treatment regimens. No differences among the various LMWH compounds were noted. Based on these results, it appears that once daily treatment with LMWH may be as effective and safe as twice daily treatment. However, the wide 95% CI implies that there is a possibility that the risk of recurrent VTE might be higher when people are treated with a once daily regimen. Thus, caution should be used especially in higher risk patients (obesity, pregnancy, massive thrombosis, and cancer) and the convenience of the once daily LMWH regimens should be weighed against the potential for lower efficacy.

**Wells PS, Anderson DR, Rodger MA, et al.** A randomized trial comparing 2 low-molecular-weight heparins for the outpatient treatment of deep vein thrombosis and pulmonary embolism. *Arch Intern Med* 2005;165:733–738.

This paper is the only randomized, controlled trial that compared two different LMWHs for the treatment of acute DVT and PE. A total of 254 outpatients received tinzaparin 175 IU/kg SC every 24 hours (215 with DVT and 39 with PE) and 251 received dalteparin 200 IU/kg SC every 24 hours (200 with DVT and 51 with PE) for at least 5 days. Warfarin was started at the same time and continued for 90 days. The primary objective was to compare the efficacy (recurrent VTE) and safety (bleeding) as a composite end point. Outcome events occurred in 4.4% of dalteparin patients and 5.9% of tinzaparin patients ( $p = \text{NS}$ ). Mortality was not different between the groups. This study found

no differences in efficacy and safety of tinzaparin and dalteparin in the outpatient treatment of DVT and PE thus either agent is acceptable to use for this indication. Convenience cost, and formulary status should also be used as part of the decision process to select the most practical agent.

#### Fondaparinux

**Buller HR, Davidson BL, Decousus H, et al.** Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med* 2003;349:1695-702.

Fondaparinux was initially investigated for prevention of VTE in orthopedic surgery. During drug development, a dosing-ranging trial in patients with symptomatic DVT was conducted which concluded that a fixed dose of fondaparinux was as safe and effective as dalteparin for the treatment of VTE. In response, two phase III trials were designed to compare the effectiveness of fondaparinux to standard treatment for DVT (MATISSE-DVT) and in PE (MATISSE-PE). It should be noted that patients with a creatinine clearance (CrCl) less than 30 mL/min were excluded from both of these trials.

MATISSE-PE was an open-label trial that randomized 2213 patients with acute symptomatic PE to either IV UFH or fondaparinux. The UFH was given on an inpatient basis as a bolus of "at least 5000 units" followed by a continuous infusion of "at least 1250 units per hour" and adjusted to maintain the aPTT at 1.5-2.5 times a control value. At day 1, aPTTs for 93% of patients randomized to UFH were above the lower limit of the therapeutic range. Fondaparinux was given as a fixed dose of 7.5 mg SC once daily, or adjusted to 5 mg once daily for patients weighing less than 50 kg or 10 mg once daily for patients weighing more than 100 kg. Among patients randomized to fondaparinux, 14.5% received at least 1 day on an outpatient basis. All patients were started on a vitamin K antagonist as soon as possible, which was adjusted to a goal INR of 2.0-3.0. Fondaparinux was continued for a minimum of 5 days and until the INR was greater than 2.0 for two consecutive days. The vitamin K antagonist was continued for 3 months. At 3 months, the incidence of recurrent VTE in patients receiving fondaparinux compared to UFH was similar (3.8% vs. 5%; 95% CI -3.0 to 0.5%) and met the pre-specified non-inferiority margin. Major

bleeding (1.3% vs. 1.1%; 95% CI -0.7 to 1.1%) and mortality (5.2% vs. 4.4%; 95% CI -1.0 to 2.6%) were similar in patients receiving fondaparinux or UFH, respectively.

**Buller HR, Davidson BL, Decousus H, et al.** Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med* 2004;140:867-73.

MATISSE-DVT used a double-blind trial that randomized 2205 patients with symptomatic DVT to fondaparinux (using the same dosing scheme as in MATISSE-PE described above) or enoxaparin 1mg/kg SC every 12 hours. The duration of initial treatment, transition to vitamin K antagonist, and duration of total treatment were similar to MATISSE-PE, except that initial treatment was given on an outpatient basis for 31.6% assigned to fondaparinux and 34.2% of patients assigned to enoxaparin. Time-in-range for warfarin therapy was not reported, but 65.4% of patients randomized to fondaparinux had an INR > 2.0 more than 70% of the time, as did 69.5% of patients randomized to enoxaparin. At 3 months, recurrent VTE had occurred in 3.9% of patients randomized to fondaparinux, and 4.1% randomized to enoxaparin (95% CI -1.8 to 1.5%), meeting the pre-specified non-inferiority margin. Major bleeding (2.6% vs. 2.4%; 95% CI -2.1% to 1.7%) and mortality (3.8% vs. 3.0%; 95% CI -0.8% to 2.3%) were similar in patients receiving fondaparinux or enoxaparin, respectively. Taken together, MATISSE-DVT and MATISSE-PE demonstrated that fondaparinux is a safe and effective alternative for initial treatment of VTE.

#### Fibrinolysis

##### Deep Vein Thrombosis

**Goldhaber SZ, Meyerovitz MF, Green D, et al.** Randomized controlled trial of tissue plasminogen activator in proximal deep venous thrombosis *Am J Med* 1990;88:235-240.

The use of UFH alone has traditionally been used in the management of DVT. However, fibrinolytic agents are an attractive option due to their ability to breakdown existing thrombi. Small investigations previously reported promising outcomes with these agents in the treatment of lower extremity DVT. The rate and dose of t-PA administration in the management of DVT has been debated. The investigators performed this randomized trial to compare the

degree of clot lysis between t-PA (n=36), t-PA plus UFH (n=17), and UFH alone (n=12). The t-PA was administered at 0.05 mg/kg/hour over 24 hours using a continuous IV peripheral infusion. The UFH was given as a 100 unit/kg bolus followed by a 1000 unit/hour continuous infusion to maintain an aPTT between 1.5 to 2.5 times control. A repeat venogram was performed within 36 hours of the study drug termination with clot lysis classified as complete, partial (more than 50%), minimal (less than 50%), or none. Bleeding was reported as major (intracranial or reduction in hemoglobin by 5 points) or minor. Plasma fibrinogen and fibrinogen degradation product levels were drawn before and after the study drug was administered. Partial or complete lysis was achieved significantly more often in the t-PA arms (28% t-PA alone and 29% t-PA plus UFH) compared to UFH alone (0%,  $p=0.04$ ). All patients who received UFH alone achieved either minimal or no lysis. One case of major bleeding occurred in the t-PA arm. No difference in minor bleeding was reported; however numerically more were reported in those patients receiving t-PA (25%) and t-PA plus UFH (12%) than UFH alone (0%,  $p=0.13$ ). Significant reductions in fibrinogen ( $p=0.0001$ ) and elevations in fibrinogen degradation products ( $p=0.0002$ ) were seen after 24 hours with the t-PA and t-PA plus UFH groups compared to the UFH alone. While no clinical efficacy outcomes were measured, this trial provides some assurance that fibrinolytic therapy does reduce clot burden better than anticoagulation alone. These data also suggest clinicians may consider anticoagulation alone in patients perceived to be at a greater risk for bleeding events.

**Schweizer J, Kirch W, Koch R, et al.** Short- and long-term results after thrombolytic treatment of deep venous thrombosis. *J Am Coll Cardiol* 2000;36:1336–1343.

Various administration techniques, fibrinolytic doses, and agents have been proposed for the acute management of DVT. All protocols have sought to improve recanalization rates and reduce bleeding complications. The impact of fibrinolytic therapy on long-term complications, such as post-thrombotic syndrome (PTS), is largely unknown. This randomized trial was designed to characterize the short- and long-term effects of five acute treatment strategies for DVT. A total of 250 patients were randomized to either (1) UFH 1000 units/hour alone, (2) local t-PA 20

mg over 4 hours for 4-7 days plus UFH, (3) local urokinase 100,000 units/hour for up to 7 days plus UFH, (4) systemic urokinase 5 million units daily over 4 hours for up to 7 days plus UFH, or (5) systemic streptokinase 3 million units daily over 6 hours for up to 7 days plus UFH. All patients received anticoagulation and compression therapy for 12 months. The primary outcomes were the number of closed vein segments and the occurrence of PTS after 12 months. Secondary outcomes included the number of closed vein segments still closed after 7 days of fibrinolytic therapy. A significant reduction in occluded vein segments occurred with both systemically administered therapies (urokinase 58%; streptokinase 57%) compared to locally administered therapies (t-PA 48%; urokinase 49%) or UFH control (37%;  $p<0.05$ ). A significant reduction in the number of patients without PTS was seen with the systemically administered therapies (urokinase 14 patients; streptokinase 23 patients) compared to locally administered therapies (t-PA 11 patients; urokinase 13 patients) and UFH control (5 patients;  $p<0.001$ ). No significant differences were observed with either primary outcome between the locally administered therapies and UFH control. A similar significant difference was observed for the number of closed vein segments after 7 days of therapy between systemic (urokinase, 67; streptokinase, 68) and local (t-PA, 105; urokinase, 103) and UFH control (295;  $p<0.01$ ). However, major bleeding was more prominent in the systemic therapies (9 major events) compared to local (3 events) and UFH control (0 events). These data support the use of systemic fibrinolytic therapy in the acute management of DVT and suggest long-term complications, such as PTS, can be improved as well.

**Watson LI, Armon MP.** Thrombolysis for acute deep vein thrombosis. *Cochrane Database Syst Rev* 2004:CD002783.

Clinical trials investigating the use of fibrinolytic agents in the treatment of DVT have been small and diverse. This Cochrane review analyzed the results of 12 trials that included a total of 668 patients with acute lower extremity DVT who had been randomized to either fibrinolytic or anticoagulant therapy. A number of outcomes were measured including mortality, venous patency, and complications (PE, recurrent DVT, PTS, and bleeding). No difference in early (RR 0.84, 95% CI 0.29 to

2.42) or late (RR 1.33, 95% CI 0.34 to 5.24) mortality was seen with fibrinolytic therapy. A significant reduction in PTS was observed with fibrinolysis compared to anticoagulation therapy (RR 0.66, 95% CI 0.47 to 0.94). Bleeding occurred significantly more often in the fibrinolytic arms (RR 1.73, 95% CI 1.04 to 2.88); however, this risk appears to be less or nonexistent when the analysis is restricted to trials with more contemporary exclusion criteria (RR 1.24, 95% CI 0.65 to 2.36). This Cochrane review helps to identify the degree and significance of the previously proposed risks and benefits of fibrinolytic therapy for lower extremity DVT. Additionally, this review found that the more restrictive exclusion criteria for fibrinolytic trials may be justified. Despite the large number of patients pooled in this analysis, no conclusions on the preferred agent, dose, and route can be made.

**Grunwald MR, Hofmann LV.** Comparison of urokinase, alteplase, and reteplase for catheter-directed thrombolysis of deep venous thrombosis. *J Vasc Interv Radiol* 2004;15:347–352.

Previous DVT treatment trials involving fibrinolytic therapy had either included one agent compared to placebo or multiple agents and multiple routes of administration making conclusions difficult. Current guidelines recommend the use of catheter-directed fibrinolysis (CDF) for acute DVT; however, the optimal agent and dose were still unclear. This retrospective analysis compared the efficacy, safety, and cost of CDF with urokinase, t-PA, and reteplase (r-PA). Patients received either urokinase 120,000 units/hour (range: 40,000–400,000 units/hour), t-PA 0.5 mg/hour (range: 0.25–2 mg/hour), or r-PA 0.75 units/hour (range: 0.5–1.0 units/hour). All patients received UFH to maintain an aPTT at less than 1.5 times control. Success rates (partial and complete fibrinolysis), safety endpoints (major and minor bleeding), and drug costs were compared. A total of 74 patients contributed a total of 82 limbs for review (38 in urokinase, 32 in t-PA, and 12 in r-PA) with no differences in baseline demographics reported. Complete fibrinolysis in the urokinase, t-PA, and r-PA arms were similar (71.1%, 65.6%, and 50% respectively,  $p=0.63$ ). Complications were also similar between agents for major (5.3% urokinase, 3.1 t-PA, and 8.3% r-PA,  $p=0.88$ ) and minor (10.5% urokinase, 12.5% t-PA, and 16.7% r-PA,  $p=0.94$ ) bleeding. Median drug costs per

limb were significantly lower for t-PA (\$488) compared to urokinase (\$6577;  $p<0.001$ ) and r-PA (\$1787;  $p<0.05$ ). The range of doses and small sample population makes interpretation difficult; however, the cost analysis may provide clinicians some guidance in practice. Given the higher number of successes, lower number of bleeds, and significantly lower cost, t-PA may be preferred over r-PA.

**Lin PH, Zhou W, Dardik A, et al.** Catheter-direct thrombolysis versus pharmacomechanical thrombectomy for treatment of symptomatic lower extremity deep venous thrombosis. *Am J Surg* 2006;192:782–788.

Both mechanical thrombectomy and fibrinolysis using catheter-based devices have been effective in the management of DVT when used alone. While thrombectomy alone is not recommended in the current guidelines, a combination of fibrinolysis and thrombectomy, called pharmacomechanical thrombectomy (PMT) is an attractive option. This trial compared treatment outcomes in patients with symptomatic DVT between PMT and CDF. Patients receiving treatment for a DVT over an eight-year period were analyzed by treatment strategy. A total of 93 patients were included (PMT,  $n=49$  vs. CDF,  $n=44$ ) representing 98 catheter interventions. Each arm used contained a mixture of fibrinolytic use including r-PA, t-PA, and urokinase (15, 25, and 12 interventions in the PMT arm respectively vs. 11, 27, and 8 interventions in the CDF arm respectively). Treatment success, defined as complete thrombus removal based on angiographic confirmation, was achieved in 75% of PMT patients compared to 70% of CDF. No statistical difference in partial success was observed between the treatment arms. Differences in the technique time was observed with patients requiring  $76 \pm 34$  minutes in the PMT group compared to  $18 \pm 8$  hours in the CDF group leading to reductions in intensive care unit time (0.6 days vs. 2.4 days;  $p<0.04$ ) and hospital stay (4.6 days vs. 8.4 days;  $p<0.02$ ). These differences translate to reductions in total hospital costs with cost differences of \$37,600 in favor of PMT ( $p<0.01$ ). These data have led to the recommendation suggesting PMT over CDF in cases where appropriate expertise and resources are available. Clinicians may also find the comprehensive description of the PMT technique a valuable addition to this resource.

### *Pulmonary Embolism*

**Goldhaber SZ, Kessler CM, Heit J et al.** A randomized controlled trial of recombinant tissue plasminogen activator versus urokinase in the treatment of acute pulmonary embolism. *Lancet* 1988;332:293-8.

Prior to the availability of t-PA, a 24-hour infusion of urokinase was the standard treatment approach in the management of acute PE in high-risk patients. Small trials suggested shorter infusion times with more specific fibrinolytic agents might yield improved clot lysis. Additionally, previous inclusion criteria only considered patients with symptoms persisting for less than 5 days. This randomized trial compared a fixed dose of t-PA infused over 2 hours (n=22) and weight-based dose of urokinase over 24 hours (n=23) in patients with symptomatic PE for up to 14 days. The t-PA was administered as a 50 mg/hour infusion for 2 hours through a peripheral vein. The urokinase dosing included a 1000 unit/pound bolus followed by a 1000 unit/pound/hour infusion for 24 hours. No patient received concomitant UFH with the fibrinolytic agent. The primary outcome was composed of two parts: (1) improvement in the pulmonary angiogram at 2 hours and (2) improvement in the perfusion lung scan at 24 hours. Major bleeding included bleeding which required surgical intervention, intracranial hemorrhage, or a fall in hematocrit of 10 points. After enrolling 45 of 50 patients, the trial was discontinued early due to significant improvements in clot lysis with t-PA. At 2 hours, 82% of the t-PA patients showed angiographic improvements compared to 48% of the urokinase patients (p=0.008). No difference in clot lysis was observed in patients with symptoms persisting for less than 5 days compared to 6-14 days. No difference in the pulmonary lung scan at 24 hours was noted. One urokinase allergic reaction was observed after approximately 2 hours of administration. No difference in major bleeding was seen; however, more urokinase patients experienced a hematocrit reduction of 10 points compared to t-PA patients (11 vs. 4; p=0.06). Several guideline recommendations have been influenced by data generated from this landmark trial. Patients with symptoms consistent with PE are considered candidates for fibrinolytic therapy up to 14 days. Additionally, shorter infusion times (2 hours) are recommended over prolonged infusion periods (24 hours).

**Goldhaber SZ, Agnelli G, Levine MN.** Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis: an international multicenter randomized trial; The Bolus Alteplase Pulmonary Embolism Group. *Chest* 1994;106:718-724.

Previous investigations using shorter administration times of fibrinolytic agents have shown benefit in patients with PE. A further reduction in both the fibrinolytic dose and administration time may provide a better safety profile; however, these reductions may not be as effective. This trial explored whether a reduced weight-based dose administered over 15 minutes was as effective as a fixed-dose administered over 2 hours. Patients were randomized to either 0.6 mg/kg (maximum 50 mg) t-PA over 15 minutes (n=61) or 100 mg t-PA over 2 hours (n=29). All patients received a bolus dose of IV UFH followed by an infusion to maintain the aPTT to less than two times the control. The primary outcome was major bleeding defined as any intracranial bleeding, hematocrit reduction of 15 points, or death due to bleeding. Lung scans and serum fibrinogen assessments were made to grade the degree of improvement before and after treatment. No difference in major bleeding was observed between the weight-based (8 patients) and fixed dose (6 patients, p=0.35) groups. Changes to lung scans were similar in the two treatment arms. Patients receiving weight-based dosing had less decline in serum fibrinogen than those who received fixed dose (p=0.007). No correlation to improvement or bleeding was observed with the fibrinogen levels. A total of 6 deaths occurred in the study with no statistical differences in the treatment arms (5 deaths in the weight-based dose vs. 1 in the fixed dose; p=0.66). However, the high mortality rate reported in the weight-based arm (8.3%) compared to previous investigations led to discontinuation of the trial after 90 patients were enrolled. Post-hoc analyses found that an unexpected high percent of death occurred at several inexperienced centers. While these data show that the safety and efficacy of weight-based dosing administered over 15 minutes is similar to fixed dose administered over 2 hours, an experienced center and clinicians should be involved in the care of patients diagnosed with PE. While guidelines suggest administering fibrinolytic agents over short periods of time, 2 hour infusions are likely preferable to shorter infusion times until more data is available.

**Agnelli G, Becattini C, Kirschstein T.** Thrombolysis vs heparin in the treatment of pulmonary embolism: a clinical outcome-based meta-analysis. *Arch Intern Med* 2002;162:2537–2541.

The use of fibrinolytic agents in patients with PE provides a more rapid resolution of the pulmonary thrombus. The impact of these surrogate endpoints on clinical outcomes is unclear. Individual trials investigating the treatment of PE are often underpowered to find significant differences in outcomes such as death and bleeding. This meta-analysis was conducted to analyze the clinical risks and benefits of fibrinolytic therapy compared to anticoagulation alone. A total of 9 randomized trials were included with 461 patients diagnosed with PE. The fibrinolytic arm was heterogeneous and included 241 patients receiving streptokinase, urokinase, and t-PA using varying doses and administration techniques. A total of 220 UFH patients were used as the comparator arm. The primary outcome was any clinical outcome including death, recurrence of PE, and major bleeding event defined as intracranial hemorrhage or a hemoglobin drop of 2 g/dL. Any adverse clinical outcome occurred in 23.2% of fibrinolytic patients compared to 25.9% of UFH patients ( $p=0.51$ ). No significant difference between fibrinolytic and UFH therapy was observed with any single clinical adverse outcome including death (4.6% vs. 7.7%;  $p=0.51$ ), recurrence of PE (6.6% vs. 10.9%,  $p=NS$ ), or major bleeding (12.9% vs. 8.6%;  $p=NS$ ). Fatal bleeding occurred in 5 patients receiving fibrinolytic therapy, while no fatal bleeding events were recorded in the UFH arm. When the efficacy outcomes are combined (death and reoccurrence), a significant reduction was observed with fibrinolytic therapy (10.4%) compared to UFH therapy (17.3%;  $p=0.03$ ). These data suggest that fibrinolytic therapy be reserved for those patients at high risk for death and recurrence, such as those patients with echocardiographic evidence of right ventricular dysfunction, and low risk for bleeding. This meta-analysis supports the guideline recommendation to consider fibrinolytic therapy based on PE severity, prognosis, and risk for bleeding.

**Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W.** Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med*

2002;347:1143–1150.

The use of fibrinolytic agents in patients diagnosed with acute massive PE with hemodynamically unstable or cardiogenic shock is well established. Large randomized trials assessing the risks and benefits of fibrinolytic therapy in patients with hemodynamically stable PE are lacking. This trial is the largest randomized trial comparing UFH and 100 mg t-PA over two hours to UFH alone in patients with acute, yet hemodynamically stable PE. A total of 256 patients with PE and pulmonary hypertension or right ventricular failure but without arterial hypotension or shock were randomized to t-PA plus UFH ( $n=118$ ) or UFH alone ( $n=138$ ). The primary endpoint was in-hospital death or clinical deterioration requiring aggressive treatment after the study medication was terminated. Secondary endpoints were recurrent PE, major bleeding, and ischemic stroke. A significant difference in the primary endpoint was observed with t-PA plus UFH (11%) compared to UFH alone (24.6%;  $p=0.006$ ). The difference observed in the primary outcome was mainly driven by the need for aggressive treatment following study medications rather than death. No significant difference in any secondary endpoint was observed. These data suggest that fibrinolytic therapy be considered in patients with submassive PE manifested with right ventricular pressure overload or dysfunction. While the benefit of this therapy does not extend to survival, patients treated with fibrinolytic therapy may experience less clinical deterioration to hemodynamic or cardiogenic compromise.

**Dong B, Jirong Y, Wang Q, et al.** Thrombolytic treatment for pulmonary embolism. *Cochrane Database Syst Rev* 2006; 2;cD004437.

Trials investigating the benefits of fibrinolytic therapy in patients with PE are hampered by several weaknesses. Design flaws (multiple agents, doses, and administration protocols), various comparators (placebo, UFH, and surgery), small sample sizes, and inconsistent outcomes make interpretation difficult. This comprehensive analysis evaluated fibrinolytic therapy in the setting of acute PE. Trials comparing two different fibrinolytic agents or doses were not included. Eight randomized trials involving 679 patients were included in this analysis. The primary outcome of this review was all-cause death, PE recurrence, and major hemorrhage. No difference was observed with

all-cause mortality (OR 0.89, 95% CI 0.45 to 1.78) and recurrence of PE (OR 0.63, 95% CI 0.33 to 1.20). While no difference in major bleeding was seen, a trend toward more bleeding in the fibrinolytic arm was exposed (OR 1.61, 95% CI 0.91 to 2.86). Significant improvements in hemodynamic outcomes and perfusion lung scans were seen with fibrinolytic therapy. These data underscore the importance of including clinical outcomes rather than surrogate endpoints such as pulmonary arterial systolic pressure, angiogram improvements, and echocardiogram changes. This investigation also sheds light on the size of a randomized trial that would be needed to accurately assess the clinical endpoints important in the treatment of PE.

#### Role of Ambulation

**Partsch H, Blattler W.** Compression and walking versus bed rest in the treatment of proximal deep venous thrombosis with low molecular weight heparin. *J Vasc Surg* 2000;32:861–869.

Historically, bed rest was recommended following the diagnosis of acute DVT because of concern that ambulation would lead to clot dislodgement and possible PE. Although data continued to emerge demonstrating the efficacy of outpatient LMWH in the treatment of acute DVT, few trials addressed how many patients were ambulating or to what extent, and therefore the comparative effects of ambulation compared to immobilization was still a relevant clinical question. This was the first published comparison of acute VTE patients being randomized to ambulation compared to immobilization immediately after diagnosis.

Thirty patients were encouraged to walk as much as possible and fitted with either inelastic compression bandages (zinc plaster bandages to a mean pressure of 50 mm Hg on the lower leg accompanied by a stretch bandage to the groin, n=15) or thigh length compression stockings (n=15), while another group of 15 was confined to strict bed rest for 9 days, except to use the toilet. All patients were treated with LMWH transitioned to oral anticoagulation at a goal INR of 2.0–3.0. Both ambulatory groups showed significant improvement compared to the immobile group in all the primary endpoints of pain (measured 2 ways), ankle and calf circumference, and clinical score. Ventilation/perfusion scans and compression ultrasounds were performed on days 0 and 9.

New PE was numerically more common in the ambulating groups (3/30 vs. 1/15), whereas extension of femoral vein clots (5/22 vs. 4/10) was less common. Neither comparison was significantly different.

This study, and others by these authors, helped to further the idea that ambulation may be safe following a DVT diagnosis. They also demonstrated that ambulation, especially in conjunction with aggressive compression and pharmacologic therapy may be more beneficial than immobility in reducing the pain and edema associated with DVT.

**Aschwanden M, Labs KH, Engel H, et al.** Acute deep vein thrombosis: early mobilization does not increase the frequency of pulmonary embolism. *Thromb Haemost* 2001;85:42–46.

This trial randomized 129 acute proximal DVT patients from one Swiss center to four days of strict immobilization or ambulation for at least 4 hours per day under the supervision of a study nurse. Of interest, the most common reason for study exclusion was mobilization being deemed not possible for many of the screened patients. As in the previous trial, all patients were hospitalized and treated with dalteparin transitioned to oral anticoagulation at a goal INR of 2.0–3.0 and only mobilized patients were provided with continuous compression bandages. It also examined pain and leg circumference, but new PE was the primary endpoint.

Over half the patients had a PE when the baseline V/Q scan was performed. New asymptomatic PE was detected in 16 patients at the repeat scan conducted on day four, 10 in the ambulation group and six in the immobile group (14.4% vs. 10%; p=NS). It was noted that the ambulatory group collectively had more risk factors (malignancy, estrogen, etc.) for VTE prior to randomization, but none of these individual differences was significant. A logistic regression analysis tested many possible determinants, but identified PE at baseline as the only factor predicting an enhanced likelihood of a new PE at day four.

Leg pain was assessed with a visual analogue scale at baseline and day four and decreased significantly in both groups upon retesting. The mean improvement in pain scores was not significantly different but was numerically greater in the immobile group. Leg circumference at the level of the thigh and lower leg also decreased in both groups by day four, but the between group comparisons were not

different. These investigators conclude that immobilization is not superior to early mobilization, but were unable to prove equivalence, as that would require a much larger number of patients than is feasible in a single center trial.

**Junger M, Diehm C, Storiko H, et al.** Mobilization versus immobilization in the treatment of acute proximal deep venous thrombosis: a prospective, randomized, open, multicentre trial. *Curr Med Res Opin* 2006; 22:593–602.

This study differed from its predecessors in that it was multicenter (eight centers in Germany) and all patients, not just the ambulatory patients, were given compression therapy throughout the evaluation period. The duration of ambulation compared to bed rest was at least 5 days, and the primary endpoint differed in that it was a combination of clot related and other factors.

Like the other trials, the 103 patients with proximal DVT were hospitalized and treated with the LMWH dalteparin before transitioning to oral anticoagulation at a goal INR of 2.0–3.0 and ambulation began on the day of VTE diagnosis. The immobility group had a numerically greater incidence of the composite primary outcome (28.0% vs. 13.5%,  $p=0.088$ ), with progression of the index thrombus at repeat ultrasound at day 10–12 most common. The immobility group also had more new PE's (8 vs. 3;  $p=NS$ ) including those deemed clinically relevant or symptomatic (5 vs. 1;  $p=NS$ ). Ten of the 11 new PE's occurred in patients with known PE at baseline. Leg pain was reduced significantly in both the immobile as well as ambulatory groups, keeping in mind that both received compression therapy in this study.

The investigators calculated that 402 patients would be required for an adequately powered trial with proof of equivalence, but enrollment was stopped prematurely because many study centers were unwilling to undertake the possibility of 5 days of strict bed rest. This trial was limited by slow patient recruitment and challenges in carrying out randomization schemes and follow-up tests, but the results did add more support to the possibility that ambulation (plus compression) is as safe as bed rest following DVT diagnosis. The inability to recruit for a fully powered study also set the stage for future pooled analyses of this topic.

**Trujillo-Santos J, Perea-Milla E, Jimenez-Puente A, et al.** Bed rest or ambulation in the initial treatment of patients with acute deep vein thrombosis or pulmonary embolism: findings from the RIETE registry. *Chest* 2005;127:1631–1636.

Data gathered from patients with acute VTE enrolled in the RIETE (Registro Informatizado de la Enfermedad ThromboEmbolica) registry as of November 2003 were retrospectively analyzed to see if ambulation status impacted the risk of new PE within the first 15 days of treatment. The registry prospectively enrolled consecutive patients with symptomatic, objectively documented VTE at 88 participating hospitals in Spain. Patients consented to participate in the registry whereby their baseline and treatment data were recorded on a computerized case report form. It appears that follow-up was dependent upon patients returning for care at these hospitals. The RIETE registry has been used many times as a data source to explore different anticoagulation issues.

After the application of exclusion criteria, 2650 patients formed the analysis cohort (2038 with DVT and 612 with PE). Over 50% of these patients were prescribed bed rest. Overall a new PE developed in a slightly greater number of patients prescribed bed rest (0.62%) compared to those that were not (0.49%;  $p=NS$ ). Five of these 15 new PE's were fatal. These results have to be interpreted with a few important caveats. Patients prescribed bed rest after an index DVT had a higher rate of cancer and recent surgery, as well as greater antiplatelet and steroid use than those not prescribed bed rest. This raises the possibility that the group not prescribed bed rest represented a healthier population. The group with initial PE was not as imbalanced, but five patients did die from the initial PE and all happened to be prescribed bed rest. A univariate analysis determined that immobility was not associated with an increased risk of new PE, but risk higher with cancer and age greater than 65.

This study demonstrates that confirmed, symptomatic PE's within the first two weeks of therapy are serious, but occur infrequently and may not be influenced by a patient's ambulation status. It provided different pieces of information on this subject, with their associated limitations, than what were provided by previous randomized, clinical trials.

Aissaoui N, Martins E, Mouly S, Weber S, Meune C. A meta-analysis of bed rest versus early ambulation in the management of pulmonary embolism, deep vein thrombosis, or both. (Epub ahead of print) *Int J Cardiol* 2008 Aug 6.

This topic was ideal for a meta-analysis because published studies had tended to be smaller and few statistically significant endpoints had been reached. Also the prospect of a future randomized trial proving superiority or equivalence of ambulation seems remote given the past difficulties with patient recruitment and current practice trends. After searching multiple databases and independently reviewing individual studies using prespecified selection criteria, the investigators pared down their original 363 references to 5 prospective studies. This included the 3 trials and 1 prospective registry previously reviewed here. A total of 3048 patients are included, although only 398 are from the four randomized studies.

The investigators provide figures depicting the RR, relative weighting, and 95% CI for each of the 5 studies, and the composite result, for all three clinical endpoints evaluated. Early ambulation was not associated with a significant risk for a new PE (RR 1.03, 95% CI 0.65 to 1.63) and trended towards a benefit in terms of the combination endpoints of new PE and new or progressive DVT (RR 0.79, 95% CI 0.55 to 1.14) and new PE and overall mortality (RR 0.79, 95% CI 0.40 to 1.56). To the investigators' credit, although statistical heterogeneity was detected only in the last endpoint, they provide a repeat analysis of the data, excluding the registry results, and including only the four randomized trials. The respective RR from the studies for the 3 endpoints outlined above were 1.10, 0.87, and 1.12 respectively.

This meta-analysis was helpful in explicitly evaluating the data points gathered from solid, but somewhat limited individual trials, each with unique methodologic features and results. The combined results suggest that ambulation may be helpful in resolution of pain and swelling and is probably not associated with an increased risk of new, symptomatic PE. This sentiment is reflected in the ACCP 2008 summary where early ambulation over initial bed rest with acute DVT is given a Grade 1A recommendation.

## Long-Term Management

### Warfarin dosing

Hull R, Hirsh J, Jay R, et al. Different intensities of oral anticoagulant therapy in the treatment of proximal-vein thrombosis. *N Engl J Med* 1982;307:1676–1681.

This was an early study that showed that the degree of intensity of oral anticoagulation is linked to bleeding risk and that different thromboplastin reagents could lead to very different patient care management of anticoagulation. These are the problems that eventually led to the adoption of the INR. In this open-label study, consecutive patients diagnosed with proximal DVT were treated with 14 days of continuous IV UFH, and on day 7, were randomized to be started on warfarin monitored either by the Simplastin reagent (which led to more intensive therapy), or the Manchester comparative reagent (which led to less intense therapy) from the National Reference Laboratory in Manchester, England. Importantly, even though each patient was randomized into having the warfarin titrated with one reagent or the other two goals that were standard at the time, all blood samples were run with both reagents. The patients were treated with warfarin for 12 weeks and followed for at least an additional 12 weeks (average, 7 months) after warfarin was stopped. A total of 49 patients were randomized into the high-intensity warfarin group and 47 patients were randomized to the low-intensity warfarin group and the demographics were well matched. The endpoints were documented VTE recurrence or bleeding occurrences. There were no differences in VTE recurrence rates between groups, but more patients in the high-intensity warfarin therapy had bleeding complications (22% vs. 4%;  $p=0.015$ ), primarily due to minor bleeding. The low-intensity group did receive on average a lower dose of warfarin compared to the higher-intensity group. Plots of the test results show that many of the patients who bled in the high-intensity group had high prothrombin times with the Manchester comparator, but were not as often elevated with the Simplastin thromboplastin.

Harrison L, Johnston M, Massicotte MP, et al. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997;126:133–136.

This study questioned the notion of "loading" warfarin with a large dose (i.e. 10 mg) compared

to starting with a common maintenance dose (i.e. 5 mg). This was an open-label randomized study in which all patients in a large, tertiary care teaching hospital requiring warfarin with a goal INR range of 2.0-3.0 were asked to participate. Patients (n=49) were randomized to start with either 5 mg or 10 mg of warfarin with subsequent dosing by two nomograms. The INR and levels of clotting factors II, VII, IX, X and protein C were measured for 5 days. Outcomes included time required to reach an INR of 2.0 – 3.0, proportion of INR values greater than 3.0, time course to reduction of factor II, VII, IX and X, and time course to reduction of protein C. The demographics are not reported, but the study states the groups were not different at baseline in regard to age, weight, frequency of acute thromboembolism, cancer, or surgical status. At 36 hours (after two doses of warfarin), 44% vs. 8% of 10 mg and 5 mg patient's INRs were greater than 2, respectively (p=0.005). At 60 hours (after 3 doses of warfarin), 36% vs. 0% of 10 mg and 5 mg patient's INRs were greater than 3, respectively (p=0.002). Also, 4 patients in the 10 mg group and 1 patient in the 5 mg group needed vitamin K, but no patients had bleeding complications. Factors II and X, the critical factors in achieving an anticoagulated status, declined at the same rate between the two groups, but factors VII and protein C decreased more rapidly in the 10 mg group and were statistically lower at 36 and 60 hours. This study was important in demonstrating that while a 10 mg starting dose may help a patient obtain a therapeutic INR more quickly, it can lead to more overanticoagulation and a more profound initial depletion of protein C creating a potential hypercoagulable state.

**Crowther MA, Ginsberg JS, Kearon C, et al.** A randomized trial comparing 5 mg and 10 mg warfarin loading doses. *Arch Intern Med* 1999;159:46–48.

This was a follow-up study to the Harrison and colleagues trial mentioned above. The primary objective of the study was to compare the proportion of patients who reached a stable INR in 5 days, which was defined as two consecutive INRs in range without any INRs exceeding 3 by using the same nomograms studied in the previously discussed trial. The trial was randomized, but not blinded and enrolled patients (n=53) in a thromboembolism hospital unit. All patients needing to be anticoagulated with warfarin to a target INR of 2.0–3.0 were

asked to participate. Patients were followed for a total of 5 days. In the 10 mg group, 24% of patients reached primary endpoint compared to 66% of patients in the 5 mg group (p<0.003). From days 2–5, the proportion of in range INRs for the 5 mg group was numerically higher each day. This trial moved many clinicians away from aggressive loading of warfarin and made the practice of initiating warfarin with the estimated maintenance dose much more common.

**Kovacs MJ, Rodger M, Anderson DR, et al.** Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism: a randomized, double-blind, controlled trial. *Ann Intern Med* 2003;138:714–719.

This study challenged the Harrison and Crowther studies as the investigators felt that starting warfarin with a 5 mg dose led to a lag in obtaining a therapeutic INR. In this trial, 201 outpatients being treated for VTE were randomized, in a double-blind fashion, to having warfarin initiated with a new, 10 mg nomogram, or the 5 mg nomogram used in the Harrison and Crowther studies. The primary objective was the time in days to a therapeutic INR greater than 1.9. Secondary endpoints included proportion of INRs in range on day 5, recurrent VTE rates at 90 days, major bleeding within 28 days, number of INRs greater than 5, number of INRs in 28 days, and 90-day survival. Patients were all treated concurrently with dalteparin or tinzaparin for at least 5 days. The mean time to reach a therapeutic INR in the 10 mg group was 4.2 days versus 5.6 days in 5 mg group (p<0.001). Additionally, 86% patients in the 10 mg group were therapeutic by day 5, compared to 45% in the 5 mg group (p<0.001). No differences were seen in the rates of elevated INRs, deaths, bleeding events, or recurrent VTE, however the rate of recurrent VTE was numerically higher in the 10 mg group.

This study conclusively showed that a 10 mg starting dose will obtain a therapeutic INR more quickly than and 5 mg starting dose in outpatients being treated for VTE. However, the results and the nomogram are not applicable to inpatients who may have many more comorbidities or patients with baseline INRs greater than 1.4. The study was underpowered to assess the treatment effects on bleeding and VTE. An important point in analysis of this study is that correct interpretation of initial INR

response is the most important factor as opposed to initial dose selection.

**Linkins LA, Choi PT, Douketis JD.** Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med* 2003;139:893–900.

This study was a meta-analysis of 29 randomized clinical trials and 4 cohort studies (n=10,757). The purpose of the analysis was to determine a reliable estimate regarding the clinical impact of bleeding due to anticoagulants in patients being treated for VTE. Randomized, controlled trials, and prospective cohort studies were included in which the presence of VTE was confirmed by objective means, patients were treated with a vitamin K antagonist for at least 3 months titrated to an INR of 2.0-3.0, and bleeding events were classified as major, minor, or fatal. Studies were excluded if they enrolled less than 100 patients, were published before adoption of the INR standard, or if patients received antiplatelet therapy as part of the trial. For the overall study, the major bleeding rate was 7.22 per 100 patient-years and the fatal bleeding rate was 1.31 per 100 patient-years. After the first 3 treatment months, bleeding rates were 2.74 and 0.63 per 100 patient-years, respectively. The case fatality rate due to major bleeding was similar for the first 3 months and for the time period after the first 3 months.

This study demonstrated that long-term treatment with vitamin K antagonist for VTE is not without risk despite the clear efficacy shown in other trials. Further, it showed that VTE patients started on vitamin K antagonists have more bleeding episodes in the first 3 months of therapy. It is therefore recommended that the risk of bleeding must be weighed against the risk of thrombosis when considering if VTE patients should be treated long-term with vitamin K antagonists. Conditions or medications that increase the bleeding risk could negate the benefit of long-term vitamin K antagonist therapy in many VTE patients. Further, measures that minimize the risk of anticoagulant bleeding, such as anticoagulation clinics, are important, particularly in the first 3 months of therapy.

#### Pharmacogenomics

**Meckley LM, Wittkowsky AK, Rieder MJ, et al.** An analysis of the relative effects of VKORC1 and CYP2C9 variants on anticoagulation related

outcomes in warfarin-treated patients. *Thromb Haemost.* 2008;100:229–39.

During the 1990s and early 2000s, a number of investigations established that genetic variants of CYP2C9, the enzyme primarily responsible for the metabolism of S-warfarin, are associated with decreased warfarin clearance, longer warfarin elimination half life, and lower warfarin dose requirements. Several studies also found that patients with these variants have a higher bleeding risk when anticoagulated with warfarin, more above range INRs, and take a longer time to reach a stable warfarin dose. Additional research confirmed that genetic variants of VKORC1, the enzyme that codes for warfarin's site of action, are associated with warfarin dose requirements to a larger degree than that of CYP2C9, and across a greater extent of the general population.

This study was conducted to assess the relative influence of CYP2C9 and VKORC1 genotype on anticoagulation outcomes. Patients were recruited from a large university anticoagulation clinic system in which both clinical and genetic information were collected. Patient with CYP2C9 variant alleles (\*2 and \*3) took longer to achieve a stable warfarin dose, spent a higher proportion of time with an elevated INR in the first month, and had a higher chance of reaching an INR greater than 5 compared to patients with the wildtype allele. This finding is likely due to the longer elimination half-life of warfarin that these alleles confer which results in a longer time to reach steady state drug levels. The only effect of VKORC1 was that patients who were homozygous for low dose haplotypes (1173C/T allele or T/T haploptype; 1639 G/A allele or A/A haploptype) had a higher risk of having an INR over 5 compared to heterozygotes. An algorithm derived from clinical and genetic information could explain 50% of the warfarin maintenance dose. This study confirmed that CYP2C9 genotype has a more substantial effect on clinical outcomes than does VKORC1 status, despite the greater effect of VKORC1 on warfarin dose requirements.

**Klein TE, Altman RB, Eriksson N, et al, for the International Warfarin Pharmacogenetics Consortium.** Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009;360:753-64.

A number of investigations have focused on the use of genetic information as well as clinical information to predict warfarin dose requirements. Among them is this trial, which

used the largest cohort of patients (n=5052) and incorporated CYP2C9 and VKORC1 information in the development of a warfarin dosing algorithm. It was retrospectively conducted and included a diverse group of patients from 21 research centers in 9 countries on 4 continents who were on warfarin with a goal INR range of 2–3. The trial included 4043 patients in a derivation cohort and another 1009 patients in a validation cohort. The primary outcome of the trial was to compare the estimated maintenance dose from the derived algorithm to the actual maintenance dose requirement in the validation cohort. An algorithm based only on clinical factors was developed and its performance was compared to that of the algorithm developed using both clinical and genetic factors.

The clinical/genetic algorithm accurately predicted 43% of warfarin dose variability in the validation cohort compared to 26% in the clinical algorithm. The clinical/genetic algorithm worked well for Caucasian, Asian, and African-American patients, and was more effective in identifying patients who needed less than 21 mg of warfarin/week (49.4% vs. 33.3%;  $p<0.001$ ) or more than 49 mg of warfarin/week (24.8% vs. 7.2%;  $p<0.001$ ) than the clinical algorithm. The clinical/genetic algorithm did not show a benefit in patients stabilized on warfarin doses of 21 mg to 49 mg of warfarin/week. Importantly, no clinical outcomes were evaluated. The models derived in this study are available on [www.warfarindosing.org](http://www.warfarindosing.org) and as a Microsoft Excel workbook at the website where the article is published.

**Anderson JL, Horne BD, Stevens SM, et al, for the Couma-Gen Investigators.** Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation*. 2007;116:2563-70.

As described above, genetic status of VKORC1 influences warfarin dose requirements, and CYP2C9 genotype influences both warfarin dose requirements and bleeding complications. As well, genetic-based algorithms can be helpful in predicting warfarin dose. However, whether predicting warfarin dose using an algorithm has any influence on clinical outcomes has not been thoroughly investigated. This is the only randomized, prospective study that has investigated whether dosing warfarin based on both CYP2C9 and VKORC1 genotype improves patient outcomes. In this trial, patients (n=206) were assigned to receive warfarin dosed using the

Kovacs 10 mg warfarin nomogram (see above) or warfarin dosed with a genetic-based algorithm. The INR was measured at least seven times over the three month study period in both groups and all dosing adjustments were performed by an unblinded clinical pharmacist who was part of the anticoagulation service. The trial found that genetic-guided doses were more accurate than algorithm predictions ( $p<0.001$ ), which resulted in fewer dosing changes and less INR monitoring. However, the primary outcome of percent out-of-range INRs was similar in both groups at the end of the study. This trial failed to show a conclusive benefit of genetic based warfarin dosing, although it suggested that patients on the extremes of warfarin dosing are those who are most likely to benefit from genetic-based dosing. It is important to note that the close monitoring of patients in both groups by an anticoagulation pharmacist may have influenced the results.

**Li C, Schwartz UI, Ritchie MD, Roden DM, Stein CM, Kurnik D.** Relative contribution of CYP2C9 and VKORC1 genotypes and early INR response to the prediction of warfarin sensitivity during initiation to therapy. *Blood* 2009; 113:3925-30.

Genetic –based dosing algorithms are useful for predicting warfarin dosing requirements, but have not yet been found to influence clinical outcomes, including bleeding complications. Given the costs associated with genetic testing, the best and least expensive predictor of warfarin dosing requirement may simply be INR response to initial warfarin doses. These investigators sought to determine whether genotyping provides information about warfarin sensitivity beyond that provided by the early INR response. In a cohort of 214 patients in whom CYP2C9 genotype and VKORC1 haplotype were determined, warfarin was initiated at a dose of 5 mg once daily and adjusted according to INR values determined on day 4. Genetic status was not used to adjust or predict dosing but was evaluated in terms of association with early measures of warfarin sensitivity, including time to INR above the lower limit of the therapeutic range, time to INR > 4, and the first stable warfarin dose. Overall, early INR values were highly associated with each of these endpoints, and were more informative than CYP2C9 and VKORC1 genotypes. After adjustment for early INR values, the first stable warfarin dose was the only outcome to which genotypes made a

meaningful contribution, but lost their predictive influence after adjustment for INR values obtained on days 7-9. The predictive value of CYP2C9 and VKORC1 genotypes are reflected in INR results and contribute little additional information than what is already obtained by evaluating INR response and cumulative warfarin dose during initiation therapy.

#### Warfarin duration

##### *Short Compared to Standard Duration*

**Schulman S, Rhedin AS, Lindmarker P, et al.** A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. *N Engl J Med* 1995;332:1661-1665.

Prior to 1995 when this study was published, the optimal duration of anticoagulation after a first episode of VTE was not clearly defined. Several poorly designed trials had suggested that it might be possible to reduce the standard duration of 3-6 months, but results were inconclusive. The DURAC study was designed to determine whether shortening the duration of anticoagulation could successfully prevent recurrent thrombosis.

The trial randomized 897 patients with a first episode of VTE (61.6% with a permanent or unknown risk factor) to either 6 weeks or 6 months of oral anticoagulation after receiving initial treatment with UFH or LMWH. After two years of follow-up, 18.1% of patients treated for 6 weeks and 9.5% of patient treated for 6 months had recurrent VTE (OR 2.1, 95% CI 1.4 to 3.1;  $p < 0.001$ ). Among patients treated for 6 weeks, a dramatic increase in the rate of recurrence immediately after discontinuation of anticoagulation was observed, which stabilized after 6 months and was then similar, although higher, than in those treated for 6 months. There were no differences in mortality (5.0% vs. 3.7%;  $p = 0.46$ ) or major bleeding (0.2% vs. 1.1%;  $p = 0.23$ ) between the two groups. Of note, patients with transient risk factors for thrombosis (surgery, trauma, travel, immobilization, pregnancy) appeared to have a lower rate of recurrence than those with permanent risk factors (8.6% if treated for 6 weeks vs. 4.8% if treated for 6 months).

This trial confirmed the value of a standard duration of anticoagulation for patients with a first episode of VTE. It set the stage for subsequent evaluations of 3 months compared to

6 months in patients with a first episode of VTE and 1 month compared to 3 months in patients with transient risk factors for thrombosis. It also pointed out the risk of recurrence when anticoagulation is discontinued and led to a number of subsequent investigations of that phenomenon.

**Kearon C, Ginsberg JS, Anderson DR, et al.** Comparison of 1 month with 3 months of anticoagulation for a first episode of venous thromboembolism associated with a transient risk factor. *J Thromb Haemost* 2004;2:743-749.

The DURAC trial described above suggested that patients with transient risk factors for thrombosis might be managed successfully with a short duration of anticoagulation. The SOFAST investigators enrolled 165 patients who had developed a first episode of VTE associated with immobilization from casting, bedrest from hospital admission, or surgery. Patients with known thrombophilias were excluded. Patients were treated initially with UFH or LMWH and were randomized to continue warfarin for 1 month or 3 months, and were followed for 11 months. The trial was stopped early due to slow accrual.

At 11 months, VTE had recurred in 6% of patients treated for 1 month, and 3.7% of patients treated for 3 months [hazard ratio (HR) 1.6, 95% CI 0.4 to 6.7]. Annualized recurrence rates were 6.8%/patient -year and 3.2%/ patient -year, a difference of 3.6%/ patient -year in favor of the longer duration of therapy (95% CI -3.8 to 11.0). There were no major bleeding events in either group. This trial does not support reducing the duration of anticoagulation to 1 month, even in patients with transient risk factors for whom the overall risk of recurrence is lower than that of patients with persistent risk factors.

**Schulman S, Lindmarker P, Holmstrom M, et al.** Postthrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. *J Thromb Haemost* 2006;4:734-742.

The original DURAC trial described above followed patients for 2 years. Of the 897 patient randomized, 545 were able to be followed for a total of 10 years. The results of that follow-up provided substantive information about the long-term consequences of VTE. At 10 years, signs of PTS were present in 56.3% of evaluated patients and 6% had severe symptoms, with no statistical

difference based on original duration of anticoagulant therapy (6 weeks vs. 6 months). Recurrent thrombosis had occurred in 29.1% of patients, again with no statistical difference based on original duration of therapy by 10 years, although it had been lower from years 1-6 in the patients treated for 6 months. Overall mortality was 28.5%, and was also no different in patients treated for 6 weeks or 6 months

The authors make the striking statement that “the diagnosis of a first event of VTE is followed by a decade with increased morbidity and mortality”. While a longer duration of initial anticoagulation appears to offer advantages during the first 6 years after the event, these differences are not sustained at 10 years. These results should be compared to those of the WODIT trial, described below, that suggest that in patients with idiopathic thrombosis, the clinical benefits of extended anticoagulation are not sustained immediately after anticoagulation is discontinued.

#### *Long-term Prevention in Unprovoked or Recurrent VTE*

**Schulman S, Granqvist S, Holmstrom M, et al.** The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *N Engl J Med* 1997;336:393–398.

Prior to this trial, it had been assumed that patients who had experienced recurrent VTE were at higher risk of additional recurrence but the optimal duration of anticoagulation was unknown. In this trial known as DURAC II, 227 patients presenting with a second episode of VTE were randomized to 6 months or indefinite oral anticoagulation after initial treatment with UFH or LMWH. The mean duration of treatment was 7.7 months for the traditional duration group, and 42.7 months for the indefinite treatment group, with a mean follow-up period of 4 years.

There was a significantly lower risk of recurrence in patients treated indefinitely compared to those treated for 6 months (2.6% vs. 20.7%; RR 8%, 95% CI 2.5 to 25.9;  $p < 0.001$ ). Noting the small sample size, there was no statistically significant difference in mortality (8.6% vs. 14.4%; RR 1.7, 95% CI 0.8 to 3.5;  $p = 0.21$ ) and only a trend toward more major bleeding complications in the patients treated indefinitely (8.6% vs. 2.7%; RR 0.3, 95% CI 0.1 to 1.1;  $p = 0.084$ ). As was seen in DURAC, there was a progressive increase in recurrent events after discontinuation of warfarin in the patients

treated for 6 months, with no recurrent thrombosis during active anticoagulation in either group. As the first study to explore long-term oral anticoagulation, the dramatic results of this trial formed the basis for a number of other investigations of indefinite treatment in idiopathic thrombosis.

**Keaton C, Gent M, Hirsh J, et al.** A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999;340:901–907.

Several of the clinical trials described above suggested that the risk of recurrent VTE is higher in patients with idiopathic thrombosis and in thrombosis associated with persistent risk factors. To determine whether a longer duration of therapy might be valuable, this trial randomized 162 patients with idiopathic thrombosis who had been treated with warfarin for 3 months to either continue oral anticoagulation indefinitely or to continue treatment with placebo. Recruitment was terminated early in response to the results of the interim analysis. Thus, the mean duration of follow-up was only 10 months (12 months for patients taking warfarin and 9 months for those randomized to placebo).

Despite early termination, the results were dramatic, as they were in DURAC II. The rate of recurrent VTE was 1.3% per patient -year in patient assigned to warfarin compared to 27.4% per patient -year in those randomized to placebo (HR 0.05, 95% CI 0.01 to 0.37;  $p < 0.001$ ). Three patients assigned to warfarin experienced a major bleeding complication compared to none in the placebo group ( $p = 0.09$ ). Thus, patients with idiopathic thrombosis have a very high rate of recurrent thrombosis when warfarin is discontinued after 3 months, and a longer duration of anticoagulation lowered the VTE recurrence rate substantially.

**Agnelli G, Prandoni P, Santamaria MG, et al.** Three months versus one year of oral anticoagulant therapy for idiopathic deep vein thrombosis. *N Engl J Med* 2001;345:165–169.

This trial was designed to determine if the benefits of extending the treatment of oral anticoagulation to one year, as investigated in the trial above, are maintained even after that longer-term therapy is discontinued. In the WODIT trial, 267 patients with idiopathic VTE who had completed 3 months of oral anticoagulation were

randomized to discontinue oral anticoagulation or to continue for a full year of therapy. The patients were then followed for a minimum of 2 additional years.

At approximately 3 years (2 years after treatment discontinuation in patients treated for a year, and 2 years, 9 months after treatment discontinuation in patients treated for 3 months), there were no differences in the rate of recurrent VTE in either group (15.7% for 1 year of treatment vs. 15.8% for 3 months of treatment). The mean time to recurrence was 11.2 months in patients randomized to discontinue therapy at 3 months compared to 16 months in those who continued therapy for a year. Thus, discontinuation of anticoagulant therapy appears to be associated with an increased risk of recurrent VTE in patients with a history of idiopathic VTE. Indefinite therapy may be the most effective strategy to prevent recurrence, but increases the risk of bleeding, inconvenience, and cost.

#### *Markers to Inform Duration of Treatment*

**Palareti G, Cosmi B, Legnani C, et al, for the PROLONG Investigators.** D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med.* 2006;355:1780–9. Erratum in: *N Engl J Med.* 2006;355:2797.

The various trials that have investigated long-term treatment of unprovoked thrombosis have concluded that while longer treatment is more effective in preventing VTE, it simply delays recurrence until after anticoagulation is stopped. Life-long anticoagulation may be the most successful approach to prevent recurrence, but it is associated with an increased risk of hemorrhage as well as inconveniences and cost. Therefore, it may be helpful to identify patients with a low risk of recurrence for whom chronic oral anticoagulation may offer limited benefit. One such potential marker is d-dimer, a fibrin degradation product.

This trial enrolled patients who had initially presented with symptomatic unprovoked DVT, PE or both, who had completed at least 3 months of oral anticoagulation with a vitamin K antagonist, and who had subsequently tested negative for thrombophilias. Of the 608 patients enrolled, 16% had been anticoagulated for less than 6 months, 51% for 7-12 months, and 33% for greater than 12 months. One month after discontinuation of oral anticoagulation, the patients were tested for d-dimer using a

qualitative method. Patients with a normal d-dimer did not resume anticoagulation. Patients with an elevated d-dimer level were randomized to either remain off anticoagulation, or to resume anticoagulation to an INR of 2.0-3.0 for an additional 18 months.

At the time of d-dimer testing, 63.3% tested negative. Over the next 18 months, VTE recurred at a rate of 4.4% per patient -year in these patients. The other 36.7% of patients had a positive d-dimer. Of those, 53.8% remained off anticoagulation and had a VTE recurrence rate of 10.9% per patient -year. The remaining 46.2% of patients with a positive d-dimer resumed anticoagulation, and had a rate of VTE recurrence plus major bleeding of 2.0% per patient -year.

Statistical analysis confirmed a higher rate of VTE recurrence in patients with a positive d-dimer who did not continue anticoagulation compared with continued anticoagulation (HR 4.26, 95% CI 1.23 to 14.6;  $p=0.02$ ); and patients with a normal d-dimer (HR 2.27, 95% CI 1.15 to 4.46;  $p=0.02$ ). This study suggests that D-dimer may play a role in identifying patients with idiopathic VTE in whom the risk of VTE recurrence is low and may not require long-term anticoagulation.

**Verhovsek M, Douketis JD, Shrivastave S, et al.** Systematic Review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. *Ann Intern Med* 2008;149:481–490.

The PROLONG study described above set the stage for further investigation of the role of d-dimer testing to determine duration of anticoagulation in patients with unprovoked VTE. This meta-analysis combined the results of 7 different high quality trials that investigated d-dimer testing, performed 3 weeks to 2 months after discontinuation of anticoagulation in a total of 1888 patients with unprovoked VTE who had been treated with anticoagulation for a minimum of 3 months. Of these patients, 48% had a positive d-dimer after discontinuation of anticoagulation, and a subsequent VTE recurrence rate of 18.2%. Comparatively, the rate of VTE recurrence in patients with a negative d-dimer after stopping anticoagulation was 7.5%. The annualized risks in each group were 8.9%/patient -year compared to 3.5%/patient -year, respectively.

This low rate of recurrent VTE in negative d-dimer patients is similar to the recurrence rate

observed in patients with provoked VTE associated with transient risk factors in whom anticoagulation is recommended for a total of 3 months. A negative d-dimer can be used in conjunction with clinical assessment and risk/benefit analysis to identify patients with unprovoked VTE who may be at low risk for recurrence and in whom the duration of anticoagulation may be shortened.

**Siragusa S, Malato A, Anastasio R, et al.** Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. *Blood*. 2008;112:511–5.

The DACUS trial tested the hypothesis that residual vein thrombosis may also be used as a marker to guide duration of therapy. Patients with a first documented idiopathic or provoked proximal DVT who had completed 3 months of oral anticoagulation were examined for residual vein thrombosis (RVT) (was defined as thrombus occupying more than 40% of the vein diameter) by compression ultrasonography.

In total, 78 patients were negative for RVT and did not continue oral anticoagulation (which included 36% provoked and 65% idiopathic thrombosis). The other 180 patients were positive for RVT and were randomized to either not continue oral anticoagulation (which included 78% idiopathic and 20% provoked thrombosis), or to continue anticoagulation for an additional 9 months for a total treatment course of 1 year (with 75% idiopathic and 25% provoked thrombosis). All patients were followed for at least 1 year after discontinuation of oral anticoagulation.

In the year of follow-up after discontinuation of warfarin, patients without RVT had a VTE recurrence rate of only 0.63% per patient -year. Comparatively, the recurrence rate was 15.2% per patient-year in the patients with RVT in whom anticoagulation was discontinued at 3 months. In the patients with RVT who continued oral anticoagulation for a year, the recurrence rate in the year after discontinuation of warfarin was 10.1% per patient -year. The differences in recurrence between patients with and without RVT were statistically significant. Thus, the absence of RVT was able to identify a group of patients, regardless of whether VTE was idiopathic or provoked, at very low-risk for recurrent thrombosis in whom discontinuation of oral anticoagulation at 3 months was a safe and

effective strategy.

**Prandoni P, Prins MH, Lensing AWA, et al.** Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep vein thrombosis. A randomized trial. *Ann Intern Med* 2009;150:577–85.

This trial was designed to further investigate the role of RVT as a marker to guide duration of anticoagulation, and to account for differences in risk of recurrence in patients with provoked compared to idiopathic thrombosis, which was not differentiated in the study described above. A total of 538 patients with a first episode of VTE who had completed 3 months of anticoagulation were randomized to either fixed-duration anticoagulation or flexible duration anticoagulation. The fixed duration was either 3 months of therapy for patients with provoked thrombosis, or 6 months of therapy for patients with unprovoked thrombosis. In the flexible-duration group, the length of therapy was tailored according to the presence of RVT. Anticoagulation was discontinued in patients without RVT, as they had completed a 3 month treatment course. In patients with RVT and provoked thrombosis, anticoagulation was continued and ultrasounds were repeated at 3 and 9 months. In patients with RVT and unprovoked thrombosis, anticoagulation was continued and ultrasounds were repeated at 3, 9, 15, and 21 months. Anticoagulation was discontinued whenever a repeat ultrasound showed that the vein had recanalized. All patients were followed for a total of 33 months.

Overall, VTE recurrence occurred in 17.2% of patients assigned to a fixed duration of anticoagulation, and in 11.9% of patients assigned to a duration guided by the presence of RVT (HR 0.64, 95% CI 0.39 to 0.99). For those patients with unprovoked VTE, the adjusted HR for the difference between fixed compared to flexible duration was 0.61 and for those with provoked VTE, it was 0.81 (p=NS). There were no differences in the incidence of major bleeding complications (p=0.68) between patients assigned to fixed duration compared to flexible duration anticoagulation. Thus, in comparison to using a fixed duration of anticoagulation for patients with a first episode of VTE, adjusting the duration of therapy based on the presence of RVT reduces the risk of recurrent thrombosis without increasing the risk of bleeding.

### Goal INR for Long-Term Treatment

**Ridker PM, Goldhaber SZ, Danielson E, et al.** Long-term, low-intensity warfarin therapy for prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;348:1425–1434.

In April 2003, the PREVENT trial stirred controversy in the medical and the lay press by suggesting that the goal INR for long-term oral anticoagulation in patients with a history of idiopathic VTE could be successfully reduced to 1.5–2.0. The trial enrolled 508 patients with unprovoked DVT or PE (28.9% with confirmed thrombophilia and 38.3% with a history of recurrent thrombosis) who had completed a median duration of 6.5 months of warfarin therapy to a goal INR of 2.0–3.0. The patients were randomized to continue warfarin at a reduced goal INR of 1.5–2.0, or to placebo, and were intended to be followed for an average of 4 years.

The study was terminated early after a mean duration of 2.1 years (maximum 4.3 years) when it became clear that the patients randomized to warfarin had a significantly lower rate of VTE recurrence than those randomized to placebo. The annualized recurrence rates were 7.2% per patient -year for placebo, and 2.6% per patient -year for low-intensity warfarin (HR 0.36, 95% CI 0.19 to 0.67;  $p < 0.001$ ). The differences in major bleeding (0.4% per patient-year vs. 0.9% per patient-year; HR 2.53, 95% CI 0.49 to 13.03) and mortality (1.6% per patient-year vs. 0.7% per patient-year; HR 0.7%, 95% CI 0.15 to 1.68;  $p = 0.26$ ) were not statistically significant. The investigators concluded that long-term low-intensity anticoagulation is an effective method to prevent recurrent VTE in comparison to placebo. For a short time, some clinicians turned to the results of this trial to justify a reduced goal INR in patients with idiopathic VTE requiring long-term oral anticoagulation.

**Kearon C, Ginsberg JS, Kovacs MJ, et al.** Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003;349:631–639.

Four months after the PREVENT trial was published, the ELATE trial appeared in print and brought some needed closure to the controversy surrounding the role of low-intensity oral anticoagulation for long-term prevention of

recurrent idiopathic VTE. The ELATE trial enrolled 738 patients with a history of unprovoked VTE (31.3% with known thrombophilias and 69% with a history of recurrent thrombosis) who had been treated with warfarin to a goal INR of 2.0–3.0 for a minimum of 3 months. Patients were randomized to continue warfarin to a standard goal INR of 2.0–3.0, or to low-intensity warfarin with a goal INR of 1.5–2.0. The mean duration of follow-up was 2.4 years.

Recurrent VTE occurred at a rate of 1.9% per patient -year in patients treated with low-intensity warfarin compared to 0.7% per patient -year in patients treated with standard-intensity warfarin (HR 2.8, 95% CI 1.1 to 7.0;  $p = 0.03$ ). There was no difference in major bleeding (1.1% per patient-year vs. 0.9% per patient-year; HR 1.2, 95% CI 0.4 to 3.0) in any bleeding (4.9% vs. 3.7%; HR 1.3, 95% CI 0.8 to 2.1) or in mortality (1.9% per patient-year vs. 0.9% per patient-year). However, standard-intensity warfarin therapy was associated with a higher rate of bleeding in patients 65 years of age, or older, and in patients with an increased number of pre-defined risk factors for bleeding.

While PREVENT showed that low-intensity warfarin was superior to placebo, the ELATE trial demonstrated that it was inferior to standard-intensity warfarin for prevention of recurrent idiopathic VTE, with no increase in bleeding risk. Standard-intensity oral anticoagulation is recommended for long-term prevention of recurrent idiopathic VTE.

### Prevention of the Postthrombotic Syndrome

**Brandjes DP, Buller HR, Heijboer H, et al.** Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet*. 1997;349(9054):759–62.

This paper reports one of the first prospective randomized studies to address the effects of graded compression stockings (GCS) on prevention of PTS in patients after a first DVT episode. A total of 194 patients with a first episode of objectively confirmed DVT were randomly assigned to no stockings ( $n = 96$ ) or made-to-measure GCS ( $n = 98$ ; knee high; 40 mmHg at the ankle, 36 mmHg at the lower calf, and 21 mmHg at the upper calf) for at least 2 years. Patients were assessed with a standard scoring system every 3 months for the first 2 years and every 6 months for at least 5 years.

The primary end point was the cumulative incidence of mild to moderate PTS. The findings of this study were remarkable in showing that although a high number of patients (60%) develop PTS within 2 years after a first DVT, a simple intervention of sized-to-fit compression stockings reduced the rate of PTS by approximately 50%. Specifically, mild to moderate PTS occurred in 20% of patients in the stocking group and 47% in the control group ( $p<0.001$ ), whereas severe PTS occurred in 11% of the GCS group and 23% in the control group ( $p<0.001$ ). Most cases of PTS occurred within 24 months of the initial acute DVT, which is in contrast to previous reports that found it may take 5 to 10 years for PTS to manifest. These findings are the basis of the current ACCP recommendations that GCS should be applied after a first DVT event for a minimum of 2 years.

**Ginsberg JS, Hirsh J, Julian J, et al.** Prevention and treatment of postphlebotic syndrome: results of a 3-part study. *Arch Intern Med* 2001;161:2105–2109.

This paper aimed to further elucidate the role of GCS in the prevention of PTS. The methodology involved a 3-part study in 202 patients evaluated at 1 year after a proximal DVT. Patients were enrolled in Study 1 if they did not have symptomatic PTS or venous valvular incompetence, Study 2 if they did not have symptomatic PTS but had venous valvular incompetence and Study 3 if they had symptomatic PTS. Study 1 patients ( $n=120$ ) were not treated and were evaluated for development of PTS every 6 months for a mean of 55 months. Study 2 patients ( $n=47$ ) were randomized to below knee GCS (20–30 mmHg) or a matched placebo stocking and followed for development of PTS every 6 months for a mean of 57 months. Study 3 patients ( $n=35$ ) were randomized to GCS (30–40 mmHg) or a matched placebo stocking and followed for every 3 months. The primary end point was treatment failure, which was defined as the development of PTS in study 1 and 2 and continued or worsening symptoms based on a global rating questionnaire in study 3. In study 1, 5% of patients were considered treatment failures which was similar to placebo treated study 2 patients ( $p=0.10$ ); in study 2, 0% of GCS and 4.3% of placebo patients were treatment failures ( $p=0.49$ ); in study 3, 61.1% of GCS and 58.8% of placebo patients were treatment failures ( $p>0.99$ ). Although GCS did not benefit the patients in study 2, it is important

to note that these were asymptomatic patients at 1 year after the initial DVT and the stockings used were only 20 to 30 mmHg compared to 30 to 40 mmHg in other studies or study 3. In study 3 the 95% CI on the 2.3% observed difference in the rates of treatment failure was -29% to +34%, thus a relative benefit of GCS of almost 30% could not be excluded. Overall, the study found that 83% of patients are asymptomatic at 1 year after DVT and if asymptomatic at 1 year, they have a low incidence of subsequent PTS within 5 years of diagnosis. In contrast, patients with symptomatic DVT had a significant increase in the incidence of PTS. In summary this study does not support the use of GCS in asymptomatic patients after a DVT. In symptomatic patients with PTS, although no benefit was demonstrated for GCS, the benefit of GCS in improving symptoms could not be completely ruled out due to the small sample size. The apparent discrepancy compared to the findings of Brandjes and Prandoni can be explained by the fact that this study enrolled asymptomatic DVT patients and GCS were not started until 1 year after the first DVT, whereas the other 2 studies enrolled symptomatic patients and started GCS early after the first DVT.

**Prandoni P, Lensing AW, Prins MH, et al.** Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004;141:249–256.

This is the third randomized controlled trial that sought to further define the role of ready-made GCS in the prevention of PTS in patients with proximal symptomatic DVT. A total of 180 patients with a first symptomatic proximal DVT were randomized to below knee GCS (30 to 40 mmHg at the ankle) for 2 years or to no GCS therapy. Patients were followed for 5 years. The primary end point was the presence and severity of PTS scored by a standardized scale. PTS developed in 44 of 90 controls (severe 10) and in 23 of 90 patients with GCS (severe 3). The majority of the events developed in the first 2 years which is consistent with the study by Brandjes and colleagues. The cumulative incidence of PTS in the control groups compared to the GCS was 49.1% vs. 24.5% at 2 years. The NNT with GCS is 4 patients to prevent one case of PTS. This study confirmed the findings of the study by Brandjes and colleagues that below knee GCS reduce the rate of PTS by approximately 50% in symptomatic patients after a first DVT.

**Kolbach DN, Sandbrink MW, Hamulyak K, et al.** Nonpharmaceutical measures for prevention of post-thrombotic syndrome. *Cochrane Database Syst Rev* 2004;CD004174.

This systematic review combined the results of three randomized trials to include 421 patients with the objective to determine the relative effectiveness of GCS in the prevention of PTS in patients with DVT. The primary outcome measure was the occurrence of PTS over time. The results indicate that GCS significantly reduced the cumulative incidence of PTS at 2 years (OR 0.3, 95% CI 0.2 to 0.5). In addition, the incidence of severe PTS was reduced (OR 0.39, 95% CI 0.2 to 0.76). These findings suggest that GCS should be added to the treatment of DVT to prevent PTS, a recommendation which is consistent with the 8<sup>th</sup> ACCP recommendations that also support the use of GCS to prevent PTS in patients with DVT. A large prospective, double blinded study that aims to randomize 800 patients is ongoing with the goal to further confirm the role of GCS in preventing PTS.

## Monitoring Issues

### Consensus Recommendations

**Fairweather RB, Ansell J, van den Besselaar AM, Brandt JT, Bussey HI, Poller L, et al.** College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy. Laboratory monitoring of oral anticoagulant therapy. *Arch Pathol Lab Med* 1998;122:768-81.

During the 1997 College of American Pathologist meeting, key literature regarding laboratory monitoring of oral anticoagulation and related critical points were reviewed and discussed. Consensus was reached on 12 points regarding the laboratory monitoring of oral anticoagulant therapy. These included testing approaches used in the clinical laboratory, cross reactivity of UFH or lupus anticoagulants on the prothrombin time, frequency of monitoring during the initiation and once stable with oral anticoagulation therapy, and standards for patient self-testing. This document provides insights on potential variability that can occur in accurately measuring a response to oral anticoagulation and provides clinicians valuable insights to understand and consider when applying laboratory results to patient care dosing decisions.

**Olson JD, Arkin CF, Brandt JT, Cunningham MT, Giles A, Koepke JA et al.** College of American Pathologists Conference XXXI on Laboratory Monitoring of Anticoagulation Therapy. Laboratory monitoring of unfractionated heparin therapy. *Arch Pathol Lab Med* 1998;122:782-788.

The available literature related to laboratory monitoring of UFH administered either by SC injection or IV infusion is reviewed. Approaches and consensus on sampling and determining an aPTT or activated clotting time value, including the influence of antithrombin, is described. Different assay approaches and calibration methods in addition to determining the therapeutic range, is addressed. Use of the activated clotting time in the setting of extracorporeal circulation and concerns for heparin-induced thrombocytopenia are included. This article provides valuable insights on how current values for monitoring UFH therapy have been determined, and the potential limitations associated with their use.

**Laposata M, Green D, Van Cott EM, Barrowcliffe TW, Goodnight SH, Sosolik RC.** College of American Pathologists Conference XXXI on Laboratory Monitoring of Anticoagulant Therapy: The clinical use and laboratory monitoring of low molecular-weight heparin, danaparoid, hirudin and related compounds, and argatroban. *Arch Pathol Lab Med* 1998;122:799-807.

This review focused on the clinical use and laboratory monitoring of selected parenteral anticoagulants including LMWH, danaparoid, and the direct thrombin inhibitors. Consensus recommendations are provided on approaches to monitoring, and in some cases, the target values for these agents in selected settings. Considerations on how each laboratory should approach testing for these agents, including use of standards, is provided. Although dosing information is provided, subsequent reviews provide more current insights.

### Heparin Monitoring

**Basu D, Gallus AS, Hirsh J, Cade J.** A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. *N Engl J Med* 1972; 287:324-327.

In this prospective analysis of 234 patients receiving IV UFH, clinical outcomes associated

with keeping the aPTT 1.5 to 2.5 times control (40 seconds) was assessed. The UFH was administered as a 5,000-unit bolus followed by an infusion of 1000 units/hour. The mean 24 hour dose of UFH was generally higher at 30,200 units (9,000 to 56,000 units) over 8.6 days with a mean aPTT of 66 seconds for VTE, while the average dose for other indications was 28,300 units (10,000 to 54,000 units) and mean aPTT of 69 seconds for 8.4 days. Patients with aPTT values below target range had a higher incidence of recurrent VTE. This study supported the practice of monitoring heparin therapy to achieve a therapeutic target aPTT value to reduce the incidence of recurrent VTE.

**Hull RD, Raskob GE, Brant RF, O'neil GF, Valentine KA.** Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. *Arch Intern Med* 1997;157:2562–2568.

The potential for recurrent VTE was explored in this retrospective analysis of three double-blind randomized clinical trials for treatment of proximal DVT. Among the 56 patients who received SC UFH or the 57 patients who received IV UFH, 57% and 23%, respectively, failed to achieve a therapeutic response during the initial 24 hours of UFH therapy. The incidence of VTE was 23% in the subtherapeutic group compared to 4% to 6% for those therapeutic at 24 hours. A lower incidence of VTE was observed in those receiving IV UFH compared to SC administration. This analysis supports that patients receiving an initial bolus of UFH followed by 30,000 units over 24 hours, have an additional benefit if the aPTT threshold is met within 24 hours of initiating therapy.

**Anand SS, Bates S, Ginsberg JS, Levine M, Buller H, Prins M, et al.** Recurrent venous thrombosis and heparin therapy: an evaluation of the importance of early activated partial thromboplastin time results. *Arch Intern Med* 1999;159:2029–2032.

This subgroup analysis of three clinical trials explored the incidence of recurrent VTE in patients receiving UFH who were not therapeutic between 24 and 48 hours after initiation of therapy. In all three trials, patients received a bolus dose of 5,000 units followed by an infusion rate of at least 30,000 units over 24 hours. The rate of recurrent VTE at 3 months was 6.7% in

those who were subtherapeutic compared to 5.3% if therapeutic ( $p=0.46$ ). This analysis suggests that if an adequate amount of UFH is initially administered, it is unclear if a therapeutic aPTT at 24 hours predicts improved outcomes. Of note is that the trials were designed to assess home compared to hospitalized treatment of DVT, and may have selected out more stable patients. The investigators do not recommend against aPTT monitoring, but encourage initiating with an adequate amount of UFH, and that best efforts should continue to target an aPTT value in the desired range.

**Levine MN, Hirsh J, Gent M, et al.** A randomized trial comparing the activated thromboplastin time with the heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. *Arch Intern Med* 1994;154:49–56.

This randomized controlled trial compared the use of the aPTT to anti-Xa activity in patients with acute VTE requiring more than 35,000 units of UFH in a 24 hour period. The infusion of UFH and incidence of bleeding was higher when the aPTT was used to dose adjust the UFH compared to anti-Xa activity, but the number of patients involved was too low to reach any statistical significance. The investigators concluded that the use of the anti-Xa assay was a safe and effective means to dose adjust UFH. Of note is that a bias in support of the anti-Xa assay may exist given the population studied (presumed heparin resistant) and potential impact of selecting patients with elevated factor VIII. In contrast, this supports a potential benefit for using the anti-Xa in this specific setting. Of note is that in other settings such as antithrombin deficiency leading to heparin resistance, the above observations may not apply.

**Raschke, R, Hirsh J, Guidry J.** Suboptimal monitoring and dosing of UH in comparative studies with LMWH. *Ann Intern Med* 2003;138:720-3.

To determine the appropriateness of aPTT monitoring in clinical trials comparing UFH to LMWH by reviewing literature published between 1984 and 2001. Of the 15 trials identified, only three used a validated aPTT range and two used a standardized protocol. Most trials did not describe if UFH therapy was optimal by providing either the frequency within the target range or if an adequate amount was

administered. The difference in outcomes for VTE or major bleeding between the trials was not significant. The investigators concluded that most clinical trials comparing UFH to LMWH in treatment of VTE might have not provided optimal UFH therapy.

#### LMWH Monitoring

**Kovacs MJ, Keeney M, MacKinnon K, Boyle E.** Three different chromogenic methods do not give equivalent anti-Xa levels for patients on therapeutic low molecular weight heparin (dalteparin) or unfractionated heparin. *Clin Lab Haematol* 1999;21:55–60.

As tests such as anti-Xa for monitoring parenteral anticoagulants are proposed, it is crucial to identify potential differences in reported values between assay methods. In this analysis using three different chromogenic anti-Xa assays along with two different instruments, observed anti-Xa activity was significantly different and independent of either the test or instrument used. Thus, target ranges can vary between clinical labs where similar numbers or ranges may not describe the same intensity of anticoagulation. Unlike the INR, an international calibration standard for measuring anti-Xa activity (and aPTT values) currently does not exist. These findings are yet another reason why routine anti-Xa monitoring for LMWH should not be conducted.

#### Oral Anticoagulation Self-Testing and Self-Management

**Menedez-Jandula B, Souto JC, Oliver A, Montserrat I, Quintana M, et al.** Comparing self-management of oral anticoagulant therapy with clinic management. a randomized trial. *Ann Intern Med* 2005;142:1–10.

In this randomized, controlled, single center trial, the quality of INR control and clinical outcomes with INR self-testing and self-management of acenocoumarol therapy was compared to management by a hematologist-staffed anticoagulation clinic. Individuals randomized to self-management received 4 hours of training in addition to being provided a dose guiding and follow-up testing protocol, with a 21% drop-out rate noted. The level of education was similar between groups. The percentage of INR values in the target range (59% self-management vs. 56% with the clinic) over approximately 1 year was similar between

groups, and consistent with previous observations of management by an anticoagulation clinic. The number of INR determinations however was three times higher in the self-management group. Major complications and mortality were higher with clinic management (7.3% and 4.1%) compared to self-management (2.2% and 1.6%). Most of the mortality however was attributed for non-thrombotic factors. Of note is that the complication rates were highest in patients having a higher INR goal of 3–4.5. Overall, this report supports that selected patients can safely self-manage their anticoagulation therapy.

**Siebenhofer A, Berghold A, Sawicki PT.** Systematic review of studies of self-management of oral anticoagulation. *Thromb Haemost* 2004;91:225–32.

In this review of the literature up to 2003, evidence from randomized controlled trials exploring the impact of patient self-management of anticoagulant therapy was reviewed. Ultimately only four trials involving 1547 patients receiving phenprocoumon or acenocoumarol were identified. Each patient completed a structured education program. Follow-up ranged from 3 months to 3 years. Overall, outcomes for major bleeding or VTE with patient self-management were similar to management by a specialized anticoagulation clinic, but better than management by general clinicians. Of note is that each study independently was unable to detect any differences. Overall, this analysis supports the potential of patient self-testing and subsequent self-dosing adjustment of their anticoagulation therapy.

**Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P.** Self monitoring of oral anticoagulation: a systematic review and meta-analysis. *Lancet* 2006;367:404–11.

In this meta-analysis of available literature up to 2005, the impact of self-monitored or self-tested warfarin therapy to standard monitoring of warfarin was explored. A total of 14 trials met inclusion criteria. Pooled estimates showed a significant reduction in VTE events, all cause mortality and major hemorrhage with self-monitoring. Self-monitoring and self-adjusting therapy showed a significant reduction in VTE events and death, but not major hemorrhage. In the seven trials that reported the mean time in

range, those receiving self-management had the highest frequency. Of note is that INR determinations were done two to five times more frequently with self-testing compared to usual management. Although not feasible for all patients, this analysis supports potential benefits of self-testing and self-adjusted dosing of warfarin.

## Outpatient Treatment

### Deep Vein Thrombosis

**Levine M, Gent M, Hirsh J, et al.** A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996;334:677–681.

This trial represents the first major investigation of the efficacy and safety of outpatient DVT treatment. Patients with acute proximal DVT were randomized to in-hospital treatment with an IV UFH bolus of 5000 units followed by an initial infusion rate of 1280 units per hour (n=253) or enoxaparin 1 mg/kg SC twice daily (n=247). Patients randomized to enoxaparin were allowed to go home immediately and hospitalized patients were allowed to be discharged early. Warfarin therapy was initiated in all patients on the second day and continued for at least 3 months to a target INR of 2.0–3.0. The primary outcome of the trial, symptomatic VTE at 3 months, occurred in 6.7% of patients randomized to UFH and 5.3% of patients randomized to enoxaparin (p=0.57). Major bleeding was also no different between the groups (1.2% UFH vs. 2.0% enoxaparin; p=0.50). While the duration of injectable anticoagulation was similar between the groups (5.5 days for UFH vs. 5.8 days for enoxaparin; p=NS), the time spent in the hospital was shorter for patients receiving enoxaparin compared to standard IV UFH (1.1 days vs. 6.5 days). Approximately half of the patients randomized to enoxaparin were not hospitalized at all, and the mean length of stay for those who were admitted was only 2.2 days.

This trial demonstrated that patients can be effectively and safely treated at home for their DVT with a LMWH, and that hospitalization is not necessary. Since not all patients can have their DVT treated as an outpatient, it is important to identify the exclusion criteria used in the trial. Patients were excluded in they had

had a previous VTE event, active bleeding or peptic ulcer disease, a familial bleeding disorder, concurrent PE, a coexisting medical condition that required hospitalization to treat that condition, likelihood of noncompliance, geographic limitations to make follow-up visits, patients with hypercoagulable states, or pregnancy. Since this was one of the first trials to evaluate outpatient DVT treatment, the selection criteria were fairly conservative. Of all the patients screened for this trial, only 33% were included. This trial is almost always referenced when there is a discussion about the feasibility of outpatient DVT treatment.

**Koopman MMW, Prandoni P, Piovella F, et al, for the Tasman Study Group.** Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *N Engl J Med* 1996;334:682–687.

This trial accompanied the previous trial as back-to-back publications in the *New England Journal of Medicine*. The trial design and outcomes were similar to the previously discussed trial. Patients with acute symptomatic proximal DVT were randomized to IV UFH (n=198) or LMWH (n=202) that could be administered at home. While the UFH dosing was similar to the previous trial, the LMWH used in this trial was nadroparin dosed twice daily. Patients weighing less than 50 kg received a total daily dose of 8200 IU, 50 kg to 70 kg received 12,300 IU, and greater than 70 kg received 18,400 IU. Warfarin therapy was initiated on the first day and continued for at least 3 months at a target INR of 2.0–3.0. The primary outcome of symptomatic VTE at 3 months occurred in 8.6% of UFH patients and 6.9% of nadroparin patients (p=NS). Major bleeding was also not significantly different between the groups (2.0% UFH vs. 0.5% nadroparin; p=NS). While the duration of injectable anticoagulant was similar between the groups (6.1 days for UFH vs. 6.5 days for nadroparin), the mean duration of hospitalization was shorter for patients receiving nadroparin (2.7 days) compared to UFH (8.1 days).

An important differentiation of this trial compared to the Levine and associates trial was that the ability of the patient to be treated at home was not considered in the inclusion criteria. Major exclusion criteria were concurrent PE, previous VTE, and pregnancy.

Therefore, more screened patients were included in this trial (69% vs. 33%), but fewer patients were able to avoid admission to the hospital (36% vs. 50%) compared to the Levine and associates trial. While only 36% of patients were able to avoid admission to the hospital, an additional 40% of patients randomized to nadroparin were able to be discharged early. A quality of life analysis was also conducted in this trial, and patients randomized to nadroparin scored better on the physical activity ( $p=0.002$ ) and social functioning ( $p<0.001$ ) portion of the Medical Outcome Study Short Form-20 analysis. Once again, DVT management with a LMWH could be done with a reduction in length of hospitalization without compromising efficacy and safety.

**Wells PS, Kovacs MJ, Bormanis J, et al.** Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin. A comparison of patient self-injection with homecare injection. *Arch Intern Med* 1998;158:1809–1812.

Investigators of this trial sought to expand the inclusion criteria of VTE patients being treated on an outpatient basis. Patients with concurrent non-massive PE and patients with previous VTE were considered for outpatient LMWH therapy in this trial, but would have been excluded in previous trials. Using this less conservative definition for outpatient eligibility, 83% of screened patients were able to be treated on an outpatient basis. The trial was conducted at two medical centers in Canada. Patients treated at one center were educated on how to give self-injections of dalteparin (200 IU SC daily) and treated at home ( $n=99$ ). Patients treated at the other center had home health nurses come to the patient's home to give the dalteparin injection ( $n=95$ ). The incidence of VTE (4.0% self-inject vs. 3.2% nurse inject) and major bleeding (2.0% self-inject vs. 2.1% nurse inject) was not significantly different between the groups. These event rates are not different to previous trials that have used more stringent inclusion criteria for eligibility for outpatient VTE treatment. Therefore, at least 4 out of 5 patients could be eligible for outpatient VTE treatment with a LMWH, and patient administration is just as effective and safe as administration from a home health nurse.

**Kearon, C, Ginsberg, JS, Julian, JA, et al, for the Fixed-Dose Heparin (FIDO) Investigators.** Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA* 2006;296,935-942.

While previous trials evaluated the feasibility of using a LMWH for outpatient VTE treatment, the FIDO investigators wanted to determine if a weight-adjusted dose of unmonitored SC UFH would also be an option. Previous use of SC UFH had always involved aPTT monitoring and dose adjustments, but this trial attempted to use a fixed, weight-based dose that was not monitored or adjusted. Patients with symptomatic or asymptomatic VTE identified by screening high-risk postoperative patients were eligible for the trial. Patients ( $n=708$ ) were randomized in an unblinded fashion to an initial SC UFH dose of 333 units/kg, followed by a fixed dose of 250 units/kg every 12 hours ( $n=351$ ) or LMWH ( $n=352$ ) [dalteparin 100 IU/kg twice daily ( $n=261$ ) or enoxaparin 1 mg/kg twice daily ( $n=91$ )]. All patients received warfarin therapy on the first or second day for at least 3 months at a target INR of 2.0-3.0. The incidence of the primary endpoint of recurrent VTE at 3 months was 3.8% in patients receiving SC UFH and 3.4% in patients receiving LMWH ( $p=NS$ ). The incidence of major bleeding was also not different between the groups (1.1% UFH vs. 1.4% LMWH). Hospital admission was able to be avoided in 72% of UFH patients and 68% of LMWH patients.

Results of this trial support the possible use of unmonitored SC UFH on an outpatient basis. Since SC UFH would typically be less expensive than LMWH, an initial thought may be to make SC UFH the optimal strategy for outpatient VTE treatment. It should be remembered that these data are from a single unblinded trial. It should also be considered that this trial screened postoperative patients for symptomatic and asymptomatic VTE, compared to other trials that only took patients presenting with symptomatic proximal DVT or PE. Nevertheless, these are the data that led to SC UFH receiving Grade 1C recommendation in the most recent edition of the ACCP guidelines. Based on the limitations of these data, LMWH should still remain the treatment of choice for outpatient treatment of VTE, but SC UFH may be an option in situations in which outpatient therapy is desired and the cost of LMWH is prohibitive.

### Pulmonary Embolism

**Kovacs MJ, Anderson D, Morrow B, Gray L, Touchie D, Wells PS.** Outpatient treatment of pulmonary embolism with dalteparin. *Thromb Haemost* 2000;83:209–211.

This prospective cohort trial sought to evaluate whether low-risk PE patients could be treated on an outpatient basis. Patients were treated with SC dalteparin 200 IU/kg once daily for least 5 days and received warfarin for at least 3 months. Patients were not considered candidates for outpatient treatment of PE if they had hemodynamic instability, hypoxia requiring oxygen therapy, admission for another medical reason, severe pain requiring parenteral analgesia, or high-risk of major bleeding. Of the 158 patients with PE who were screened, 32% had one of the above exclusion criteria and were treated completely in the hospital. The remaining 108 patients were treated on an outpatient basis, with 81 (51%) able to avoid any hospitalization, and 27 who were discharged early (mean 2.5 days). At 3 months, patients receiving outpatient therapy for PE had a recurrent VTE rate of 5.6%, major bleeding 1.9%, and death 3.7%.

Although there was no comparator group, this trial represents one of the first published investigations into the ability to treat patients with PE on an outpatient basis. While it is traditional to treat PE on an inpatient basis, only one-third of the patients were not eligible for outpatient therapy using these selection criteria. Similar to the outpatient DVT trials, most patients could completely avoid hospitalization and still have acceptable efficacy and safety. The rates of recurrent VTE and major bleeding were similar to those found in inpatient PE trials with other LMWHs. None of the deaths (n=4) were due to PE or major bleeding.

**Janjua M, Badshah A, Matta F, Danescu LG, Yaekoub AY, Stein PD.** Treatment of acute pulmonary embolism as outpatients or following early discharge. A systematic review. *Thromb Haemost* 2008;100:756–61.

This systematic review provides an excellent collection of the key trials that have evaluated the efficacy and safety of outpatient PE treatment. For inclusion in the analysis the manuscripts had to describe their inclusion and exclusion criteria as well as the efficacy and safety outcomes. In trials in which patients with PE were completely treated as outpatients (n=6) the rate of recurrent

PE was 0% to 6.2% and major bleeding was 0% to 2.8%. In the two trials in which patients with PE were discharged early ( $\leq 3$  days) there was no incidence of recurrent PE, and major bleeding occurred in 0% to 2.7% of patients.

The tables in this manuscript are well done and can be very helpful for an institution that is trying to implement an outpatient PE treatment program. Table 1 includes a description of the trials that treated PE completely on an outpatient basis. The table has the references, size of the trials, inclusion and exclusion criteria, and the treatments that were used. The inclusion and exclusion criteria are typically quite similar with some increased detail in some of the trials. Table 2 describes the methods for defining the efficacy and safety outcomes, and table 3 provides the results from the individual trials. Finally, there is a brief, but good discussion on identifying low-risk PE patients and references on the different predictor tools that can be used.

**Jiménez D, Yusen RD, Otero R, et al.** Prognostic models for selecting patients with acute pulmonary embolism for initial outpatient therapy. *Chest* 2007;132:24–30.

Deciding which patients with PE can be safely treated as outpatients and which patients need to be hospitalized is a critical part to the development of any outpatient VTE program. There have been a number of predictor models developed to help answer this question. Two of the most common models are the PE severity index (PESI) and the Geneva model. The PESI uses a number of criteria to place patients with PE into classes I – V, with classes I and II representing patients at low-risk of mortality. The Geneva model also uses different criteria to place patients into either low-risk or high-risk categories. The investigators of this trial compared these two models in a cohort of 599 patients with confirmed PE to determine the discriminatory power of the models. The investigators also compared their cohort to the original validation cohorts for each model, which strengthens the manuscript.

The PESI identified fewer patients as low-risk compared to the Geneva (36% vs. 84%;  $p < 0.0001$ ). Both prediction models were able to identify a difference in mortality between low- and high-risk groups in this patient cohort (0.9% vs. 10.7% for PESI and 5.6% vs. 15.5% for Geneva), but the difference in mortality in low-risk patients as defined by each model was significantly different (0.9% PESI vs. 5.6%

Geneva;  $p < 0.0001$ ). The differences in predicting recurrent VTE events or major bleeding was not different between the models. The PESI had a higher sensitivity (100% vs. 35%) and a lower specificity (13% vs. 85%) for mortality compared to Geneva. The positive predictive value of PESI was 8.2% and Geneva was 15.5%. The negative predictive value for PESI was 100% and Geneva was 94%. Finally, the PESI had a greater discriminatory power to predict 30 day mortality than the Geneva (C-statistic 0.76 vs. 0.61;  $p = 0.002$ ). Therefore, the PESI model is able to select patients at low-risk of 30 day mortality better than the Geneva model, but the models are similar in their ability to predict patients who will have recurrent VTE or major bleeding.

## Special Populations

### Cancer Patients

**Meyer G, Marjanovic Z, Valcke J, et al.** Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med* 2002;162:1729–35.

This randomized, open label, multicenter trial in France compared enoxaparin 1.5 mg/kg daily for 3 months with initial enoxaparin transitioned to warfarin targeted to an INR goal of 2.0–3.0 for patients with active cancer and new VTE. The primary outcome was the combined rate of symptomatic, objectively confirmed recurrent VTE or major bleeding over the 3-month treatment period. Over half the patients had metastatic disease and were receiving treatment of their cancer.

The combined endpoint was significantly higher in the warfarin group (21.1%) compared to the LMWH group (10.5%) when analyzed in terms of time to event ( $p = 0.04$ ). The risk of VTE recurrence appeared to be similar in both groups, but a surprisingly high incidence of major bleeding accounted for 17 of the 22 events recorded. Fatal bleeding occurred in 6 patients, all in the warfarin group. Overall mortality was numerically higher in the warfarin group (22.7% vs. 11.3%;  $p = 0.07$ ).

By design, the INR was required to be measured by the local investigator at least once a week until day 90 of the trial. The mean number of INR measurements was 2.4 per week, with only 41% in the therapeutic range. The investigators did not disclose what proportion of

the remaining values were above or below goal but did report the INR was elevated in 8 of the 12 major bleeding events in patients taking warfarin. Four centers accounted for over half of the 146 patients enrolled in the trial before the steering committee stopped the study early secondary to slow recruitment. While the high bleeding rates in this trial seem out of line with subsequent results and experience, it was one of the first to suggest a relative advantage of prolonged LMWH in this population and did illustrate the challenges of managing warfarin in patients with cancer.

**Lee AYY, Levine MN, Baker RI, et al, for the Randomized Comparison of Low-Molecular Weight Heparin versus Oral Anticoagulation therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators.** Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003;349:146–53.

This larger randomized, open label, multicenter trial comparing dalteparin versus oral anticoagulation for 6 months in cancer patients with a new, symptomatic proximal DVT or PE helped solidify the current grade 1A recommendation by the ACCP of using LMWH for the first 3 to 6 months in this population. Approximately two thirds of this cohort also had metastatic disease and were receiving treatment for their cancer. The CLOT trial also demonstrated a relative advantage with the use of LMWH to treat VTE in cancer patients, but with comparable safety and enhanced efficacy. It enrolled patients from 48 centers in eight countries, was adequately powered, provided treatment over an extended study period, and had well defined, objective measures of recurrent VTE and bleeding.

In the 672 patients studied the rate of the primary endpoint, symptomatic recurrent VTE, was halved in the group receiving LMWH relative to the group begun on LMWH and transitioned to long-term warfarin (9% vs. 17%;  $p = 0.002$ ). Over half of the thrombotic events in the warfarin group occurred when the INR was greater than 2.0. Unfortunately, despite the reduction in recurrent VTE, the overall mortality rate was unchanged at approximately 40% in each group, primarily due to progressive cancer. A post-hoc analysis of this data demonstrated improved survival in solid tumor patients without metastases receiving LMWH and serves

as a basis for continued research. In this trial the rate of major bleeding was non-significantly higher with LMWH over warfarin (6% vs. 4%). The INR was drawn in warfarin patients at least once every two weeks and was in the therapeutic range 46% of the time. Half of the major bleeds in the warfarin group occurred when the INR was greater than 3, but there was no fatal bleeding in this group.

**Hull RD, Pineo GF, Brant RF, et al, for the LITE Trial Investigators.** Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med* 2006;119:1062–72.

This 200 patient, multicenter Canadian trial in cancer patients with proximal DVT was part of a prospectively planned substudy of a larger trial (LITE = Long-term Innovations in TreatmEnt program) examining the LMWH tinzaparin compared to usual anticoagulation care. Therefore the comparison groups here were LMWH daily for 3 months compared to a validated protocol of IV UFH transitioned to warfarin for 3 months. Because of the possibility of randomization to IV UFH, patients eligible for initial outpatient therapy were excluded from this trial. After completing the randomized treatment, patients from either group could be placed on oral anticoagulation if the treating physician felt it was indicated.

The primary outcome measures were documented recurrent VTE, death, or bleeding during the 3 month study period. The patients or primary care physicians were also contacted by telephone at 1 year to aid in assessing recurrent VTE or death at that time. The rate of recurrent VTE was lower in the group receiving LMWH at 3 months (6% vs. 10%;  $p=NS$ ) and 12 months (7% vs. 16%;  $p=0.044$ ). The 3 month time point is probably a truer measure of the comparative treatment effects between the groups. While more patients originally randomized to warfarin for 3 months received it during the 3 to 12 month time frame (57 vs. 37) they did so for a shorter period of time compared to those who received LMWH for 3 months and then began warfarin. Major bleeding at three months and mortality at both 3 and 12 months were essentially the same in both groups. The trial specified that the INR be performed every 1–2 weeks in warfarin patients, but the authors only reported that INR control was “similar to other studies”. Overall these results lend some further support to those of Lee and colleagues in

demonstrating enhanced efficacy and similar safety of LMWH in this population.

**Akl EA, Rohilla S, Barba M, et al.** Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev* 2008(1):CD006649.

Whereas the other trials in this section examined three to six months of secondary prophylaxis of VTE in cancer patients this review examines the impact of the initial 5 to 10 days of treatment selected for the index VTE on subsequent mortality and likelihood of VTE recurrence. These authors systematically collected efficacy and safety data from all the controlled trials of acute VTE treatment in which cancer patients were not excluded and patient groups received similar long-term anticoagulation. The initial treatments evaluated were UFH, LMWH, and fondaparinux. There were 26 studies identified in which patients with cancer represented a treatment subgroup. Despite the review authors taking steps such as searching review articles and contacting the primary authors for incompletely reported data, only 15 studies provided data to be reviewed, 13 of which compared LMWH to UFH.

A pooled analysis of over 800 patients with cancer from the 11 of 13 studies that reported mortality data at 3 months showed a statistically significant reduction in mortality with the use of LMWH compared to UFH (RR 0.71, 95% CI 0.51 to 0.97). No heterogeneity or publication bias was present. Ten of the 11 studies were published between 1991 and 1997 and may have used different treatment regimens. Eight of the 11 studies demonstrated numerically less mortality with LMWH, but none was significantly different as these studies were not adequately powered to evaluate this subgroup. Three studies accounted for over 75% of the weighting. The overall results did not change when three studies of lower methodologic quality were excluded. Only three of the 15 randomized clinical trials, representing 371 patients, had data regarding the incidence of recurrent VTE. While the pooled benefit was similar to that of mortality, it was not significant as evidenced by the wide confidence intervals (RR 0.78, 95% CI 0.29 to 2.08). The possible mortality benefit reflected in this pooled data is part of the rationale behind the ACCP preference for initial treatment of acute VTE with SC LMWH rather than IV UFH.

## Obese Patients

**Wilson SJ, Wilbur K, Burton E, Anderson DR.** Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low molecular weight heparin for the treatment of venous thromboembolism. *Haemostasis* 2001;31:42–8.

The effect of body weight on the anticoagulant response of a weight-based dose of LMWH is limited. The use of anti-Xa blood monitoring may provide some reassurance to practitioners regarding the safety and efficacy of weight-based dosing of anticoagulant agents in obese patients. These investigators conducted a prospective cohort study to determine the effect of body weight on treatment doses of dalteparin. Patients diagnosed with VTE received dalteparin 200 anti-Xa units/kg SC once daily based on actual body weight and without dose capping. Thirty-seven patients were stratified into one of three weight classes: (1) within 20% of ideal body weight (IBW) (n=13), (2) 20–40% of IBW (n=14), and (3) greater than 40% of IBW (n=10). The primary outcome of this investigation was the mean trough anti-Xa level on day 3 and day 5 and mean peak anti-Xa level on day 3. Secondary outcomes included clinical endpoints such as hemorrhagic and thromboembolic complications. Mean trough anti-Xa levels on day 3 were 0.12 units/mL, 0.11 units/mL, and 0.11 units/mL, respectively (p>0.2). Similar mean trough findings were observed on day 5 (p>0.2). Mean peak anti-Xa levels on day 3 were 1.01 units/mL, 0.97 units/mL, and 1.12 units/mL, respectively (p>0.2). No hemorrhagic or thromboembolic complications were observed in any patient up to 90 days following therapy. These findings suggest that body weight does not have a clinically significant effect on the response to treatment doses of dalteparin. This investigation supports weight-based dosing of LMWH in obese patients using both laboratory and clinical endpoints and confirms that dose-capping is not justified.

**Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A et al.** Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med* 2001;134:191–202.

Therapeutic enoxaparin has traditionally been recommended for VTE as a twice-daily regimen without laboratory monitoring. This dosing scheme has been compared to IV UFH in several

investigations. Investigators in this trial enrolled 900 patients with symptomatic VTE to receive SC enoxaparin 1 mg/kg twice daily, SC enoxaparin 1.5 mg/kg once daily, or dose-adjusted IV UFH. Overall, 405 (45%) of these patients were obese (body mass index greater than 27.2kg/m<sup>2</sup> in men and greater than 26.0 kg/m<sup>2</sup> in women) and equally distributed across all three regimens. A non-significant trend toward increased recurrent VTE was observed in obese patients. Obese patients receiving once daily enoxaparin experienced a recurrent VTE (7.3%) compared to twice daily (3.4%) and IV UFH (2.5%). This pre-specified subgroup analysis suggests that twice daily enoxaparin may be preferred over once daily enoxaparin in obese patients.

## Patients with Renal Dysfunction

**Thorevska N, Amoaeng-Adjepong Y, Sabahi R, Chiopescu I, Salloum A, Muralidharan V et al.** Anticoagulation in hospitalized patients with renal insufficiency: a comparison of bleeding rates with unfractionated heparin vs enoxaparin. *Chest*. 2004;125:856–63.

The rate of bleeding in patients with renal insufficiency receiving either twice daily enoxaparin or IV UFH at full treatment doses was explored in this single center retrospective cohort analysis that included 620 patients with estimated glomerular filtration rates (GFR) less than 60 mL/min determined by the Modified Diet in Renal Disease Method (MDRD). The major bleeding rates were similar between agents at 26.3 per 1000 patient days with UFH compared to 20.7 per 1000 patient days with enoxaparin. Patients with severe renal insufficiency (GFR less than or equal to 20 mL/min) receiving enoxaparin had a 154% excess incidence of minor bleeding compared to UFH. Declining renal insufficiency, female gender and duration of anticoagulation therapy was associated with increased incidence of major bleeding complications. Of note is that the median age was 80 years old, that the MDRD equation may overestimate GFR compared to other methods, and that the dose of enoxaparin was not adjusted for renal dysfunction, potentially creating a higher risk for major bleeding.

**Lim W, Dentali F, Eikelboom JW, Crowther MA.** Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med* 2006;144:673–684.

In this meta-analysis involving 12 trials (n=4971) reported up to 2005, anti-Xa activity and risk for major bleeding with the use of a LMWH was evaluated in patients with a CrCl either above 30 mL/min or below. Dialysis dependent patients were excluded. Most of the trials involved the use of enoxaparin in acute coronary syndrome or atrial fibrillation. Trials in which LMWH was both dose adjusted and non-dose adjusted for renal insufficiency were included. A significant increase risk for major bleeding was observed with a CrCl of 30 mL/min or lower (5.0% vs. 2.4%; p=0.013). The use of non-dose adjusted enoxaparin had a higher incidence of bleeding compared to adjusted dose. The three studies involving tinzaparin and dalteparin did not find a correlation in anti-Xa activity and renal insufficiency, supporting a lower dependence on renal function for elimination compared to enoxaparin. Major bleeding however for these two agents could not be assessed. Of note with the analysis was an asymmetrical funnel plot suggesting some publication bias. The investigators concluded that the non-dose adjusted enoxaparin had elevated anti-Xa levels and increased risk for bleeding in patients with a CrCl 30 mL/min or less.

**Falga C, Capdevila JA, Soler S, Rabunal R, Munoz-Torrero JFS, Gallego P et al, for the RIETE Investigators.** Clinical outcome of patients with venous thromboembolism and renal insufficiency. Findings from the RIETE registry. *Thromb Haemost* 2007;98:771-6.

The RIETE program is an ongoing multi-center, prospective registry from four countries of patients presenting with confirmed VTE. From this registry, several questions have been explored and published by the various investigators involved. In this particular analysis, 3-month outcomes in patients with a CrCl less than 30 mL/min were compared to those above 30 mL/min. Of note is that patients with a CrCl below 30 mL/min were frequently excluded in clinical trials, prompting an analysis of this group within the registry data. In those with renal insufficiency, significantly higher rates of mortality, major bleeding, and fatal bleeding were observed. The incidences of fatal PE exceeded the rate of fatal bleeding when a PE was initially present. The mean LMWH dose was similar between groups (~179 units/kg/day), and long-term vitamin K antagonist dose to reach a goal INR of 2.0-3.0 was less if renal insufficiency

was present. Other reports from the registry have identified age over 80 (which would be expected to have lower estimated GFR) as a similar risk factor, and that the incidence of mortality, VTE recurrence and major bleeding was similar between full dose LMWH (mean 191 units/kg/day) and those with bleeding concerns receiving a lower LMWH dose (mean 122 units/kg/day).

#### Pregnant Patients

**Brill-Edwards P, Ginsberg JS, Gent M, et al, for the Recurrence of Clot in This Pregnancy Study Group.** Safety of withholding heparin in pregnant women with a history of venous thromboembolism. *N Engl J Med.* 2000;343:1439-44.

This multicenter, prospective cohort study challenged the conventional wisdom at the time that most women with prior VTE should receive heparin prophylaxis during subsequent pregnancies. This was a relevant question because the estimates of VTE risk for this situation varied widely at that time, it was thought that fatal PE as an initial manifestation of VTE recurrence was rare, and anticoagulation during pregnancy was associated with certain risks and inconveniences. The trial showed that past idiopathic VTE and known thrombophilia increase the risk of recurrent VTE in pregnancy, but that the overall risk is low, especially in the absence of those two conditions.

One hundred twenty five pregnant women with a single previous episode of VTE had bilateral ultrasound performed upon study entry. Approximately one third of the prior events were idiopathic in nature whereas about two thirds were attributed to a transient risk factor (pregnancy, oral contraceptives, surgery, trauma, etc.). Antepartum prophylaxis was withheld, but postpartum prophylaxis was initiated within 24 hours of delivery and continued for 4-6 weeks. Specific procedures were followed in the event signs or symptoms of VTE occurred. Women with known thrombophilia were excluded at entry, but blood was drawn from 95 women for evaluation of thrombophilia after completion of the trial.

The rate of VTE was small with only three antepartum VTE's (2.4%) and three post partum VTE's detected. None of the post partum events occurred while taking the prescribed warfarin prophylaxis. Twenty-five of the 95 women tested positive for a thrombophilia. All three post-

partum events occurred in women with either a past idiopathic VTE or a detected thrombophilia (5.9%) whereas no events happened in women lacking either of these factors. Data tables are presented whereby risk of antepartum or postpartum recurrence can be calculated for different combinations of scenarios such as past idiopathic compared to reversible VTE and positive versus negative thrombophilia.

As a result of this trial the ACCP refined their recommendation that clinical antepartum surveillance and postpartum prophylaxis is the preferred management for women with no thrombophilia and a single prior VTE secondary to a transient risk factor. The most current recommendation now allows for this or antepartum prophylaxis if the transient risk factor was pregnancy or estrogen related.

**Greer IA, Nelson-Piercy C.** Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood* 2005;106:401–7.

Primarily extrapolating safety and efficacy outcomes from non-pregnant patients, and based upon studies showing that LMWH did not cross the placenta, they began to be used during pregnancy. Whereas the ACCP stated in the 1998 edition that “there is insufficient evidence to endorse LMWH for routine clinical use in pregnant patients” by the 2001 edition they declared that “LMWHs are suitable for routine clinical use in pregnant patients”. This evolution occurred despite a lack of data from randomized, comparative trials or prospective case series in this population of patients. These authors, after excluding reports related to artificial heart valves or those deemed methodologically deficient or duplicative investigations, reviewed 64 studies or case reports published before 2004 involving 2777 pregnancies.

Tables detail the principal indication and specific LMWH used for prophylaxis or to prevent adverse pregnancy outcomes (2603 pregnancies) or treatment (174). Enoxaparin was used in over half of the treatment cases and slightly under half the time for prophylaxis. Dalteparin and nadroparin accounted for most of the rest. Although the numbers are small, it is reassuring that the recurrent VTE rate in the treatment was very low at 1.15%, comparing favorably to similar data in non-pregnant patients. Significant bleeding occurred at a rate of 1.72%, although the primary cause in two of

three cases was most likely obstetrical with the LMWH possibly playing a contributory role. Although not a primary outcome, successful pregnancy was reported over 96% of the time when LMWH was used for VTE prophylaxis or treatment. This review summarizes a wide variety of potential adverse effects and very relevant efficacy parameters and details these events by individual LMWH agent and subdivides them by indication. The overall event rates reported (VTE 0.86%, arterial thrombosis 0.50%, and significant bleeding 1.98%) and concise discussion serve as a valuable summary of LMWH use in pregnancy.

**Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J.** Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines, 8th ed. *Chest*. 2008;133:844S-886S.

This section of the ACCP guidelines offers a comprehensive evaluation on a broad array of pregnancy related topics. The scope and depth of material covered in this chapter represents a significant expansion from their last guidelines published in 2004. The summary of recommendations is broken down by section and conveniently placed at the beginning of the chapter. The underlying values and preferences are also provided here to assist with clinical interpretation. New sections in 2008 are devoted to the use of anticoagulants in nursing women, VTE risk and prevention following cesarean section, and the prevention of recurrent pre-eclampsia in women without thrombophilia. The section addressing mechanical heart valves in pregnancy places additional emphasis on risk factor assessment, states the decision should be strongly influenced by patient preferences, and now contains the suggestion to use oral anticoagulation over heparin in pregnancy with high risk valves where concerns exist about the safety and efficacy of LMWH or UFH.

A new section is also devoted to summarizing LMWH therapy, including its lower rates of heparin-induced thrombocytopenia and osteoporosis, and concludes with the preference of LMWH over UFH for the prevention and treatment of VTE in pregnancy. In the section on treatment of VTE in pregnancy a Grade 1A recommendation given to adjusted dose LMWH or adjusted dose UFH for at least 5 days of therapy. It is also suggested that pregnant patients with acute VTE should receive

anticoagulants for at least 6 weeks post partum and the minimum total duration of therapy (including antepartum use) be 6 months.

It should be noted that primarily due to the lack of high quality clinical anticoagulation studies in the pregnant population and the breadth of topics covered, 20 of the 38 recommendations in this chapter are Grade 2C, denoting a weak recommendation (“we suggest”) derived from low or very low quality evidence. In contrast, only 4 of the 38 are Grade 1A.

**Duhl AJ, Paidas MJ, Ural SH, et al, for the Pregnancy and Thrombosis Working Group.** Antithrombotic therapy and pregnancy: consensus report and recommendations for prevention and treatment of venous thromboembolism and adverse pregnancy outcomes. *Am J Obstet Gynecol.* 2007;197:457.e1–e21.

This review offers a contemporary alternative to the ACCP guidelines mentioned above. It is an outgrowth of an expert meeting organized and supported by Aventis Pharmaceuticals. Specific subgroup discussions were conducted followed by a roundtable discussion of all topics by all participants. This led to an initial draft document that was subsequently revised and published. The 13-member working group maintained full and independent responsibility for the content of the consensus document. This group used the US Preventive Service Task Force grading of evidence to rate their recommendations. Somewhat similar to ACCP, 21 of the 32 consensus panel recommendations offered here are class C—based primarily on consensus and expert opinion. The recommendations are contained in sections located throughout the sixteen pages of text, but are not presented in a summary section. Easy to read tables and figures augment the extensive text, supported by nearly 200 references.

This review offers recommendations regarding the measuring of antithrombin levels, appropriate use of regional anesthesia, and target anti-Xa LMWH levels not found in the ACCP review. The treatment sections are quite similar and in general agreement. As to be expected, the interpretation of some existing data and to what degree of detail preferences are stated do vary between the two reviews. For instance, this working group offers that “maternal anticoagulation with warfarin prior to delivery of the infant should be avoided where possible”. Also, whereas this working group summarizes

prevention of recurrent VTE in pregnant women with four recommendations, the ACCP addresses the possible scenarios with eight separate recommendations, often with multiple options.

#### Patients with Hypercoagulable Conditions

**Crowther MA, Ginsberg JS, Julian J, et al.** A comparison of two intensities of warfarin for prevention of recurrent thrombosis in patients with antiphospholipid antibody syndrome. *N Engl J Med* 2003;349:1133–1138.

This was the first randomized, double-blind, controlled trial to challenge the practice of targeting a high-intensity of warfarin anticoagulation for patients with antiphospholipid antibody syndrome. In this trial, patients (n=114) who had objectively confirmed arterial or venous thrombosis were randomized to high-intensity warfarin (INR range 3.1–4.0) compared to standard-intensity warfarin (INR range 2.0–3.0). To be included in the trial, patients needed positive test for antiphospholipid antibodies (lupus anticoagulant or IgG anticardiolipin antibody or both) meeting the criteria set by the International Society on Thrombosis and Haemostasis. Patients with bleeding diathesis, intracranial hemorrhage history, stroke, gastrointestinal bleeding in the last 3 months, contraindications to warfarin, confirmed thrombosis history with an INR over 2, pregnancy/planned pregnancy, or geographic locations problems making follow-up difficult were excluded from the trial. Recurrent thrombosis occurred in 10.7% of the high-intensity warfarin patients compared to 3.4% in the standard-intensity arm (p=NS). No bleeding differences were found between the groups.

The recommendation from this study was that standard-intensity warfarin is appropriate for patients with antiphospholipid antibody syndrome with history of thrombosis. However, patients in the high-intensity warfarin arm only had their INR in range 40% of the time, compared to 71% of the time in the standard-intensity arm. The type of thromboplastin reagents used were not reported.

**Finazzi G, Marchioli R, Brancaccio V, et al.** A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost* 2005;3:848–853.

Shortly after the Crowther publication, this

similar trial was published with remarkably similar results. In this trial, patients (n=109) who had confirmed lupus anticoagulant and/or moderate to high anticardiolipin antibodies plus a history of arterial or venous thrombosis were included in the trial. Patients were randomized in an open-label fashion to high-intensity warfarin (INR range 3.0–4.5) or standard therapy (either warfarin, INR range 2.0–3.0 for thromboembolic disease or aspirin 100 mg daily for non-embolic arterial disease). The thromboplastin used was recorded, but these results were not reported. Recurrent thrombosis occurred in 11.1% of patients in the high-intensity warfarin arm compared to 5.5% in the standard therapy arm (p=NS). There was more minor bleeding in the high-intensity arm (27.8% vs. 10.9%; p=0.027), but overall and major bleeding outcomes were not different.

This trial confirmed the results of the Crowther trial, but this trial did not address the possible effect of different thromboplastin reagents nor did it answer how patients with these conditions who have a thrombotic event while already on anticoagulation therapy should be treated.

**Lim W, Crowther MA, Eikelboom JW.** Management of antiphospholipid antibody syndrome: a systematic review. *JAMA*. 2006;295:1050–7.

This article was a comprehensive review of the literature regarding how to manage antiphospholipid antibody syndrome. It proposes a very helpful algorithm to help guide therapy for antiphospholipid antibody syndrome patients. The algorithm also contains an evidence grade that the management recommendations are based upon. Key findings of the review include defining what patients seems to be at highest risk for thrombosis, recommending standard intensity warfarin (INR goal 2.0–3.0) for patients with thrombosis based on the Crowther and Finazzi studies, and use of aspirin or warfarin (INR goal 1.4–2.8) for patients with stroke and one positive antiphospholipid antibody syndrome test. (Note that the last case would not necessarily fit the formal definition of antiphospholipid antibody syndrome as tests need to be positive twice 12 weeks apart to rule out transient antibody elevation). Areas that require more study include the role of prophylactic therapy in patients with antiphospholipid antibodies without thrombosis history, discerning the best

treatment of noncerebrovascular arterial thrombosis, management of patients who have thrombosis despite therapeutic INRs on warfarin, and treatment of female patients who have had multiple fetal losses and have antiphospholipid antibodies.

**Baglin T, Luddington R, Brown K, et al.** Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet* 2003;362:523–526.

This prospective, cohort trial was aimed at determining the influence of inherited thrombophilia on the risk of recurrent VTE. Starting in 1997, the investigators enrolled new VTE patients in an outcome database and patients were offered thrombophilia testing after they had completed anticoagulation therapy for the VTE event. Patients (n=570) were followed for 2 years. Patients with antiphospholipid antibodies, malignancy, mesenteric vein thrombosis, or cerebral vein thrombosis were excluded from the study. Patients were then stratified into four groups: (Group A) surgery in the last 6 weeks, (Group B) pregnancy associated VTE, (Group C) unprovoked VTE, and (Group D) non-surgery risk factors for VTE. Risk of recurrence was highest for the unprovoked VTE group (19.4%) and lowest in the pregnancy related VTE group and the surgical related VTE groups, both of which had no VTE recurrences. The unprovoked group also had a higher recurrence rate than the group with non-surgery related VTE risk factors (8% in the non-surgery risk factor group, p=0.004). The presence of inherited thrombophilia did not influence the risk of recurrence (HR 1.5, 95% CI 0.82 to 2.77; p=0.187). This result did not vary when the group A and B patients were excluded (HR 1.34, 95% CI 0.73 to 2.46; p=0.351).

In conclusion, this trial suggest that clinical presentation (i.e., unprovoked thrombosis) is a more important fact in determining recurrent VTE risk than the presence of thrombophilia. However, since some thrombophilias occur at a very low incidence, this trial could be underpowered when assessing their effects on VTE recurrence.

**Ho WK, Hankey GJ, Quinlan DJ, et al.** Risk of recurrent venous thromboembolism in patients with common thrombophilia: a systematic review. *Arch Intern Med* 2006;166:729–736.

This was a meta-analysis aimed at determining

the relative risk of VTE recurrence in patients with factor V Leiden and prothrombin G20210A thrombophilias after discontinuation of anticoagulation therapy. Studies that were included had to be of cohort design where the outcomes of patients with these thrombophilias were compared to patients without, the VTE event was the first event, the VTE needed to be treated appropriate with a heparin product and at least 3 months of warfarin, patients had to be followed at least 6 months after warfarin was discontinued, and all clinical events needed objective confirmation. Studies were omitted when the duration of anticoagulation was unclear, were family studies, were pediatric or obstetric studies, or involved unusual sites (mesenteric, renal, upper limb, or cerebral sinus clots). If studies included cases that were reported in multiple articles, only the most current information was utilized. In the factor V Leiden arm of the study (n=3104), heterozygous carriers were found to have an increased risk of recurrence (OR 1.41, 95% CI 1.14 to 1.75). In the prothrombin G20210A arm of the study (n=2903), heterozygous carriers were found to have an increased risk of recurrence (OR 1.72, 95% CI 1.27 to 2.31). In conclusion, this study showed that these two polymorphisms increase risk for VTE recurrence, but the effect was modest. Due to the modest finding and since these are the most common thrombophilias that are encountered in the general population (factor V Leiden was found in 21.4% of patients in this analysis and prothrombin G20210A was found in 9.7% of patients), this trial still leaves open the possibility that testing for these conditions may not be the best strategy to determine the length of therapy after unprovoked VTE.

### Pharmacoeconomics

**Gould MK, Dembitzer AD, Sanders GD, Garber AM.** Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis. *Ann Internal Med* 1999;130:789-99.

This analysis evaluated the cost-effectiveness of treating VTE with fixed dose LMWH or adjusted dose UFH from a societal perspective. A decision model design was used and clinical outcome probabilities were based on the results of a well done meta-analysis of clinical trials evaluating LMWH compared to UFH for VTE treatment. The cost estimates used were mainly derived

from Medicare reimbursement data. Table 3 of the manuscript gives a detailed description of the different costs considered in this analysis. Total cost for inpatient treatment of VTE was \$26,516 with SC LMWH and \$26,361 with IV UFH. While the cost of initial therapy was higher in the LMWH group, it was eventually offset by the improved efficacy and reduced costs for early complications. From the societal perspective, LMWH provide an increase in quality-adjusted life expectancy of approximately 0.02 years. While this seems like a minimal difference, it does produce a \$7820 per quality-adjusted life saved. This would be considered a highly cost effective therapy, but unfortunately most payers and providers do not typically consider the societal perspective of cost-effective analysis. In the sensitivity analysis, LMWH therapy was cost saving if as few as 8% of patients were treated at home, 13% of patients were able to be discharged early, or the cost of the LMWH was reduced by 31%. While the costs used in this trial are about 10 years old, all costs should have increased proportionally in both groups.

**O'Brien B, Levine M, Willan A, et al.** Economic evaluation of outpatient treatment with low-molecular-weight heparin for proximal vein thrombosis. *Arch Intern Med* 1999;159:2298-2304.

This article is an economic analysis of the Levine and associates trial presented in the outpatient DVT treatment section of this manuscript. While the trial itself included patients with both hospital and community-acquired VTE, the investigators considered only the economic data available for the 300 patients who presented with community-acquired proximal DVT. Of these, 151 patients were treated with inpatient IV UFH and 149 patients who received SC enoxaparin. The clinical results of this cohort of patients were similar to the results of the overall study population. A cost analysis and a cost-effective analysis from a societal perspective was conducted for the 3 months of follow-up in the trial. Total costs included health care costs, patient travel costs, and productivity costs as a result of time off work. Patients receiving UFH had a mean cost per patient of \$5323 compared to \$2278 for patients receiving enoxaparin. Since the results are presented in 1997 Canadian dollars, the proportion of the results is probably more useful than the actual dollar amounts. Therefore, data from this trial confirms that outpatient DVT

treatment with a LMWH provided similar efficacy and safety at a meaningful reduction in costs per patient.

**Spyropoulos AC, Hurley JS, Ciesla GN, de Lissovoy G.** Management of acute proximal deep vein thrombosis. Pharmacoeconomic evaluation of outpatient treatment with enoxaparin vs inpatient treatment with unfractionated heparin. *Chest* 2002;122:108–14.

The investigators of this pharmacoeconomic analysis wanted to provide a US health maintenance organization (HMO) perspective to the cost effective analysis of outpatient DVT treatment previously conducted by the Canadians. Therefore, they conducted a retrospective analysis of patients in their HMO who would have been eligible for the Levine and associates trial. Patients were treated with IV UFH administered inpatient (1995 to 1996, n=64) or SC enoxaparin administered primarily outpatient (1997 to 1998, n=65) and transitioned to warfarin therapy for at least 3 months at a target INR of 2.0–3.0. Approximately 50% of the patients receiving enoxaparin were treated completely on an outpatient. Recurrent VTE occurred in three patients receiving UFH (4.7%) and one patient receiving enoxaparin (1.5%), and there was only one episode of major bleeding that occurred in a patient receiving enoxaparin. Since the objective of the trial was to evaluate cost and not outcomes, there are too few patients to determine if these differences are statistically different. Table 4 in the manuscript has a useful and detailed description of the cost used in the analysis for anyone who may want to do a similar analysis in their own institution or HMO. The mean cost per patient was \$11,930 for patients receiving inpatient UFH and \$9,347 for patients receiving outpatient enoxaparin. Therefore, these data demonstrate that outpatient DVT treatment with a LMWH can provide a cost savings of approximately \$2,500 per patient compared to inpatient IV UFH from a US HMO perspective.

**Tillman DJ, Charland SL, Witt DM.** Effectiveness and economic impact associated with a program for outpatient management of acute deep vein thrombosis in a group model health maintenance organization. *Arch Intern Med* 2000;160:2926–32.

The investigators of this analysis sought to evaluate the effectiveness and cost impact of a clinical pharmacy outpatient DVT program.

During the 2-year analysis (March 1996 to March 1998) there were 428 patients with acute DVT in the Kaiser Permanente Colorado Region HMO. Of these patients 391 (91.4%) were enrolled in the outpatient DVT program, and 78% were able to completely avoid hospitalization. The only patients not considered for outpatient therapy were those who required hospitalization for another disease state, patients with PE, patients with active bleeding, or pregnancy. The 90 day incidence of a recurrent VTE event or major bleeding was 4.6%, similar to that seen in controlled clinical trials (3.5% to 9.4%). The mean direct cost for outpatient DVT treatment in this HMO was \$1868 per patient, which calculated to a cost savings of \$2828 per patient compared to inpatient treatment with IV UFH. Table 3 in the manuscript contains a description of the cost used in this analysis as well as an extensive sensitivity analysis conducted by the authors. Based on these findings there was a total cost savings of \$1,108,587 over the 2 years of the clinical pharmacy-administered outpatient DVT program. Data such as these can be used as justification for supporting of clinical pharmacy anticoagulation services.

**Aujesky D, Smith KJ, Cornuz J, Roberts MS.** Cost-effectiveness of low-molecular-weight heparin for the treatment of pulmonary embolism. *Chest* 2005;128:1601–10.

While previous pharmacoeconomic analyses have focused on the use of LMWH compared to UFH for the management of DVT, this analysis specifically evaluated the treatment of PE. The investigators calculated cost and cost effectiveness with a Markov model in a hypothetical cohort of 60-year-old patients with acute submassive PE. Clinical outcome probabilities were based on the results of a well-done meta-analysis of clinical trials evaluating LMWH compared to UFH for PE treatment. The cost estimates used were mainly derived from Medicare reimbursement. Table 1 of the manuscript is 2.5 pages long and gives an extensive description of the different costs considered in this analysis. Total cost for inpatient treatment of PE was \$221 (1.7%) lower with SC LMWH (\$12,780) compared to IV UFH (\$13,001). While the cost of initial therapy was higher in the LMWH group, it was eventually offset by the improved efficacy and reduced costs for early complications. From the societal perspective, LMWH provided an increase in quality-adjusted life expectancy of approximately

0.184 years. While this seems like a minimal difference, it does produce a \$1,209 per quality-adjusted life-year saved. This would be considered a highly cost effective therapy. In the sensitivity analysis, LMWH therapy was cost saving if as few as 5% of patients were treated at home, 8% of patients were able to be discharged early, or the cost of the LMWH was reduced by \$51.

### Quality Improvement

**Chiquette E, Amato MG, Bussey HI.** Comparison of an anticoagulation clinic with usual medical care. *Arch Intern Med* 1998;158:1641-7.

This was the first substantive, observational report evaluating clinical outcomes in newly anticoagulated patients cared for in a pharmacist-managed anticoagulation clinic compared to usual medical care. Patients enrolled in the anticoagulation clinic had a lower incidence of INR values over 5 (7% vs. 14.7%) and longer (9.8% vs. 3.5%) and spent less time at an INR greater than 5 (13% vs. 23.8%) than patients managed by usual medical care. The incidence of significant bleeding (8.1% vs. 35%), major fatal bleeding (1.6% vs. 3.9%) and thrombotic events (3.3% vs. 11.8%) were lower in patients managed by the anticoagulation clinic. The lower rate of warfarin related hospitalization (5% vs. 19%) and visits to the emergency department (6% vs. 22%) reduced costs by at least \$162,058 per 100 patients, clearly demonstrating the positive impact on improved patient care and cost savings when warfarin management is provided by a specialized clinic.

**Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ.** Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. *Chest* 2005;127:1515-22.

Using a large outpatient database from a single HMO centralized telephone call back clinic, the impact of an anticoagulation management service run by clinical pharmacists was compared to usual care in this retrospective, observational analysis. The primary outcome was complications related to anticoagulant therapy (major bleeding, thromboembolism, or fatal bleeding or thromboembolism) and was 39% lower in the patients managed by the anticoagulation service. In addition, the number of patients within the INR target range was

higher in the anticoagulation management service compared to usual care (63.5% vs. 55.2%;  $p < 0.001$ ). No difference in major bleeding or fatal complications was noted, however, the incidence of higher INRs during major bleeding was reduced (4.3% vs. 3.1%) with pharmacist oversight. This analysis involving 6,645 patients demonstrated that pharmacist-managed anticoagulation in the outpatient setting reduced thromboembolic complications by increasing the amount of time the INR was in the target range.

**Mamdani MM, Racine E, McCreadie S, Zimmerman C, O'Sullivan TL, Jensen G, Ragatzki P, Stevenson JG.** Clinical and economic effectiveness of an inpatient anticoagulation service. *Pharmacotherapy* 1999;19(9):1064-74.

This analysis provided one of the first evidence that pharmacists involved in managing anticoagulation therapy in the inpatient setting can improve outcomes while reducing associated costs. In this report 50 patients in either a pharmacist-managed or usual care group were assessed. Although no difference in the primary therapeutic endpoint of time between starting heparin therapy and surpassing the aPTT therapeutic threshold occurred, earlier initiation of warfarin and shorter hospital stays (5 vs. 7 days;  $p = 0.05$ ) were noted. This investigation demonstrated a significant cost savings while improving the management of inpatients requiring anticoagulation therapy.

**Dager WE, Branch JM, King JH, White RH, Quan RS, Musallam NA et al.** Optimization of inpatient warfarin therapy: Impact of daily consultation by a pharmacist managed anticoagulation service. *The Annals of Pharmacotherapy* 2000;34(5):567-72.

This analysis also provided one of the first evidence that pharmacists involved in managing anticoagulation therapy in the inpatient setting can improve outcomes while reducing associated costs. In this report warfarin management with a pharmacist consultation was compared to a historical cohort. A reduction in hospital stay and critical INR values in addition to the number of days over target were observed when adding management advice from a pharmacist. Although the numbers were too small to reach statistical significance, readmission rates for bleeding or thromboembolism at 3 months were lower with pharmacist assistance. This investigation also demonstrated a significant cost

savings while improving the management of inpatients requiring anticoagulation therapy.

**Bond CA, Raehl CL.** Pharmacist provided anticoagulation management in United States hospitals: death rates, length of stay, medicare charges, bleeding complications, and transfusions. *Pharmacotherapy*. 2004;24:953–63.

This analysis used the 1995 National Clinical Pharmacy database and the 1995 Medicare database for hospitals to evaluate the impact of pharmacist-managed inpatient anticoagulation services in 717,396 patients in 955 hospitals. The presence of either an inpatient warfarin management service or an inpatient heparin management service provided by pharmacists resulted in a significant reduction in mortality, bleeding complications, number of transfusions used, and hospital length of stay. These significant clinical outcomes resulted in considerable cost savings. This document is the most compelling evidence to date supporting that anticoagulation therapy managed by pharmacists in the inpatient setting leads to improved patient care while reducing associated cost of care.

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