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Introduction

Pulmonary embolism (PE) remains a major challenge in medicine. Historically, any type of physician may be called on to diagnose and manage PE. Frustratingly, mortality rates may approach 30% in medical patients with untreated PE. With rapid identification and appropriate therapy, however, mortality is dramatically reduced. Early and accurate diagnosis of this potentially fatal condition is therefore of the utmost importance.

Although much has been written on risk assessment, less attention has been given to the recent technologic advances that enable quick and accurate diagnosis of PE. Pulmonary angiography has long been held to be the “gold standard” for definitive diagnosis, yet newer modalities have emerged to challenge this assumption. Recently, computed tomographic pulmonary angiography with or without imaging of the lower extremities has all but replaced traditional angiography. In the first article of this supplement to The American Journal of Medicine, Drs. Seth Clemens and Kenneth V. Leeper review the evidence on the relative accuracies and limitations of these newer modalities, concluding with how they fit into an algorithm for first-line evaluation of PE.

Additionally, this supplement focuses on several areas of active controversy. The ease of introduction of inferior vena cava filters and the advent of retrievable devices have led to their expanded use. Yet, according to current evidence-based guidelines, they are recommended only for patients with proven venous thromboembolism (VTE) and an absolute contraindication for anticoagulation, a complication of anticoagulation, or recurrent VTE despite adequate anticoagulation. Dr. Mark A. Crowther reviews the limited evidence currently available on these devices.

Although outpatient management of patients with deep vein thrombosis is becoming more widely accepted, outpatient treatment of persons with PE remains an area of uncertainty. Yet, new data are emerging to show that outpatient treatment may be feasible for selected patients who are deemed to be at low risk based on careful risk stratification. Following an overview of the pathogenesis and epidemiology of PE, Drs. Teresa L. Carman and Amjad AlMahameed discuss risk stratification and the available evidence, benefits, and therapeutic options pertaining to outpatient management of these patients.

Thromboembolic disease is now the leading cause of maternal death in the United States. Pregnant women are at increased risk of thrombosis both during pregnancy and postpartum, due to a relative hypercoagulable state that is thought to have evolved to protect them from hemorrhage. Anticoagulation in these patients is challenging, requiring consideration of both maternal and fetal issues. After a review of risk factors for thrombosis in pregnancy and indications for VTE prophylaxis, Dr. Andrea H. James discusses options for prophylaxis, initiation of anticoagulation, and diagnosis and management of VTE in pregnancy, as well as management at parturition and postpartum.

Finally, in today’s world of third-party payers and managed care medicine, pharmacoeconomics is assuming an ever-increasing role. The economic burden posed by VTE is considerable, and pharmacoeconomic analyses have become a useful tool for helping clinicians select appropriate therapy from among similarly effective and safe therapies. In the last article of this supplement, I discuss factors that may affect the relative costs of different approaches to treatment and review recent clinical and pharmacoeconomic data comparing fondaparinux with enoxaparin.

We hope that readers will find the articles in this supplement both thought provoking and useful as a guide for detection and management of an important condition that is potentially devastating, yet treatable if detected in a timely manner.

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References

Newer Modalities for Detection of Pulmonary Emboli

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ABSTRACT

Pulmonary embolism (PE) is the third most common cardiovascular disease after myocardial infarction and stroke in the United States. Early and accurate diagnosis of this condition is imperative because many patients die within hours of presentation. Clinical and laboratory tests can be used to accurately determine the pretest probability of PE. When necessary, imaging techniques are then used to exclude or diagnose PE. Pulmonary angiography is the reference standard for the diagnosis of PE, but it is invasive and has a high morbidity and mortality rate. Ventilation and perfusion (V/Q) scanning in the past has been recommended as the initial diagnostic test for PE; however, this technique also has limitations. Recently, new modalities for the diagnosis and exclusion of PE have been evaluated. These techniques include V/Q single photon emission computed tomography (SPECT), single- and multi-detected computed tomography, and magnetic resonance angiography (MRA) including gadolinium-enhanced MRA, real-time magnetic resonance imaging (RT-MR), and magnetic resonance perfusion imaging.

KEYWORDS: Computed tomography; Diagnosis; Magnetic resonance angiography; Pulmonary embolism; Radiouclide imaging

Pulmonary embolism (PE) is the third most common cardiovascular disease in the United States. In 1999, 140,000 individuals were discharged from the hospital with an acute PE diagnosis. Mortality rates range from 3.5% to 15% and can be as high as 31% to 58% when shock is present. Early and accurate diagnosis of this condition is imperative because PE is unsuspected in 70% of patients who die of the disease. Approximately 65% of patients will die within 1 hour of presentation of PE and 92.9% expire within the first 2.5 hours.

Pulmonary angiography is the reference standard for the diagnosis and exclusion of PE. However, it is invasive (Table 1) and morbidity and mortality rates range from 3.5% to 6% and 0.2% to 0.5%, respectively. In addition, data from a subanalysis of the landmark Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study suggest only moderate reader agreement for identifying PE in smaller, subsegmental arteries. Because newer tests with improved safety have been developed, pulmonary angiography is rarely used as a first-line test for the diagnosis or exclusion of PE.

Ventilation and perfusion (V/Q) scanning in the past was the recommended initial diagnostic test for the evaluation for PE in guidelines last updated in 1999 by the American Thoracic Society (ATS). The major benefit of the V/Q scan is its safety. It is not invasive and radiation exposure is <2.5 mSv. This is 3.76 to 11.2 times lower than the radiation exposure from a computed tomography (CT) scan of the chest. V/Q scanning is also the only imaging modality that does not pose a threat of end-organ toxicity. Because of its safety profile, it is still the recommended study for pregnant or nursing women with suspected PE.

Many of the guidelines for the performance and interpretation of V/Q scans were established in the initial PIOPED study. A planar scanning technique with Xenon gas for the ventilation component was used to collect 2-dimensional (2D) images. Scans were classified into normal, high, intermediate, low, or very low probability categories according to predefined criteria. Clinical pretest probability was also determined.
In patients without prior history of PE, a high-probability scan had a positive predictive value (PPV) of 88%. PPV improved to 96% when combined with a high clinical probability, effectively diagnosing PE. The negative predictive value (NPV) of a normal scan was 96%, high enough to rule out PE regardless of clinical probability. Normal scans were uncommon in this study, occurring in only 14% of patients. The NPV of a low-probability scan was 88% and improved to 96% when combined with a low clinical probability. Thus, a low-probability scan with a low clinical probability score rules out PE as definitively as a normal scan. Finally, 39% of the patients had intermediate scans and 32% of these patients had angiographically proven PE. Although, as shown by the PIOPED study, indeterminate readings are common, the incidence of an indeterminate reading may be as low as 9% if patients present with a normal chest x-ray.

The major limitation of the V/Q scan is that a clot is not directly visualized; its presence is assumed when a mismatched defect is observed. Although a clot is the most likely cause of a mismatch, there are other extravascular causes. These can often be detected with a recent chest x-ray. Also, in theory, a clot must be occlusive or a mismatch will not be visualized. Additional limitations of V/Q scanning are that it captures only 2D images and the radiolabeled isotope used for the ventilation portion of the test is not standardized.

Although there has been much debate on risk stratification and treatment, less attention has been given to the significant advances in the quick and accurate exclusion or diagnosis of PE. Recently, new modalities for the diagnosis and exclusion of PE, particularly CT pulmonary angiography with or without additional imaging of the lower extremities, have been evaluated. This technology has rapidly expanded from single-detector CT to multidetector machines and technologies. The CT scan has some limitations and is not available for all patients with suspected PE. For this reason, other modalities, such as pulmonary magnetic resonance angiography (MRA), are being studied. This article will review these new modalities and their benefits and limitations in clinical practice.

### PRETEST PROBABILITY

The concept of pretest probability is important because most of the diagnostic modalities discussed in this article have their sensitivities, specificities, and predictive values ad-
justed based on the probability of PE before testing. The pretest probability for PE can be most useful when determined using both clinical and laboratory methods.13,15,16

Two methods, the Wells score and the Geneva score, were devised and validated to generate a clinical pretest probability in patients with suspected PE.17,18 Both methods divide patients into low, intermediate, and high PE probability groups. Both methods have similar accuracy, but neither is accurate enough to reliably diagnose or exclude PE on its own.19

D-dimer testing is another method that has been used to evaluate patients with suspected PE. PE results in elevated levels of D-dimer, a fibrin degradation product. The D-dimer is elevated with increased clot lysis and suggests the presence of thrombosis. D-dimer levels are often elevated in other conditions such as infection, active inflammatory disorders, malignancy, pregnancy, and liver failure. Therefore, the D-dimer assay has a very low specificity for PE, ranging from 38% to 83% depending on the assay used, and cannot rule in PE as a diagnosis.20 The D-dimer assay has excellent sensitivity; a normal D-dimer level can rule out PE without further work-up.21

Many methods are available to measure D-dimer levels and they are not all of equivalent utility (Table 2).20 The major methods include the enzyme-linked immunosorbent assay (ELISA); rapid quantitative ELISA; rapid semiquantitative ELISA; rapid qualitative ELISA; and the quantitative, semiquantitative, and whole-blood latex agglutination methods.20 To date, only the VIDAS D-dimer assay (bioMérieux, Inc., Marcy l’Etoile, France), a rapid quantitative ELISA, has been shown to have a high enough sensitivity (96.4%)21 to rule out PE in the absence of a calculation of clinical pretest probability.21,22

Several studies have evaluated the sensitivity of a negative D-dimer result combined with a low or intermediate clinical probability score.15,16,23 These studies demonstrated that a negative D-dimer by rapid quantitative ELISA can be combined with a clinical probability score to exclude PE as a diagnosis and can eliminate further work-up in 32% to 44% of patients with suspected PE.15,16 Caution should be taken with other, less sensitive D-dimer laboratory methods, and this rule may not apply to the latex agglutination assays.

NEWER MODALITIES FOR RADIOGRAPHIC IMAGING FOR PULMONARY EMBOLISM

V/Q Single Photon Emission Computed Tomography

V/Q single photon emission computed tomography (SPECT) may improve both the sensitivity and specificity of the V/Q scan. In a study in artificially embolized pigs, lung SPECT scanning improved the sensitivity of planar scanning from 64% to 91% and the specificity from 79% to 87%.24 In a retrospective study, Reinartz and colleagues analyzed 83 patients who had undergone 4-slice spiral CT, V/Q planar, and V/Q SPECT. Using the diagnosis of a consensus panel as the reference standard, the sensitivity, specificity, NPV, and PPV for the SPECT technique were 97%, 91%, 98%, and 90%, respectively.

This study used a protocol that differed from that used in the PIOPED study. In addition to the SPECT technique, technetium aerosol was used for the ventilation portion of the V/Q scan. Technetium is believed to be superior to other isotopes that have been used in the past for the ventilation portion of the V/Q scan. Xenon, the initial radioisotope used for V/Q scanning in PIOPED, has a low (1% to 3%) efficiency of pulmonary deposition.26,27 Technetium is approximately 5 times smaller in diameter (90 nm) than xenon and has nearly a 20% efficiency of pulmonary deposition. Few data exist on the extent to which this may improve the results of V/Q scanning. A study by Trujillo and colleagues did demonstrate that the use of technetium decreased the false-negative rate by 9% and the number of indeterminate scans by 18% compared with PIOPED.

V/Q scan interpretation also differed from that proposed by the PIOPED investigators. In the Reinartz group’s study, all mismatched defects, regardless of level, were considered to be PEs. Scans were read as either “embolism confirmed” or “embolism disproved,” eliminating the indeterminate interpretation. Indeterminate readings greatly limit the utility of traditional V/Q scans. An indeterminate result is nondiagnostic and requires further testing. This reading is fairly common, occurring in 39% of cases,13 delaying the time to diagnosis, decreasing the convenience to the patient and physician, and increasing the cost of the work-up. Although normal and high probability readings can be helpful in the correct clinical setting, these interpretations are less frequent, occurring 14% and 13% of the time, respectively.13 Improving the interpretation criteria is perhaps the single most important improvement that can be made to V/Q scanning. Eliminating or minimizing the indeterminate reading without sacrificing sensitivity and specificity would make it a much more attractive test.

Finally, the SPECT technique also has the potential to improve interpretation of the V/Q scan by incorporating computerized interpretations. In a retrospective study of 53 patients by Reinartz and colleagues, traditional reader and automated computer algorithm interpretations were compared with the decision of a consensus panel as to whether PE was present or absent (Table 3). As in their previous study, scans were read as either positive or negative for PE. The computer algorithm resulted in the generation of an artifact in the area of the pulmonary recesses that resulted in 5 false-positive results; however, when the automated and conventional methods were combined, there was only 1 false-positive finding and the sensitivity and specificity were 95% and 97%, respectively. Furthermore, the automated technique correctly evaluated 12 patients who had highly heterogeneous scans because of restrictive or obstructive disease.29

In sum, a normal V/Q scan remains the most sensitive test in the evaluation of PE, continues to be the safest test,
and is still the recommended test for patients who are pregnant, nursing, or who have moderate-to-severe renal failure. Early studies with the SPECT technique suggest it improves the accuracy of the V/Q scan, and it should be the preferred technique for the acquisition of V/Q images. In addition to the SPECT technique, ultrafine aerosols such as technetium should become the standard for the ventilation images. The studies by Reinartz and colleagues\(^2\)\(^{5,29}\) suggest that SPECT technique with ultrafine aerosol can improve the interpretation of the V/Q scan by allowing a PE present or absent reading to be made when all mismatch defects are considered to be PEs regardless of anatomic location. This does not appear to affect the sensitivity of the V/Q scan; however, the data for this are preliminary. The PIOPED categories, although problematic, have been thoroughly studied and validated over 20 years. Although the results of retrospective studies have been promising, all of these techniques should be evaluated prospectively before being used in everyday practice.

**Computed Tomography of the Chest**

**Single-Detector Spiral (or Helical) Computed Tomography Angiography.** Single-detector spiral (or helical) computed tomography angiography (SCTA) uses a single detector and x-ray source that rotate around a patient, allowing multiple cross-sectional images to be obtained as the patient slides through the scanner. This was an important advancement to CT imaging of the pulmonary vasculature, especially for PE. First, it allows the entire study to be completed in 25 to 30 seconds. Nearly 90% of patients evaluated for PE are able to hold their breath throughout the study, eliminating motion artifact from breathing.\(^3\)\(^0\) Second, the spiral technique allows thin 3-mm slices to be obtained, leading to more accurate imaging of the vasculature. By 2001, SCTA had surpassed the V/Q scan as the initial test for the evaluation of PE.\(^3\)\(^1\) However, reports of its accuracy are conflicting. Several studies reported a high specificity but low sensitivity in the evaluation of PE. In studies that used pulmonary angiography as the standard, SCTA specificity ranged from 81% to 100%, but the sensitivity was much lower, ranging from 60% and 67%.\(^3\)\(^2\)-\(^3\)\(^5\) It was concluded that SCTA was inadequate as a stand-alone test for first-line use in the evaluation of PE,\(^3\)\(^4\),\(^3\)\(^5\) especially for clot in the subsegmental pulmonary arteries and arteries of the right middle and lingular lobes.\(^3\)\(^2\),\(^3\)\(^3\)

Blachere and colleagues\(^3\)\(^6\) subsequently evaluated 179 patients with suspected PE using the decision of a consensus panel as the reference standard, with few pulmonary angiograms performed. SCTA specificity was 93.6% and, in contrast to previous results, sensitivity was 94.1%. Lower extremity ultrasound further improved results. Further, in a study by Baile and colleagues,\(^3\)\(^7\) SCTA was equivalent to

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<table>
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<tr>
<th>Table 2</th>
<th>Sensitivity of the α-dimer based on the laboratory technique</th>
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<tbody>
<tr>
<td></td>
<td>Mean (Range)</td>
</tr>
<tr>
<td>ELISA</td>
<td>95% (85%–100%)</td>
</tr>
<tr>
<td>Rapid quantitative ELISA</td>
<td>95% (83%–100%)</td>
</tr>
<tr>
<td>Rapid semiquantitative ELISA</td>
<td>93% (79%–100%)</td>
</tr>
<tr>
<td>Rapid qualitative ELISA</td>
<td>93% (74%–100%)</td>
</tr>
<tr>
<td>Quantitative latex agglutination</td>
<td>89% (81%–98%)</td>
</tr>
<tr>
<td>Semiquantitative latex agglutination</td>
<td>92% (79%–100%)</td>
</tr>
<tr>
<td>Whole blood agglutination</td>
<td>78% (64%–92%)</td>
</tr>
</tbody>
</table>

ELISA = enzyme-linked immunosorbent assay.
Adapted from *Ann Intern Med.*\(^2\)\(^0\)

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Diagnostic efficiency of an automated algorithm compared with conventional reading for interpretation of single photon emission computed tomography ventilation perfusion scans</th>
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<tbody>
<tr>
<td></td>
<td>Conventional Reading</td>
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<tr>
<td>Sensitivity</td>
<td>91%</td>
</tr>
<tr>
<td>Specificity</td>
<td>97%</td>
</tr>
<tr>
<td>NPV</td>
<td>94%</td>
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<tr>
<td>PPV</td>
<td>95%</td>
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<tr>
<td>Accuracy</td>
<td>94%</td>
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NPV = negative predictive value; PPV = positive predictive value.
Adapted with permission from *J Nucl Med.*\(^2\)\(^9\)
pulmonary angiography in a pig model with a methacrylate cast of the pulmonary vasculature as a standard. The sensitivity of pulmonary angiography was 87% and not statistically different from that of single-detector CT scanning.

Several follow-up studies were performed to see whether the sensitivity of SCTA could be improved. A study by Perrier and colleagues found that SCTA combined with lower extremity ultrasonography (N = 299) had a sensitivity of only 70%, despite the fact that ultrasonography improved the false-negative rate from 30% to 21%. In a similar study, when clinical probability was low or intermediate and SCTA and lower extremity ultrasonography were negative, the incidence of venous thromboembolism (VTE) in the absence of therapy was 1.8% at 3 months. Of concern, 16% of patients with a negative SCTA had positive lower extremity ultrasonography that resulted in treatment. Regardless, this study suggested that a negative SCTA with lower extremity ultrasound in the correct clinical setting was sufficient for ruling out PE as a diagnosis.

Benefits and Limitations of SCTA. Despite its poor sensitivity, several factors make SCTA a desirable method for evaluating PE. SCTA does have high specificity, and a positive finding can be treated with confidence. Unlike the V/Q scan, SCTA directly identifies the presence of a clot, and false-positive results, such as extraluminal compression, radiation effects, and others that may be reported with the V/Q scan, are eliminated. In addition, SCTA allows imaging of the lung parenchyma, chest wall, and mediastinum, so that alternative diagnoses may be made when PE is absent, eliminating the need for additional studies. Kim and colleagues reported that 67% of patients in whom PE was ruled out by SCTA had a finding that suggested or confirmed an alternative diagnosis such as pneumonia, pulmonary fibrosis, or trauma. Similar findings were reported in 2 other studies in which SCTA identified an alternative diagnosis in 31% and 21.2% of patients. Regardless of the discrepancy in rates, these findings are important because neither the V/Q scan nor pulmonary angiography can reliably detect alternative conditions.

Contributing to the poor sensitivity of SCTA is its resolution. Although it visualizes main, lobar, and segmental arteries relatively well, it does not image the subsegmental arteries well. Subsegmental PEs may account for 6% to 30% of all emboli. At best, SCTA detects 61% to 79% of these clots.

CT scanning is a significant source of radiation exposure in the hospital setting. Although CT scans account for only 4% of all radiologic examinations performed, they account for 40% to 75% of medical radiation exposure. The measured effective dose from CT scans has been estimated at 7.5 mSv, and doses of 50 to 200 mSv begin to increase the risk for cancer. This is especially true in patients who receive serial studies and in women who receive radiation to the breast. Exposure of women aged <35 years to radiation from CT scanners may increase the risk for breast cancer by 102%. Radiation exposure is also a concern in pregnancy. Studies using Monte Carlo models have suggested that helical CT scans can be used in pregnancy, but current guidelines still recommend V/Q scanning for the evaluation of PE. Although shielding with bismuth can be performed, it may reduce the average dose to the female breast by only 57%.

Reaction to the contrast used to perform the SCTA can also limit its utility. Mild reactions to contrast media including flushing, nausea, vomiting, and pruritus occur in up to 15% of patients. Severe and very severe reactions including convulsions, laryngeal edema, bronchospasm, and cardiovascular collapse occur much less frequently (0.22% and 0.04% of patients, respectively). The use of low-osmolality contrast media decreases the incidence of all of these reactions. Contrast-induced nephropathy (CIN), a long-recognized complication from iodinated contrast exposure, is another limitation of CT scanning. It is the third most common cause of acute renal failure in the hospital setting, and it is associated with increased in-hospital mortality, 1-year mortality, and increased length of hospital stay. Although generally self-resolving, CIN can result in the need for dialysis.

Finally, in a recent study of CT angiography of the chest, as many as 25% of patients had a contraindication for the test. Preexisting renal failure and pregnancy were the primary conditions that prevented this mode from being used as the primary test for the evaluation of PE.

Multidetector Spiral Computed Tomography: Improving on an Improvement. Multidetector spiral computed tomography (MDCT) technology quickly followed SCTA, improving on the same concept. With MDCT, multiple detectors are staggered and rotated around the patient as they slide through the CT scanner. Initially, 4 detectors were used for MDCT, but this quickly progressed to 6-, 8-, 10-, 16-, 32-, and 64-detector technology. The use of more detectors shortens the time of the study to <10 seconds and allows for cuts as thin as 0.5 mm to be obtained. This greatly improves the resolution of the study, allowing for imaging out to sixth-order pulmonary arteries. Consequently, MDCT improves the detection of segmental and subsegmental PEs, decreasing false-negative results and improving sensitivity.

Thinner slices have also allowed for computed reconstruction of the axial images into 3D models, which, although not yet demonstrated, may decrease the amount of artifact and number of false-positive findings. Thin slices also allow CT images to be reconstructed retrospectively using electrocardiographic reconstruction based on their relation to the R-R interval. This eliminates cardiac artifact, allowing better visualization of the coronary arteries and thoracic aorta.

Several important articles published in recent years have evaluated MDCT for the evaluation of PE. The primary objective of PIOPED II, published in 2006, was to determine the accuracy of MDCT for the diagnosis and exclusion of PE in patients with suspected PE. PIOPED II enrolled
824 patients with a component of a composite reference standard (Table 4) that was either positive or negative for PE. Patients underwent MDCT of the chest followed by CT venography (CTV) of the lower extremities. The majority of MDCT studies were performed with 4-row detector scanners, but 8- and 16-row detector scanners were also used. Results were compared with a composite reference standard (Table 4).

The sensitivity and specificity of MDCT of the chest alone were 83% and 96%, respectively. Sensitivity and specificity were 90% and 95%, respectively, with MDCT/CTV. These results suggest that MDCT has sufficient specificity to diagnose PE without further testing, but, due to a false-negative rate of 17%, it does not appear to be adequate as a stand-alone test to rule out PE as a diagnosis. However, MDCT/CTV may adequately rule out PE in most patients. When the clinical assessment does not agree with the MDCT/CTV findings, additional tests are necessary.

This study was important for its evaluation of MDCT in the diagnosis and exclusion of PE, but was also important in that it studied a set of tests, the composite reference standard (Table 4), that could be used in lieu of MDCT or pulmonary angiography to diagnose or exclude PE. Because pulmonary angiography is particularly poor at identifying PEs at the subsegmental artery level and MDCT has an improved ability to visualize PEs at this level, MDCT could be positive when pulmonary angiography is negative. To address this problem, the PIOPED investigators created a composite standard that, when satisfied, could diagnose or exclude PE (Table 4). The study was not designed to calculate the specificity of the composite reference standard; however, of 590 patients with a composite reference standard negative for PE, only 2 (<1%) had a follow-up event in the next 6 months. This suggests that the composite standard is a powerful set of tests that can be used to reliably exclude PE without pulmonary angiography or CT scanning.

Two studies have validated the use of MDCT. Perrier and colleagues evaluated patients with an abnormal d-dimer test or a high clinical probability for PE by the modified Wells score. Patients underwent CT scanning of the chest, with MDCT performed in 88% of patients. A total of 1,436 patients had negative CT scans and were not treated. The incidence of a VTE event in these patients at 3 months was 1.3%. An alternative diagnosis was found in 21.5% of patients with a scan that was negative for PE. Interestingly, the incidence of PE in this population (20%) was comparable or even lower compared with previous studies, suggesting that MDCT does not result in additional false-positive results or in the detection of smaller, potentially clinically irrelevant PEs. These results suggest that MDCT in patients with suspected PE, abnormal d-dimer, or high clinical probability is adequate for the evaluation of PE without further diagnostic testing.

Limitations of MDCT. One concern with MDCT is that it detects PE at the subsegmental level. PEs isolated to the subsegmental level were found in 7% of the patients in the study by Perrier and colleagues. Furthermore, all studies have reported detection of isolated subsegmental PEs with MDCT in as many as 36% of patients. The significance of subsegmental PEs, especially those in arteries out to the fifth and sixth generation, is unknown, as is the importance of treating them. Subsegmental PEs may not be acutely dangerous to the patient, but may predict the potential for a future, more severe embolism. It may also identify patients at risk for the development of pulmonary hypertension. Regardless of importance, MDCT does not seem to increase the diagnosis of PE even at the subsegmental level. If the use of MDCT did lead to an increased diagnosis
of isolated subsegmental clots, the incidence of PE in MDCT studies should be higher than those performed with other methods. In the original PIOPED study, the incidence of PE was 33% with pulmonary angiography,\textsuperscript{13} compared with 23.3%,\textsuperscript{49} 26%,\textsuperscript{56} and 20.4%\textsuperscript{16} with MDCT in the PIOPED II, Perrier, and Christopher Studies, respectively. It should be noted that these studies used mostly 4-detector scanners and more detectors should increase the detection of subsegmental PE and may affect the incidence of PE in future studies.

As with SCTA, MDCT exposes patients to radiation exposure and the risk of CIN. It is worth noting that radiation exposure is significantly greater with MDCT. A 4-row MDCT may increase radiation exposure by 30% to 100% when compared with SCTA. Additional detectors do not increase exposure, mostly because they enable the scans to be completed in a shorter time with more efficient use of radiation.\textsuperscript{42} Finally, about 25% of patients with a suspicion of PE will have a contraindication for MDCT scanning, such as pregnancy or renal insufficiency that will require alternative tests.

In sum, single- or multidetector CT scanning has an excellent specificity for the diagnosis of PE, and patients with a positive study should be treated with confidence. Overall, these studies demonstrate that, due to its low sensitivity, the utility of SCTA as the sole, initial test for the evaluation of PE is in question and further study is warranted. SCTA does not appear to have adequate sensitivity to exclude PE as a diagnosis, but imaging of the lower extremities with either ultrasonography or CTV can improve its ability to exclude PE.

The advantages of MDCT over SCTA include decreased time to complete the study, and a negative 4-detector CT scan can be used to rule out PE as a diagnosis with a 3-month risk for a subsequent VTE of only 1.3% to 1.7%.\textsuperscript{16,56} CTV of the lower extremity would further decrease this risk.\textsuperscript{49} At the same time, use of 4-detector MDCT scans does not appear to increase the incidence of PE and does not result in increased use of anticoagulation therapy. However, in the near future, 4-detector MDCTs are likely to be replaced by 16-, 32-, and 64-detector scanners that will detect smaller PEs of unknown significance. The results of many of the studies that have been discussed likely cannot be generalized to these new scanners. These smaller PEs may not be acutely dangerous to the patient, but they may predict the potential for a future, more severe embolism or for the development of pulmonary hypertension from chronic thromboembolic disease. These patients will likely need to be treated differently than a patient with a single acute PE.

Finally, although MDCT scanners are an excellent first-line test for the evaluation of PE, they are not without risk to the patient, and the number of CT scans should be limited. At the least, MDCT scanning should be reserved for patients with either a high clinical Geneva score, PE-likely modified Wells score, or those with an abnormal D-dimer test regardless of clinical probability.

**Magnetic resonance angiography**

Recent advances in magnetic resonance imaging (MRI) technology have made imaging of the chest, and particularly the vascular structures, feasible. Specifically, the development of parallel imaging has greatly decreased the amount of time necessary to complete a study, allowing images to be acquired during a short breath hold of 20 seconds.\textsuperscript{66} MRI is attractive for 2 reasons. First, it does not use ionizing radiation to generate images, and it is thought to be completely harmless to a patient. Although not well established, it is felt to be safe for use during pregnancy. Second, the contrast agent used is thought to be much less nephrotoxic. There are even some MRI techniques that can image the pulmonary vasculature without the use of contrast. Data on the accuracy of these techniques is still limited but growing, and MRI with MRA of the pulmonary vasculature is making its way into clinical practice.

The 3 most commonly used MRI techniques are gadolinium-enhanced MRA (Gd-MRA), real-time MRI (RT-MR), and magnetic resonance (MR) perfusion. The accuracy for the evaluation of PE differs with the different techniques.

**Gd-MRA.** Gd-MRA is perhaps the most common MRA method currently used to evaluate a patient for PE. In the largest study of Gd-MRA, conducted by Oudkerk and colleagues,\textsuperscript{61} 118 patients underwent Gd-MRA followed by pulmonary angiography, and 2 independent readers interpreted the Gd-MRAs. Gd-MRA sensitivity was 77% and specificity was 98%. Although Gd-MRA identified all emboli in the central and lobar arteries, its sensitivity was only 40% for isolated subsegmental emboli. Sensitivity improved to 72% when all subsegmental emboli were included. Similar results were reported in smaller studies\textsuperscript{62,63} and in a study that compared Gd-MRA with 16-row MDCT as the reference standard.\textsuperscript{64}

The high specificity of Gd-MRA allows patients with a positive study to be treated for PE with confidence. However, at this time, its sensitivity as a single test is not high enough to reliably exclude PE, particularly in the distal, subsegmental arteries. Larger, prospective studies are needed before Gd-MRA gains routine use as the initial test for the evaluation of PE. A study by the PIOPED investigators is currently underway that will compare Gd-MRA with a composite reference standard in 710 patients.

**RT-MR.** RT-MR uses technology similar to that used for electrocardiographically gated CT scanners to acquire images of moving organs. When used for the evaluation of PE, RT-MR is timed to take images gated to a patient’s respiratory cycle. This modality has 2 advantages. First, it eliminates the need for a breath hold. Second, RT-MR sequences produce T2-weighted images, which allow for imaging of thrombus without the need for contrast.\textsuperscript{65}
In a study by Haage and colleagues, pigs with artificially induced PE were evaluated by pulmonary angiography (standard), CT scanning using 3-mm slices, Gd-MRA, and RT-MR. The sensitivities for CT, Gd-MRA, and RT-MR were 71.0%, 80.3%, and 97.7%, respectively. RT-MR detected all but 1 of the emboli detected by pulmonary angiography. There were no subsegmental emboli in this study because the size of the artificial emboli was greater than the diameter of the subsegmental arteries. Based on these results, RT-MR for the evaluation of PE was studied in humans.

There are few published studies comparing RT-MR with other modalities. In a study by Kluge and colleagues, 62 patients with signs and symptoms of PE underwent 16-row MDCT (standard), Gd-MRA, RT-MR, and MR perfusion imaging. The incidence of PE was 31% and the sensitivity and specificity of RT-MR were 85% and 98%, respectively. The sensitivity of RT-MR was superior to that of Gd-MRA (77%), and the specificities were essentially the same. Although RT-MR showed continued excellent specificity, its sensitivity was not nearly what might be expected based on the preclinical study and does not appear to be high enough to allow its use as a stand-alone test for the evaluation of PE.

Aside from a possible increased sensitivity, RT-MR provides additional benefits over Gd-MRA. In a second study, Kluge and colleagues went on to compare RT-MR with Gd-MRA for the evaluation of PE. There was no true reference standard for this study, and sensitivity and specificity calculations should be viewed with caution and are not discussed. The secondary objective of this study was to determine which test was better tolerated by patients and less prone to artifact. Patients were staged based on their level of dyspnea from asymptomatic to severe with decreased blood pressure. Studies were defined as nondiagnostic if ≥3 lobar arteries or ≥50% of the segmental arteries could not be visualized or could not be evaluated for PE secondary to blurring of the vasculature. There were no nondiagnostic studies using RT-MR regardless of dyspnea stage, whereas 36% of Gd-MRA studies in patients with dyspnea and agitation were nondiagnostic, as were 5 of 5 Gd-MRA studies in patients with severe dyspnea and decreased blood pressure. The nondiagnostic studies were attributed to motion or breathing artifact. The results of these studies suggest that RT-MR has increased sensitivity compared with Gd-MRA and produces fewer nondiagnostic studies.

**MR Perfusion.** MR perfusion images use contrast agents that cause local disturbances in a magnetic field that can be measured by an MR scanner. Gadolinium is frequently the contrast agent used, and perfusion studies can be performed immediately after Gd-MRA. The patient does not need to perform a breath hold for an optimal study. Perfusion images do not directly image vascular structures, but rather generate a signal based on the volume of blood in a region. MR perfusion studies act in a similar fashion as nuclear medicine perfusion studies, in that areas where blood flow is decreased or absent suggest areas where blood flow is obstructed. This acts as indirect evidence of PE. Although clinical studies of MR perfusion are limited, it is hoped that MR perfusion will perform better with respect to identifying peripheral thrombus in the subsegmental arteries than Gd-MRA and RT-MR.

Kluge and colleagues evaluated the agreement of MR perfusion with SPECT perfusion in 41 patients with suspected PE. MR perfusion identified 14 of 15 patients with PE by SPECT. The k-scores for agreement between the methods were 0.98, 0.83, and 0.69, at the lobar, segmental, and subsegmental levels, respectively. In a second study that compared MR perfusion with 16-row MDCT in 62 patients with suspected PE, the sensitivity and specificity for MR perfusion were 100% and 91%, respectively.

Contrast-enhanced perfusion studies frequently are performed in conjunction with Gd-MRA. Kluge and colleagues evaluated this method in a study using 16-row MDCT as the reference standard. The protocol called for initial RT-MR followed by Gd-MRA and, finally, perfusion MR. The combined protocol results were defined as the consensus interpretation between 2 blinded radiologists after the 3 tests were reviewed. This combined protocol had a sensitivity and specificity of 100% and 93%, respectively. The average time for a patient to complete all 3 studies was 9 minutes and 56 seconds.

**Advantages and Limitations with MRI.** To date, MRI is not thought to be harmful. Although not thoroughly studied in pregnant women, it is thought to be safe in this population as well. It is finding increasing utility for the diagnosis of conditions in both the woman and the fetus that are not completely identified by ultrasound. In addition, there is no known end-organ toxicity from exposure to MRI.

The major concern with MRI for the evaluation of PE is its lack of sensitivity. Although there are few studies of this technique to date, there is already a trend toward a reproducible sensitivity in the range of 75% to 93%. In the future, combining MRI with imaging of the lower extremities may prove to be adequate to rule out PE.

There are contraindications for MRI, the most important of which is the presence of an electronic implanted device. Fatal arrhythmias have been attributed to cardiac pacemaker malfunctions during an MRI, and pacemakers are considered an absolute contraindication. Nerve stimulators, continuous medicine pumps (e.g., epoprostanol), cardiac defibrillators, insulin pumps, cochlear implants, and some prosthetic devices should be considered contraindications as should residual metallic fragments (shrapnel, bullets), which may move during the course of an MRI. Although rare, burns in patients with tattoos have been reported.

Gadolinium-based contrast agents are thought to be less toxic than ionic contrast agents used for fluoroscopy and CT scanning. The incidence of adverse events associated with gadolinium contrast is 1.47%. At least 69% of these reactions are mild in nature. Severe reactions, such as anaphylaxis, occur in 0.0003% of patients. Gadolinium, a preg-
to be progressive, and may be fatal.\textsuperscript{71}

clusively in patients with chronic renal insufficiency, tends
have been reported worldwide since 1997) that occurs ex-
fibrosis (NSF). NFD/NSF is a rare condition (only 215 cases
recently have been implicated in the development ofnephro-
genic fibrosing dermopathy (NFD)/nephrogenic systemic
fibration (FDA)–approved doses, gadolinium-containing agents
addition of contrast with respect to the risk to the patient for
this condition.

In sum, MRI and MRA of the pulmonary vasculature is
a rapidly developing technology for evaluating PE. The
accuracy of MR for evaluating PE is dependent on the
technique used. When these techniques are used as stand-
alone tests, they have a high specificity for diagnosing PE,
but sensitivity is not high enough to reliably exclude PE
without additional testing. However, when combined to
evaluate PE, these techniques have a sensitivity and speci-
ficity that rivals 4-row MDCT.

Although encouraging, the data for MRI are insufficient
to suggest this as a first-line study for the evaluation of PE.
Although more attractive than V/Q scanning because there
is direct visualization of thrombus and no risk of an inde-
terminate reading, it should probably be ranked below this
modality as well. Although not ideal, the reproducible de-
pendability of readings such as normal, low-probability, and
high-probability V/Q scans will allow the physician to make
treatment decisions with more confidence than with MRI.
Additional large, prospective studies such as PIOPED III
may provide data to better support MRI in the future.

Although MRI is very safe, the addition of gadolinium
contrast adds additional risk to the study. Currently, RT-MR
can be performed without contrast. There are also MR
perfusion techniques that eliminate the need for contrast as
well. Until these techniques are better studied, it is unlikely
that they will replace V/Q scanning as the test of choice for
pregnant patients or patients with end-stage renal disease.

Current evidence supports the use of an algorithm that
incorporates clinical probability, d-dimer testing, and MDCT
scanning for first-line evaluation of suspected PE. When clini-
cal probability is low or intermediate by the Geneva score or
PE-unlikely by a modified Wells score, a d-dimer assay should
be obtained. If the d-dimer is negative, PE can be ruled out,
preventing further testing in one third of patients with sus-
pected PE. If the d-dimer is high or the clinical probability
is high, MDCT of the chest should be performed. The decision
to treat can be made based on the results of this study. Con-
current CTV of the lower extremity may be performed to
further improve the sensitivity of the study. No additional
contrast is needed, and the additional time and risk to the
patient is negligible. This is a simple, efficient, and accurate
strategies for most patients; however, this algorithm will be
contraindicated in one sixth to two thirds of patients, most of
whom will be pregnant or have renal insufficiency.

In this population, d-dimer assay is still useful, and this
part of the algorithm should remain intact. V/Q scanning,
ideally using SPECT technique, is probably the best test to
use in these patients because of its well-documented safety
profile. An indeterminate reading is still a possibility and
would likely require further work-up. If MRI is the chosen
modality, a combined study using RT-MR, Gd-MRA, and
contrast-enhanced MR perfusion seems to have an accuracy
that is adequate for the evaluation of PE. However, this is
based on only 1 fairly small study; larger studies must be
performed.

Contrast studies should be avoided in patients who are
pregnant or who have advanced renal failure and should be
used with caution in those with moderate renal insuffi-
ciency. RT-MR should be the preferred imaging technique
in this population so that gadolinium contrast can be
avoided. In the absence of contrast, MRI is essentially
harmless to a patient. In the few studies of this technique,
the sensitivities and specificities have been shown to be
similar to those of SCTA. Intuitively, it stands that its
results should be interpreted in a similar fashion. Specific-
ally, negative exams should not be satisfactory for ruling
out PE, and additional testing, such as imaging of the lower
extremities, should be pursued to verify a negative finding.
This may change as more data become available on MRI,
but to date, there have been no clinical validation studies
that determine treatment based on the result of MR tech-
niques. Until that time, caution should be used when making
treatment decisions based on their results.

**SUMMARY**

In the past 10 years, a wealth of data have emerged con-
cerning the best way to diagnose or exclude PE. The optimal
method must be sensitive (important because untreated PE
is often fatal) and specific (important to avoid unnecessary
anticoagulation). In addition, the number of tests required to
achieve an adequate sensitivity and specificity must be min-
imized for patient safety and improved cost-effectiveness.

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Pfizer Inc., and has received honoraria from Kimberly-Clark, Ortho-McNeil, and Pfizer Inc.

References


Inferior Vena Cava Filters in the Management of Venous Thromboembolism

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ABSTRACT

Inferior vena cava (IVC) filters, both retrievable and permanent, are indicated for the prevention of pulmonary embolism (PE) in patients contraindicated for anticoagulant therapy, in those with anticoagulant therapy complications, and perhaps for those with recurrent PE despite therapeutic anticoagulation. Because of the lack of randomized controlled trials (only 1 has been published), clinicians have little evidence-based information to assist them in determining proper use of IVC filters. The introduction of retrievable filters and the ease of insertion have stimulated increased use of these devices without strong evidence or follow-up to assess either efficacy or longer-term clinical outcomes. Current evidence-based guidelines recommend IVC filter insertion only in patients with proven venous thromboembolism and an absolute contraindication for anticoagulation. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Deep vein thrombosis; Evidence based practice; Inferior vena caval filters; Pulmonary embolism; Recurrent thrombosis

Systemic anticoagulation is the therapy of choice for all forms of venous thromboembolism (VTE); however, anticoagulant therapy is contraindicated in a small subgroup of patients. Without anticoagulation, patients with VTE are at high risk for developing pulmonary embolism (PE), which is fatal in as many as 25% of patients.1 Interruption of the inferior vena cava (IVC) with implantable filtering devices should be considered in patients with VTE in whom anticoagulation is contraindicated.2 Filters are typically placed within the infrarenal IVC and function to capture emboli that would result in PE.3

Institution or resumption of anticoagulation is recommended as soon as possible in all patients in whom IVC filters are placed2 because filters are not effective for deep venous thrombosis (DVT) prevention and can, in fact, be associated with recurrent DVT, presumably owing to increased outflow obstruction at the level of the filter.4

Both permanent and retrievable filters are approved in the United States for the prevention of PE in individuals with acute DVT or PE. Despite their approval, there is a striking lack of rigorously performed clinical studies, and there are known safety concerns that warrant careful consideration of the use of IVC filters.4–6 However, with the introduction of retrievable filters, bedside insertion techniques, and ultrasound guidance, the use of IVC filters has rapidly increased and expanded beyond the recommended indications. The purpose of this article is to review the recommended and expanded indications for IVC filters in the management of VTE and to discuss the lack of data to support expanded indications as well as the safety and efficacy concerns with their use.

INDICATIONS FOR INFERIOR VENA CAVA FILTERS

Recommended Use

Evidence-based guidelines from the American College of Chest Physicians (ACCP) recommend IVC filter placement only in those patients with proven VTE with a contraindication for anticoagulation, a complication of anticoagulation treatment, or recurrent VTE despite adequate anticoag-
ulation treatment (Table 1). Although not specifically included in the ACCP guidelines, the insertion of IVC filters in patients with recurrent PE complicated by pulmonary hypertension is also a widely recognized indication.5

Filter insertion is only indicated in patients with proven VTE, and either an absolute contraindication for anticoagulant therapy or a planned major surgery.7 High risk for bleeding, such as an intracranial bleed, uncorrected major coagulopathy, or incomplete spinal cord injury associated with suspected or proven perispinal hematoma is often considered a contraindication for anticoagulation. However, the risk for bleeding as a complication of anticoagulant therapy should be evaluated in the context of both the risks of filter placement and the potential reduction in future VTE with systemic pharmacologic therapy.7,8

Expanded Indications

Despite the strong recommendations against their use, a complete lack of evidence of their safety and efficacy, their invasiveness and known potential toxicity, and the potential medicolegal peril associated with their unneeded placement, there has been a recent dramatic expansion of IVC filter use. A retrospective study conducted through the National Hospital Discharge Survey (NHDS) database found that the number of IVC filters placed in the US increased almost 25-fold, from an estimated 2,000 placed in 1979 to an estimated 49,000 placed in 1999.9

IVC filters are often used for indications beyond those specified in evidence-based guidelines. Commonly proposed uses include treatment of DVT in patients with cancer or burn injury or pregnant patients who do not have a high risk for bleeding, and PE prophylaxis in high-risk trauma or surgical patients with contraindications for anticoagulation; following thrombectomy, embolectomy, or thrombolysis of DVT; or in patients with limited cardiopulmonary reserve or a free-floating ileofemoral thrombus (Table 1).5,10,11 The use of IVC filters in these patient populations is of concern. There are proven effective options for VTE management in these patient populations and there are no controlled data to support broadening of IVC filter indications beyond those recommended by guidelines. In addition, the use of filters in these situations is likely to increase the risk for acute VTE, placing the patient at risk for both the acute and chronic complications of VTE and the additional risks associated with the consideration of the need for anticoagulation.2,7

A multicenter prospective registry of 5,451 patients with confirmed acute DVT enrolled between October 2001 and March 2002 at 183 sites that reported current usage patterns for IVC filters highlighted the apparent overuse of IVC filters as first-line therapy for VTE in preference to effective and less invasive pharmacologic options.3 In this study, 14% of patients enrolled (781 of 5,451) had IVC filters implanted. The most common indications for filter placement in this study were contraindication for anticoagulant therapy (42%) and primary PE prophylaxis in patients with proven DVT (33%); major bleeding from previous anticoagulation therapy (13%) and failure of previous anticoagu-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Use of inferior vena cava filters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommended use according to evidence-based guidelines</strong></td>
<td></td>
</tr>
<tr>
<td>• Proven VTE with contraindication for anticoagulation</td>
<td></td>
</tr>
<tr>
<td>• Proven VTE with complications of anticoagulation treatment</td>
<td></td>
</tr>
<tr>
<td>• Recurrent VTE despite anticoagulation treatment (failure of anticoagulation)</td>
<td></td>
</tr>
<tr>
<td><strong>Expanded use (not guideline recommended)</strong></td>
<td></td>
</tr>
<tr>
<td>• Recurrent PE complicated by pulmonary hypertension</td>
<td></td>
</tr>
<tr>
<td>• Patients with DVT and limited cardiopulmonary reserve or chronic obstructive pulmonary disease</td>
<td></td>
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<tr>
<td>• Patients with large, free-floating ileofemoral thrombus</td>
<td></td>
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<tr>
<td>• Following thrombectomy, embolectomy, or thrombolysis of DVT</td>
<td></td>
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<tr>
<td>• High-risk trauma patients (head and spinal cord injury, pelvic or lower extremity fractures) with a contraindication for anticoagulation</td>
<td></td>
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<tr>
<td>• High-risk surgical patients with a contraindication for anticoagulation</td>
<td></td>
</tr>
<tr>
<td>• Patients with DVT who have cancer, burns, or are pregnant</td>
<td></td>
</tr>
<tr>
<td><strong>Contraindications for filter placement</strong></td>
<td></td>
</tr>
<tr>
<td>• Chronically thrombosed IVC</td>
<td></td>
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<tr>
<td>• Anatomical abnormalities preventing access to the IVC for filter placement</td>
<td></td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
Adapted from Chest.2 Prog Cardiovascular Dis,5 Blood,10 J Am Coll Surg,11 and J Vasc Interv Radiol.12
lation therapy (11%) were additional reasons for filter insertion.³

**INFERIOR VENA CAVA FILTER EFFICACY AND SAFETY**

Clinically meaningful data on the safety and efficacy of IVC filters are lacking. Only 1 randomized controlled trial has been conducted on IVC filter insertion in patients with VTE⁴,⁶; all other published data are primarily from consecutive case series or retrospective case reports.¹⁰,¹²–¹⁶ Overall, the studies in the literature failed to collect data in a consistent form to allow comparative assessment of the relative safety and effectiveness of the IVC filters.¹⁰,¹²,¹⁷ Most published studies lacked controls and used various methodologies and differing patient populations. In addition, in the majority of studies, data were obtained for follow-up by chart reviews, questionnaires, or clinic visits and only a minority of patients had optimal radiologic follow-up evaluations such as ultrasound, computed tomography, and venacavograms.¹⁰ Thus, event rates, particularly for DVT in patients with a filter, may be underestimated.

**Efficacy**

In the only prospective randomized controlled trial of IVC filters, patients were randomly assigned to receive a permanent IVC filter (n = 200) or no filter (n = 200) and received either unfractionated heparin (n = 205) or low–molecular-weight heparin (n = 195).⁴ At 12 days, there was a significant reduction in recurrent PE in patients who had had a filter inserted; however, there was no significant improvement in mortality or other outcomes. At 2 years, recurrent PE was reduced with filter placement, but not significantly; however, recurrent DVT was significantly increased (20.8% vs. 11.6%, P = 0.02). At 8 years, results were consistent with the results from the 2-year period. Occurrence of postthrombotic syndrome likewise was similar in both groups at 2 and 8 years.⁵ A comprehensive review of published data with permanent filters (mean duration of follow-up ranging from 6 to 18 months) reported an incidence of recurrent PE ranging from 2.6% to 3.8% and fatal PE ranging from 0.3% to 1.9%, depending on the type of filter (Table 2).¹⁰

In 2003 and 2004, the US Food and Drug Administration (FDA) approved the percutaneous retrievable capacity of 3 existing permanent filters.¹⁸ The proposed clinical advantage of a retrievable IVC filter is the ability to avoid the long-term complications associated with permanent filters by their removal when anticoagulation becomes a viable option.¹⁸,¹⁹ However, published data suggest that retrievable filters often are not removed.¹³–¹⁶,²⁰–²² A retrospective chart review reported that 35% of retrievable filters were ultimately not removed for reasons including clinical necessity and patient discharge with indwelling filter for unknown reasons.²³ Importantly, indications for a retrievable filter are no different than those for permanent filters (Table 1).

Available evidence suggests that permanent and temporary filters have similar safety and efficacy.¹³–¹⁶,²⁰–²²,⁴⁴–⁵⁶ One of the largest prospective case series described placement of 50 temporary retrievable IVC filters in 47 patients.²⁷ Indications for IVC filter insertion included documented DVT and a contraindication for anticoagulation (n = 32), presumed high risk for PE with a temporary contraindication for anticoagulation (n = 12), and PE despite DVT prophylaxis with a temporary contraindication for full anticoagulation (n = 3). Contraindications for anticoagulation included major trauma with pelvic fracture, a planned operation, and a DVT complicating childbirth. The filters were retrieved 1 to 12 days after placement (mean, 7.3 days). There were no PE or new DVT occurrences while the filters were present, but 2 patients developed a PE during or after filter removal. Additionally, 2 filters migrated and required repositioning or replacement, 1 patient developed an IVC thrombosis, and 18% of filters contained thrombi, with 2 requiring surgical removal because of trapped thrombi. This report highlights the real toxicities of temporary filter placement, particularly as a proportion of these filters were placed in the absence of acute DVT (for which they are not indicated) or in the setting of “soft contraindications” for anticoagulants (such as recent childbirth).

Despite a complete lack of prospective evidence to document their safety and efficacy, temporary IVC filters are frequently placed in patients who have suffered trauma. This practice is justified by the perception that these patients have a particularly high risk for bleeding, which will be

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**Table 2 Compilation of inferior vena cava (IVC) filter data**

<table>
<thead>
<tr>
<th>Filter Type</th>
<th>Patients (N)</th>
<th>Follow-up Duration, Months (range)</th>
<th>PE, % (range)</th>
<th>DVT, % (range)</th>
<th>IVC Thrombosis, % (range)</th>
<th>Postphlebitic Syndrome, % (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stainless Steel Greenfield</td>
<td>3,184</td>
<td>18 (1–60)</td>
<td>2.6 (0–9), fatal 0.9</td>
<td>5.9 (0–18)</td>
<td>3.6 (0–18)</td>
<td>19 (0–47)</td>
</tr>
<tr>
<td>Titanium Greenfield</td>
<td>511</td>
<td>5.8 (0–81)</td>
<td>3.1 (0–3.8), fatal 1.7</td>
<td>22.7 (0–36)</td>
<td>6.5 (1–31)</td>
<td>14.4 (9–20)</td>
</tr>
<tr>
<td>Bird’s Nest</td>
<td>1,426</td>
<td>14.2 (0–60)</td>
<td>2.9 (0–4.2), fatal 0.9</td>
<td>6 (0–20)</td>
<td>3.9 (0–15)</td>
<td>14 (4–41)</td>
</tr>
<tr>
<td>Simon Nitinol</td>
<td>319</td>
<td>16.9 (0–62)</td>
<td>3.8 (0–5.3), fatal 1.9</td>
<td>8.9 (8–11)</td>
<td>7.7 (4–18)</td>
<td>12.9 (6–44)</td>
</tr>
<tr>
<td>Vena Tech</td>
<td>1,050</td>
<td>12 (0–81)</td>
<td>3.4 (0–8), fatal 0.3</td>
<td>32</td>
<td>11.2 (0–28)</td>
<td>41 (24–59)</td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; PE = pulmonary embolism.

Adapted with permission from Blood.¹⁰
exacerbated by pharmacologic prophylaxis. There is no evidence to support this practice. A large randomized clinical trial supports the fact that pharmacologic prophylaxis is both safe and effective in these patients, and there are no randomized prospective evaluations of temporary IVC interruption in this setting.

Safety
Complications related to insertion occur in 4% to 11% of patients with IVC filters, but result in death in only approximately 0.12% of patients. The most common adverse events associated with IVC filter placement are thrombotic complications. Thrombotic complications include insertion-site thrombosis (2% to 28%) and IVC thrombosis (3.6% to 11.2%). An increased frequency of recurrent DVT (5.9% to 35.7%) and postphlebitic syndrome (12.9% to 41%) have also been reported, possibly because IVC filters can impair lower extremity venous drainage. Other complications include migration (in rare cases to the heart), penetration of the IVC, filter fracture, vena caval obstruction, and guidewire entrapment.

The use of retrievable filters can avoid some of the thrombotic complications with permanent filters; however, prolonged dwell times are commonly reported with a retrieval rate as low as 35% reported in 1 study. There is a notable paucity of published information on long-term outcomes in patients implanted with retrievable filters that were not removed in a timely manner. Several case reports of uneventful dwell times of nearly 1 year have been published; however, prolonged dwell times can result in removal problems due to adherence of fibrotic material to the struts of the IVC filters. Epithelialization of the struts is a concern, and has been observed within 12 days, suggesting that wall damage might occur during the removal process. Repositioning or replacement of retrievable filters with permanent filters may be required to prevent epithelialization. In addition, emboli captured within the filters and documented residual IVC thrombus can prevent filter removal.

SUMMARY
IVC filter placement, whether permanent or retrievable, is recommended only in those patients with proven acute VTE and a current contraindication for anticoagulation, a complication of anticoagulation (bleeding), or (perhaps) recurrent PE despite adequate anticoagulation. Use of IVC filters for prevention of PE in patients who do not have an acute DVT has not been compared with pharmacologic prophylaxis, is likely to result in clinicians not using proven prophylaxis in such patients, and is not supported by evidence-based treatment recommendation. The increased number of filters placed, particularly with the introduction of retrievable IVC filters, is of concern. Given the lack of randomized controlled data, invasiveness, the high cost of the devices and procedures, and the uncertainty around their complication rate, IVC filters should not be used outside of those indications recommended in evidence-based guidelines. To provide additional evidence to justify current treatment practices, a randomized comparison of temporary IVC interruption with pharmacologic prophylaxis is required in patients perceived to be at high risk for both thrombosis and bleeding.

CONFLICT OF INTEREST
Mark A. Crowther, MD, MSc, reports no conflict of interest with the sponsor of this supplement article or products discussed in this article.

References
Outpatient Management of Stable Acute Pulmonary Embolism: Proposed Accelerated Pathway for Risk Stratification

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ABSTRACT

Pulmonary embolism (PE) is a major health problem and a cause of worldwide morbidity and mortality. The current standard therapy for acute PE encourages admitting patients to the hospital for administration of parenteral anticoagulation therapy as a bridge to oral vitamin K antagonists. Prognostic models that identify patients with stable (nonmassive) acute PE (SPE) who are at low risk for adverse outcome have recently been reported. Based on these risk stratification models, hospital-based therapy is warranted for patients with PE who meet the criteria associated with a high risk for adverse outcome. However, a growing body of evidence suggests the feasibility of partial outpatient management and accelerated hospital discharge (AHD) in a subset of patients with SPE. Prospective validation of these risk stratification models for predicting patient suitability for AHD is needed. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Anticoagulation; Pharmacotherapy; Pulmonary embolism; Risk stratification; Treatment; Venous thromboembolism

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are manifestations of the same disease process referred to collectively as venous thromboembolism (VTE). Despite increased awareness and wider employment of reliable thromboprophylactic strategies, the incidence of first-time symptomatic VTE remains high at 71 to 117 cases per 110,000 population. Up to 33% of all patients with symptomatic DVT manifest PE at the time of presentation. Nearly 50% of individuals with proximal (i.e., suprapopliteal or above-the-knee) DVT have radiographic evidence of a coexistent PE, and most fatal emboli are likely to arise from this region. Although the risk of embolization may be lower with untreated distal (i.e., calf vein or infrapopliteal) DVT, proximal propagation is seen in as many as 25% of such thrombi, further increasing the risk for PE. Patients with a history of PE are almost 4 times more likely to die of recurrent VTE in the following year than are patients who are treated for DVT alone.

It is estimated that about 237,000 nonfatal and 294,000 fatal cases of PE occur in the United States each year. A total of 34% of VTE-related deaths were due to sudden massive PE and 59% followed undiagnosed PE. PE presents with a wide clinical spectrum and largely nonspecific symptoms; therefore, timely diagnosis requires a high degree of clinical suspicion. Studies suggest that 55% to 94% of PEs in medical patients are not diagnosed until autopsy. These numbers most likely have been underestimated because autopsies are not routinely conducted in contemporary practice. It has been suggested that up to 27% to 68% of fatal PE cases are potentially preventable. Thus, rigorously screening for VTE risk factors and implementing effective thromboprophylaxis, along with prompt diagnosis and early therapy of suspected cases, is warranted.
**RISK STRATIFICATION**

Acute PE generally can be classified as either massive PE or nonmassive SPE. Patients with massive acute PE have a uniformly poor prognosis and the first few hours is the critical period when the majority of deaths occur. It is during this narrow window when prompt diagnosis and rigorous treatment strategies can save lives. Hemodynamic instability with systemic hypotension, cardiogenic shock, severe dyspnea, or respiratory failure at the time of presentation defines a physiologically massive PE. Massive acute PE is associated with increased risk for early mortality. According to reports from the International Cooperative Pulmonary Embolism Registry (ICOPER), the incidence of mortality at 3 months in patients with hemodynamic instability was 58% compared with 15% in patients who were hemodynamically stable. Radiographically large PE has been defined as angiographic obstruction of ≥50% or ≥2 lobar arteries.

SPE, on the other hand, is not associated with hemodynamic instability or respiratory failure and has a much lower risk for mortality (<5%). These patients may be asymptomatic, or may present with mild or moderate dyspnea, cough, pleuritic chest pain, or other clinical complaints. The mortality in SPE is significantly higher (26%) if these patients experience recurrent PE. SPE remains a serious condition and clinicians should focus on preventing recurrent emboli, particularly early after the initial PE, and not be deceived into inaction by the low initial mortality rate.

Using clinical factors alone, many patients presenting with acute PE can be classified as either unstable, thus requiring intensive inhospital therapy, or stable and at low risk for adverse events and potentially amenable to accelerated hospital discharge (AHD). Table 1 outlines important predictors of adverse outcomes in patients with acute PE. The Geneva Risk Score (GRS) is a clinical scoring system that has undergone both internal and external validation. The GRS was developed using multivariate analysis of clinical factors present at the time of admission in 296 consecutive patients with confirmed PE. Independent predictors of adverse outcome were history of cancer, congestive heart failure, previous DVT, systolic blood pressure <100 mm Hg, arterial oxygen pressure <8 kPa, and acute DVT on ultrasonography at the time of presentation. Risk scores were assigned to each variable and cross-validated (Table 2). During the 3-month follow-up, 2.2% (4 of 180) of low-risk patients (a score ≤2) experienced an adverse clinical outcome, including death, recurrent thromboembolism, or bleeding, compared with 26% in high-risk patients (score of ≥3). A recent retrospective study externally validated the GRS for identifying patients with acute PE who were at low risk for an adverse clinical outcome.

A second retrospective study derived a prediction rule for PE outcomes by randomly selecting 10,354 of 15,531 individuals discharged from 186 US hospitals with a diagnosis of PE. In all, 11 demographic, comorbid conditions and physical examination findings were validated as predictors of 30-day all-cause mortality and other severe nonfatal complications, such as cardiogenic shock and cardiopulmonary arrest during hospitalization (Table 1, see clinical...
More than 20% of patients enrolled in the study did not present with any of these variables, and thus were deemed to be at low risk. The incidences of 30-day mortality and serious adverse outcomes in the low-risk group were low (0% to 1.6% and 0.1% to 1.1%, respectively) compared with the high-risk group (4.0% to 11.4% and 1.9% to 2.1%, respectively).

Despite the valuable information provided by the initial clinical assessment, there is a subgroup of patients with PE who may appear well but decompensate shortly thereafter owing to right ventricular compromise. In this setting assessment of right ventricular function and the use of biomarkers may be helpful to further risk stratify these patients. Right ventricular dysfunction (RVD) can be evaluated on the basis of physical examination, electrocardiography, and chest computed tomography (CT). Moderate or severe RVD in normotensive patients is an indicator of physiologically large emboli and is associated with worse prognosis, including up to 10% mortality. Although echocardiography may be useful for risk stratification, it should not be used alone to establish the diagnosis of PE. Tests for cardiospecific biomarkers, in particular cardiac troponins (cTnT and cTnI) and brain natriuretic peptides (BNPs) may be used for objective risk stratification of patients with acute PE (Table 1). These tests are readily available, inexpensive, reproducible, and accurate. Patients with elevated BNP and troponin levels are more likely to have RVD and benefit from closer observation. Low BNPs and troponin levels have a high negative predictive value for inhospital death and other adverse outcomes, including the need for pressor support, mechanical ventilation, intensive care transfer, and prolonged length of stay. These patients may be candidates for AHD. Biomarkers should be evaluated both at presentation and after 12 hours because a delayed release (particularly troponin) may be observed after 6 to 12 hours.

In addition to formal clinical assessment, our practice frequently incorporates the use of biomarkers and measures of RV function (such as echocardiography and CT scan) to further risk stratify patients. Recent reports have called for incorporating cardiac biomarkers into PE management decision algorithms (Figure 1), although such a strategy has not been adopted by formal consensus guidelines.

**GUIDELINES AND CURRENT STANDARDS FOR TREATMENT OF PULMONARY EMBOLISM**

The American College of Chest Physicians (ACCP) has developed guidelines for initial treatment of acute PE (Table 3). Although the ACCP recommends considering systemic thrombolysis (grade 2B; see Table 3 for explanation of grades) or surgical embolectomy (grade 2C) for patients presenting with massive PE, the use of these therapies in patients with SPE is controversial. Surgical embolectomy carries operative mortality ranging from 20% to 50%, and the incidence of major bleeding complications with thrombolytic therapy is twice that seen in patients treated with heparin alone.

For nearly half a century, intravenous infusion of unfractionated heparin (UFH) followed by oral administration of warfarin has been the cornerstone of treatment for acute
The full anticoagulant effects of warfarin are seen only after 4 to 5 days of administration. Thus, in patients with acute VTE, warfarin must always be administered in conjunction with a rapidly acting parenteral anticoagulant. UFH has pharmacologically limiting properties, including a poor dose-response curve and a relatively narrow therapeutic window, requiring close monitoring and frequent dose adjustments. These issues make its use in the outpatient setting somewhat difficult. In addition, in some patients, UFH may cause immune-mediated thrombocytopenia and thrombosis.

The use of newer anticoagulants with better bioavailability and more consistent therapeutic response along with recent advances in risk stratification have led to improved treatment outcomes in patients with VTE. UFH has pharmacologically limiting properties, including a poor dose-response curve and a relatively narrow therapeutic window, requiring close monitoring and frequent dose adjustments. These issues make its use in the outpatient setting somewhat difficult. In addition, in some patients, UFH may cause immune-mediated thrombocytopenia and thrombosis.

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Table 3  American College of Chest Physicians (ACCP) recommendations for the initial treatment of patients with acute pulmonary embolism (PE)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Diagnosis/Symptoms</th>
<th>Recommendation</th>
<th>Grade/Level of Evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous UFH or LMWH</td>
<td>Objectively confirmed nonmassive PE</td>
<td>Short-term treatment with SC LMWH or IV UFH</td>
<td>1A</td>
</tr>
<tr>
<td></td>
<td>High clinical suspicion of PE</td>
<td>Treatment with anticoagulants while awaiting the outcome of diagnostic tests</td>
<td>1C+</td>
</tr>
<tr>
<td></td>
<td>Acute nonmassive PE</td>
<td>LMWH over UFH</td>
<td>1A</td>
</tr>
<tr>
<td></td>
<td>Acute nonmassive PE</td>
<td>Initial treatment with LMWH or UFH for ≥5 days</td>
<td>1C</td>
</tr>
<tr>
<td>Systemically and locally administered thrombolytic drugs</td>
<td>Most patients with PE</td>
<td>Recommend against systemic thrombolytic therapy</td>
<td>1A</td>
</tr>
<tr>
<td></td>
<td>Acute massive PE</td>
<td>Consider thrombolytic therapy</td>
<td>2B</td>
</tr>
<tr>
<td></td>
<td>Most patients with PE</td>
<td>Recommend against use of mechanical approaches</td>
<td>1C</td>
</tr>
<tr>
<td></td>
<td>Patients with acute massive PE who are unable to receive thrombolytic therapy</td>
<td>Consider use of mechanical approaches</td>
<td>2C</td>
</tr>
<tr>
<td>Catheter extraction or fragmentation</td>
<td>Most patients with PE</td>
<td>Recommend against pulmonary embolectomy</td>
<td>1C</td>
</tr>
<tr>
<td></td>
<td>Patients with acute massive PE who are unable to receive thrombolytic therapy</td>
<td>Consider pulmonary embolectomy</td>
<td>2C</td>
</tr>
<tr>
<td>Pulmonary embolectomy</td>
<td>In patients with PE with a contraindication for, or a complication of anticoagulant treatment, as well as in those with recurrent thromboembolism despite adequate anticoagulation</td>
<td>Placement of an inferior vena caval filter</td>
<td>2C</td>
</tr>
</tbody>
</table>

IV = Intravenous; LMWH = low-molecular-weight heparin; RCT = randomized clinical trial; SC = subcutaneous; UFH = unfractionated heparin.

*Explanation of grades of recommendation and levels of evidence:
● Grade 1: Strong recommendation; certain that benefits do, or do not, outweigh risks, burden, and costs.
● Grade 2: Weaker recommendation; less certain of the magnitude of benefits and the impact of risks, burden, and costs.
● Level of evidence A: RCTs with consistent results.
● Level of evidence B: RCTs with inconsistent results or with major methodologic weaknesses.
● Level of evidence C: Observational studies or from a generalization from 1 group of patients included in RCTs to a different, but somewhat similar, group of patients who did not participate in those trials. If generalizations are secure or observational study data are compelling, grade C+ can be designated.

Adapted from Chest.4,39

VTE. The full anticoagulant effects of warfarin are seen only after 4 to 5 days of administration. Thus, in patients with acute VTE, warfarin must always be administered in conjunction with a rapidly acting parenteral anticoagulant. UFH has pharmacologically limiting properties, including a poor dose-response curve and a relatively narrow therapeutic window, requiring close monitoring and frequent dose adjustments. These issues make its use in the outpatient setting somewhat difficult. In addition, in some patients, UFH may cause immune-mediated thrombocytopenia and thrombosis.

The efficacy and safety of once-daily subcutaneous fondaparinux for the initial treatment of PE were recently prospectively evaluated in comparison with continuous intravenous UFH in 2,213 subjects enrolled in the phase 3, randomized Mondial Assessment of Thromboembolism Treatment Initiated by Synthetic Pentasaccharide with Symptomatic Endpoints (MATISSE-PE) trial.51 The aim of MATISSE-PE was to compare the rates of VTE recurrence...
Table 4  Prospective studies evaluating outpatient anticoagulation therapy following acute pulmonary embolism (PE)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Group</th>
<th>Treatment</th>
<th>Outcomes</th>
<th>Key Results</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells et al., 1998 (Canada)</td>
<td>n = 194; Low risk* with DVT and/or PE treated as</td>
<td>Dalteparin (100 U/kg bid or 200 U/kg qd) administered at home for ≥5 days</td>
<td>Recurrent VTE</td>
<td>3.6% (7/194)</td>
<td>Small no. of patients with PE</td>
</tr>
<tr>
<td></td>
<td>(n = 194)</td>
<td>Major hemorrhage</td>
<td></td>
<td>2.0% (4/194)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minor hemorrhage</td>
<td></td>
<td>5.1% (10/194)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death</td>
<td></td>
<td>7.2% (1/194)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent VTE</td>
<td></td>
<td>5.6% (6/108)</td>
<td>81 patients were managed exclusively as</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major hemorrhage</td>
<td></td>
<td>1.9% (2/108)</td>
<td>outpatient treatment</td>
</tr>
<tr>
<td>Kovacs et al., 1998 (Canada)</td>
<td>n = 108; Patients with PE treated as outpatients</td>
<td>Dalteparin (200 U/kg qd) administered at home for ≥5 days</td>
<td>Death at 8–12 wk</td>
<td>0 (0/90)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major hemorrhage</td>
<td></td>
<td>0 (0/46)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent VTE</td>
<td></td>
<td>0 (0/46)</td>
<td></td>
</tr>
<tr>
<td>Labas et al., 2001 (Slovakia)</td>
<td>n = 106; Patients diagnosed with DVT and/or PE</td>
<td>Enoxaparin (1 mg/kg bid) administered for ≥7 days</td>
<td>Death at 3-mo follow-up</td>
<td>2.3% (1/43)</td>
<td>Small no. of patients with PE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major hemorrhage</td>
<td></td>
<td>0 (0/43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent VTE</td>
<td></td>
<td>0 (0/93)</td>
<td></td>
</tr>
<tr>
<td>Beer et al., 2002 (Switzerland)</td>
<td>n = 43; Patients with symptomatic PE at low predicted risk†</td>
<td>Nadoparin 171 U/kg administered for 5–10 days</td>
<td>Recurrent PE</td>
<td>2.3% (1/43)</td>
<td>Small no. of patients with PE</td>
</tr>
<tr>
<td>Rhodes et al., 2005 (United</td>
<td>n = 107; Patients with confirmed PE treated as</td>
<td>Warfarin coadministration for 6–12 mo</td>
<td>Bleeding at 3 mo</td>
<td>0 (0/43)</td>
<td></td>
</tr>
<tr>
<td>Kingdom)</td>
<td>outpatients§</td>
<td>Tinzaparin (175 U/kg qd) for ≥6 days</td>
<td>Death at 3 mo</td>
<td>0 (0/43)</td>
<td>Outcome data only available for treatment</td>
</tr>
<tr>
<td>Olsson et al., 2006 (Sweden)</td>
<td>n = 102; Patients with symptomatic small or</td>
<td>Warfarin coadministration</td>
<td>Significant adverse events§</td>
<td>0 (0/143)</td>
<td>phase</td>
</tr>
<tr>
<td></td>
<td>medium-sized PE quantified by V/Q scan**</td>
<td>Clinical symptoms and repeat V/Q scan assessed at day 5 to evaluate</td>
<td>during the treatment phase</td>
<td>0 (0/143)</td>
<td>V/Q scans at late follow-up were only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>recurrent PE</td>
<td></td>
<td>0 (0/143)</td>
<td>performed in 58% of patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death after 1–4 mo</td>
<td></td>
<td>8.5% (5/59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Required hospitalization</td>
<td></td>
<td>4% (4/100)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5% (5/100)</td>
<td></td>
</tr>
</tbody>
</table>

DVT = deep vein thrombosis; VTE = venous thromboembolism; V/Q = ventilation/perfusion.

*Patients were eligible for outpatient treatment if they had been objectively diagnosed with DVT, unless they had massive pulmonary embolism, high risk for major bleeding or an active bleed, phlegmasia, or were hospitalized for reasons that prevented discharge.43

†Causes of death included cancer (n = 11), sepsis (n = 1), myocardial infarction (n = 1), and sudden death not attributed to PE (n = 1).

‡Patients were eligible for outpatient treatment if they had been objectively diagnosed with PE, and did not meet any of the following criteria: admitted to the hospital for another reason; experienced active bleeding or were at high risk for major bleeding, hemodynamic instability, or pain requiring narcotics; required oxygen therapy; were aged <18 years, or were at risk for poor adherence.44

§Deaths not attributed to bleeding complications or PE.

¶Based on risk score assessment described by Wicki et al., 2000.46

‖Patients were eligible for outpatient treatment if they had been objectively diagnosed with PE, and were not at the highest risk for major bleeding (intracerebral bleed within the last 6 months, gastrointestinal bleed in the last month, or verified bleeding disorder). Patients with renal or liver failure, pregnancy, or gross hypertension were evaluated on an individual basis.47

¶¶Significant adverse events included bleeding, thromboembolic complications, and death.

ittal Patients were excluded if PE was extensive, defined as ≥7 segments with reduced perfusion (representing >40% of the total lung perfusion); had severe, concomitant lung disease such as COPD, pneumonia, and heart failure; had other reason for hospitalization (e.g., recent surgery, bleeding, or severe pain).48

‖‖Causes of death included cancer (n = 11), renal insufficiency (n = 1), cerebral bleeding (n = 1), and massive pleural effusion/thoracocentesis (n = 1).

during the 3-month follow-up period and major bleeding and death during the initial treatment period. Fondaparinux was administered as a once-daily subcutaneous dose of 7.5 mg (adjusted to 5 mg and 10 mg for patients weighing <50 kg and >100 kg, respectively). Only 42 (3.8%) of 1,103 patients who received fondaparinux had recurrent VTE events compared with 56 (5.0%) of 1,110 patients assigned to receive UFH, for an absolute difference of −1.2 percentage points in favor of fondaparinux (P = NS). Major and nonmajor bleeding, thrombocytopenia, and mortality were similar in both groups during the entire period of the study.

The current ACCP recommendations for SPE involves admitting all patients to the hospital for administration of parenteral anticoagulation therapy, either UFH or LMWH, as a bridge to warfarin with a minimum of 5 days of overlap until a therapeutic international normalized ratio (INR) >2.0 is achieved. Warfarin should be continued for a minimum of 6 to 12 months. Fondaparinux was not yet approved for treatment of DVT and PE when the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy developed treatment guidelines; therefore, this option was not included when the guidelines were released in 2004.

**BENEFITS OF OUTPATIENT TREATMENT**

There is growing evidence that AHD and partial outpatient therapy is feasible for patients with nonmassive SPE. Partial outpatient treatment of PE via an AHD program may be offered to patients deemed to be at low risk for mortality, recurrent PE, or major bleeding complications; who have a home environment with adequate support; and who are able to self-administer the medications (see Tables 1 and 2 for risk stratification criteria).53,54 In 1 study, up to 83% of VTE patients qualified for outpatient treatment. Benefits of outpatient management include improved quality-of-life measures, increased physical activity and social functioning, reduced length of stay, and substantial cost savings. Pharmacoeconomic analyses of outpatient treatment for DVT reported cost reductions of 34% to 64%. Agnelli and colleagues reported >$2,400 in cost savings per patient when acute PE was treated on an outpatient basis. However, despite these incentives, clinicians are rightfully disinclined to send home patients who might be at risk for an unfavorable outcome.6

Several studies have demonstrated successful outpatient therapy with LMWH as a bridge to warfarin for the treatment of acute SPE (Table 4). In addition, 158 patients in the fondaparinux group of the MATISSE-PE trial were permitted early discharge and received fondaparinux partly on an outpatient basis. Of these patients who had recurrent VTE, and none had major bleeding or died during initial treatment. In light of the current data and the consideration for AHD with partial outpatient therapy of acute PE, there is a need to accurately predict patient suitability for this type of therapy. It is likely that identification of low-risk patients with acute PE will facilitate less complex treatment and allow for earlier discharge without sacrificing efficacy or safety.

### SUMMARY

Acute PE has a wide clinical spectrum, ranging from asymptomatic patients to those presenting with sudden death. The clinical course in patients who survive an initial thromboembolic episode can be complicated by recurrent nonfatal VTE, fatal PE, postthrombotic syndrome, and chronic thromboembolic pulmonary hypertension. Early identification of high-risk patients with acute PE who are at increased risk for adverse outcomes remains a challenge in clinical practice. A substantial subset of patients with stable PE may be amenable to outpatient treatment; however, appropriate risk stratification is necessary to identify these candidates. Outpatient treatment in these patients can reduce hospital stay, improve patient quality of life, and decrease healthcare costs. Further studies are needed to establish clear clinical pathways that prospectively use contemporary risk stratification criteria for AHD of patients presenting with acute SPE.

Treatment of acute PE with LMWH or fondaparinux administered in an outpatient setting for appropriately selected patients is at least as effective and safe as conventional inpatient treatment with UFH in preventing recurrent VTE, without increasing the risk for major bleeding when patients are closely monitored. Phase 3 clinical trials have shown fondaparinux to be an effective alternative to LMWHs and UFH for the outpatient treatment of DVT; additionally, these trials have shown it to be efficacious in inpatient and partial outpatient treatment of PE. Fondaparinux currently is the only FDA-approved medication for partial outpatient treatment of SPE.

### CONFLICT OF INTEREST

These authors report the following conflicts of interest with the sponsor of this supplement article or products discussed in this article. Teresa L. Carman, MD, has served as a member of the Speakers’ Bureau for Bristol-Myers Squibb Company. Amjad AlMahameed, MD, has served as a member of the Speakers’ Bureau for sanofi-aventis and GlaxoSmithKline.

### References


59. Buller H, for the MATISSE Investigators. Initial outpatient treatment of venous thromboembolism with fondaparinux: the MATISSE trials. Poster presented at the Annual Meeting of The International Society on Thrombosis and Haemostasis; August 6, 2005; Sydney, Australia.


Prevention and Management of Venous Thromboembolism in Pregnancy

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ABSTRACT

Normal pregnancy is accompanied by an increase in clotting factors. The resulting hypercoagulable state has likely evolved to protect women from hemorrhage at the time of miscarriage and childbirth. During pregnancy, women are 4 times more likely to suffer from venous thromboembolism (VTE) compared with when they are not pregnant. Relative to pregnancy, the risk postpartum is even higher. The incidence of VTE is approximately 2 per 1,000 births, and VTE accounts for 1 death per 100,000 births, or approximately 10% of all maternal deaths. The most important risk factors during pregnancy are thrombophilia and a history of thrombosis. A history of thrombosis increases the risk for VTE to 2% to 12%. Thrombophilia increases not only the risk for maternal thrombosis but also the risk of poor pregnancy outcome. Despite the increased risk for thrombosis during pregnancy and the postpartum period, most women do not require anticoagulation. Those who do require anticoagulation include women with current VTE, women on lifelong anticoagulation, and many women with thrombophilia or a history of thrombosis. Recommended options for anticoagulation in pregnancy are limited to heparins, which do not cross the placenta. Low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin because LMWH has a longer half-life and is presumed to have fewer side effects. The longer half-life is a disadvantage around the time of delivery, when unfractionated heparin, with its shorter half-life, is easier to manage. For women who develop or are at high risk for heparin-induced thrombocytopenia or severe cutaneous reactions, fondaparinux is probably the agent of choice. Women who do not require lifelong anticoagulation, but require anticoagulation during pregnancy, will still require anticoagulation for the first 6 weeks postpartum. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Venous thromboembolism; Pregnancy; Deep vein thrombosis; Pulmonary embolism
riage and childbirth. Indeed, in the developing world, the leading cause of maternal death is still hemorrhage. In Western Europe and the United States, where hemorrhage is successfully treated or prevented, the leading cause of maternal death is now thromboembolic disease.

INCIDENCE OF VENOUS THROMBOEMBOLISM DURING PREGNANCY AND THE POSTPARTUM PERIOD

During pregnancy and the postpartum period, women are 4 times more likely to suffer from venous thromboembolism (VTE) than when they are not pregnant. The rate of VTE among women of childbearing age is approximately 50 per 100,000 woman-years, whereas the overall rate among pregnant and postpartum women is approximately 200 per 100,000 woman-years. Compared with the risk during pregnancy, the risk for thrombosis is even higher after delivery. The rate during pregnancy is approximately 100 per 100,000 woman-years, whereas the rate during the postpartum period is approximately 500 per 100,000 woman-years, or 5 times higher. Indeed, 1 out of every 3 or 4 pregnancy-related venous thromboembolic events occurs postpartum. Half of these events occur during the first 2 weeks after delivery.

During pregnancy and the postpartum period, venous thromboembolic events are 4 times more common than arterial events. Of these venous thromboembolic events, approximately 80% are deep vein thromboses (DVT) and 20% are pulmonary emboli (PE). The overall risk for VTE is approximately 2 per 1,000 births. VTE accounts for 1 death per 100,000 births, which is approximately 10% of all maternal deaths.

Women are at risk not only for the immediate morbidity and mortality associated with DVT and PE, but also for the long-term morbidity associated with the postthrombotic syndrome. In fact, the majority of ultimately develop sequelae that range from edema and skin changes to recurrent thromboses and ulceration. An unknown number of women may suffer permanent lung damage from PE.

RISK FACTORS FOR THROMBOSIS DURING PREGNANCY

In a review of 53 cases of pregnancy-related DVT, the 2 most important risk factors during pregnancy were diagnosed thrombophilia, present in 24% of cases, and a history of thrombosis, present in 15% of cases. An analysis of 14,335 records from the Nationwide Inpatient Sample showed that other statistically significant medical risk factors for VTE during pregnancy were anemia, heart disease, sickle cell disease, lupus and obesity (Table 1). Pregnancy and delivery complications that increased the risk, were hyperemesis, fluid and electrolyte imbalance, antepartum hemorrhage, cesarean delivery, postpartum infection, and transfusion.

Both acquired and inherited thrombophilia increase the risk for maternal thrombosis. Several studies have compared the prevalence of inherited thrombophilia in women who experienced VTE in pregnancy versus those who did not. Factor V Leiden and the prothrombin gene mutation each confer approximately a 10-fold increased risk for VTE in pregnancy. Combined they confer an increased risk of approximately 70-fold, which is similar to the approximately 80-fold increased risk associated with homozygosity of factor V Leiden.

Homozygosity, let alone heterozygosity, for the MTHFR C677T polymorphism does not confer any increased risk for VTE in pregnancy. The risk of VTE during pregnancy in women with antithrombin, protein C or protein S deficiency is hard to quantify. There are few studies and the definition of deficiency varies from study to study. The absolute risk in women with antithrombin deficiency has been reported to be as high as 40% to 68%. The absolute risk in women with protein C or S deficiency has been reported to range from 0% to 22%. The risk for VTE in pregnancy women with the antithrombin syndrome has been reported to be 30%. There is some controversy as to whether women who have not had a thrombosis, and are diagnosed solely on the basis of poor pregnancy outcome, are at the same risk.

Evidence suggesting that they are was reported by Erkan and coworkers, who found a rate of 7.4 per 100 patient-years in women who did not receive thromboprophylaxis after delivery.

INDICATIONS FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS DURING PREGNANCY

Despite the increased risk for thrombosis during pregnancy and the postpartum period, most women do not require anticoagulation. In most cases, the risks for anticoagulation outweigh its benefits. The risk of maternal bleeding com-

### Table 1: Risk factors for peripartum venous thromboembolism

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>7.1</td>
<td>6.2–8.3</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>51.8</td>
<td>38.7–69.2</td>
</tr>
<tr>
<td>History of thrombosis</td>
<td>24.8</td>
<td>17.1–36.0</td>
</tr>
<tr>
<td>Antiphospholipid syndrome</td>
<td>15.8</td>
<td>10.9–22.8</td>
</tr>
<tr>
<td>Sickle-cell disease</td>
<td>6.7</td>
<td>4.4–10.1</td>
</tr>
<tr>
<td>Lupus</td>
<td>8.7</td>
<td>5.8–13.0</td>
</tr>
<tr>
<td>Obesity</td>
<td>4.4</td>
<td>3.4–5.7</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.6</td>
<td>2.2–2.9</td>
</tr>
<tr>
<td>Hyperemesis</td>
<td>2.5</td>
<td>2.0–3.2</td>
</tr>
<tr>
<td>Fluid and electrolyte imbalance</td>
<td>4.9</td>
<td>4.1–5.9</td>
</tr>
<tr>
<td>Antepartum hemorrhage</td>
<td>2.3</td>
<td>1.8–2.8</td>
</tr>
<tr>
<td>Postpartum infection</td>
<td>4.1</td>
<td>2.9–5.7</td>
</tr>
<tr>
<td>Transfusion</td>
<td>7.6</td>
<td>6.2–9.4</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>2.1</td>
<td>1.8–2.4</td>
</tr>
</tbody>
</table>
Applications with heparin or low-molecular-weight heparin (LMWH) is reported to be as high as 2%.

In addition to maternal risks, anticoagulants may pose fetal risks, even with the use of agents that do not cross the placenta. There is a fine balance of hemostatic factors at the uteroplacental interface and, in most women, this balance is achieved with the normal changes of pregnancy.

This is not necessarily true in women with a history of thrombosis or thrombophilia. Women with a history of VTE who receive anticoagulation have a 0% to 2% risk of a recurrent event in pregnancy, but women who do not receive anticoagulation have a 2% to 12% risk. Because pregnancy increases the risk of thrombosis 4-fold, including in women who have a history of thrombosis, women who are not on lifelong anticoagulation will likely require anticoagulation during pregnancy, or, at a minimum, during the postpartum period. Women with a history of recurrent thrombosis will likely be on lifelong anticoagulation and will require conversion from warfarin to heparin or LMWH because of warfarin’s effects on the fetus.

Although some experts would recommend thromboprophylaxis for all pregnant women with inherited thrombophilia, anticoagulation is probably not necessary if there is no personal history of thromboembolism or poor pregnancy outcome. The exceptions, because of their especially high risk for thrombosis, are women with antithrombin deficiency, homozygosity for the factor V Leiden mutation or the prothrombin gene G20210A mutation, or heterozygosity for both mutations (compound heterozygosity).

In the antiphospholipid syndrome, an acquired thrombophilia, several studies have demonstrated that anticoagulation improves the outcome of pregnancy. In inherited thrombophilia, until very recently, only case reports and case series demonstrated the role of anticoagulation in improving the outcome of pregnancy, but a recent randomized trial showed improved outcomes in women with inherited thrombophilia and a history of a single fetal loss >10 weeks’ gestation. A total of 69 of 80 women who took enoxaparin 40 mg/day had a healthy live birth, compared with 23 of 80 who took low-dose aspirin.

Although there are no large trials demonstrating the maternal or fetal benefits of anticoagulation in pregnancy, currently recommended indications include the conditions listed below. Full-dose (adjusted dose) anticoagulation is recommended for the prevention of VTE in women with a need for lifelong anticoagulation or with antiphospholipid syndrome with a history of thrombosis.

Full-dose (adjusted dose) or an intermediate or moderate dose, as described in Table 2, is recommended for women with antithrombin deficiency and women with homozygosity for the factor V Leiden mutation, the prothrombin gene G20210A mutation or compound heterozygosity for both mutations.

Thromboprophylaxis with low-dose anticoagulation is recommended for women with a history of unprovoked thrombosis, antiphospholipid syndrome with a history of poor pregnancy outcome as the only clinical criterion (plus use of low-dose aspirin), or thrombophilia and poor pregnancy outcome.

Close observation (assessment of signs and symptoms of thrombosis at routine prenatal visits) may be an option for women with thrombosis in the setting of transient risk factors or with thrombophilia but no history of thrombosis. None-theless, these women should be considered for thromboprophylaxis during the first 2 to 6 weeks postpartum.

### OPTIONS FOR VENOUS THROMBOEMBOLISM PROPHYLAXIS IN PREGNANCY

Unique aspects of anticoagulation in pregnancy include both maternal and fetal issues. During pregnancy, there is an increase in blood volume of 40% to 50% and an increase in

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**Table 2** Protocols for thromboprophylaxis in pregnancy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-dose “Low dose”</td>
<td>5,000 U sc q 12 hr</td>
<td>5,000 U sc q 12 hr &lt; 8 wk</td>
</tr>
<tr>
<td>Moderate dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Low dose”</td>
<td>q 12 hr to target anti-factor Xa level of 0.1–0.3 U/mL</td>
<td>q 8 or 12 hr to target mid-interval aPTT in therapeutic range</td>
</tr>
<tr>
<td>Adjusted dose “Full dose”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Low dose”</td>
<td>Enoxaparin 40 mg qd</td>
<td>Enoxaparin 40 mg qd or 30 mg bid before 28 wk, then</td>
</tr>
<tr>
<td>Adjusted dose “Full dose”</td>
<td>Dalteparin 5,000 U qd</td>
<td>Dalteparin 40 mg bid after 28 wk</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin 4,500 U qd</td>
<td>Enoxaparin 1 mg/kg bid with target of anti-factor Xa level of 0.5–1.0</td>
</tr>
<tr>
<td></td>
<td>Enoxaparin 1 mg/kg bid or 1.5 mg/kg qd</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dalteparin 100 U/kg q 12 hr or 200 U/kg q 24 hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tinzaparin 175 U/kg qd</td>
<td></td>
</tr>
</tbody>
</table>

Note: aPTT = acute partial thromboplastin time; sc = subcutaneous. Adapted from Chest and ACOG Practice Bulletin No. 19.
the volume of distribution. An increase in glomerular filtration results in increased renal excretion of drugs eliminated by this route. Additionally, there is an increase in protein binding of heparin. The critical period for organogenesis is from the 4th to the 8th week after conception. Because 45% of pregnancies are unintended, many women do not realize that they are pregnant. Warfarin taken during this period is associated with a 14.6% to 56% reported risk for miscarriage and carries up to a 30% risk for congenital anomalies.

Placental transfer of warfarin in later pregnancy can result in fetal bleeding or stillbirth. Long-term sequelae include a 14% reported risk for adverse neurologic outcome and a 4% reported risk of low intelligence quotient (IQ).

The preferred agents for anticoagulation in pregnancy are heparin compounds. Neither heparin nor LMWH crosses the placenta and both are considered safe in pregnancy. Disadvantages of unfractionated heparin include the necessity of parenteral administration, a 2% risk for major bleeding, a 2% to 36% risk for reduced bone density, a 2% risk for vertebral fracture and a risk for heparin-induced thrombocytopenia (HIT). Although the risk for HIT is low in pregnancy, and may be lower than in nonpregnant patients, the actual risk is unknown.

There are few comparative studies in pregnancy, but in nonpregnant patients, LMWHs has been found to be as safe and effective as unfractionated heparin. Although parenteral administration is still required, potential advantages of LMWH over unfractionated heparin are less bleeding, a more predictable response, a lower risk for HIT, a longer half-life, and maybe less bone loss. However, in a recently completed randomized trial of low-dose unfractionated heparin versus enoxaparin for thromboprophylaxis in pregnancy, the incidence of clinically significant bone loss was 2% to 2.5% and was no different in women who took unfractionated heparin compared with those who took enoxaparin. Another study found that bone loss in women who took LMWH was approximately 4%, no different than bone loss in controls. An advantage of LMWH over unfractionated heparin is less bruising at injection sites. A disadvantage of LMWH is that it is more expensive. Also, its longer half-life may be a problem at the time of delivery.

Long-term therapy with fondaparinux, the new selective factor Xa inhibitor, may result in less bone loss than either unfractionated or LMWH. In cell culture, osteoblasts have been shown to have significantly higher mitochondrial activity and protein synthesis when treated with fondaparinux compared with treatment with either unfractionated heparin or LMWH. Data on the use of fondaparinux in pregnancy, however, are limited. Although Lagrange et al observed no transplacental passage of fondaparinux using a perfused cotyledon model, Dempfle et al found transplacental passage of fondaparinux in 5 women who took it for 1 to 101 days because of heparin allergy. Anti–factor Xa levels in umbilical cord plasma of newborns were found to be one tenth the concentration of maternal plasma. The clinical significance of this finding is unknown, but no adverse effects were noted in the newborns. Fondaparinux is effective in preventing VTE, but may not be effective in reducing the risk for pregnancy loss in women for whom it is prescribed for that indication, such as women with the antiphospholipid syndrome. Unlike heparin or LMWH, fondaparinux does not prevent fetal death in mice with antiphospholipid antibodies.

At the present time there are insufficient data to justify the routine use of fondaparinux for prophylaxis of VTE in pregnancy. Nonetheless, fondaparinux is probably the anticoagulant of choice in cases of severe cutaneous allergies or HIT in pregnancy.

**INITIATING ANTICOAGULATION DURING PREGNANCY**

Women on lifelong anticoagulation may be converted from warfarin to LMWH before pregnancy or as soon as possible after conception. The problem with conversion after conception is the inconvenience and discomfort of parenteral administration of heparins and the risks associated with their long-term use. The problem with conversion after conception is that the half-life of warfarin is 36 to 42 hours, and it may remain in the maternal circulation for several days, increasing the risk for miscarriage and congenital anomalies. Only a few women are candidates for warfarin rather than heparins during pregnancy. Candidates include women with mechanical heart valves and certain other unusual conditions.

Women who are not on lifelong anticoagulation, but are candidates for thromboprophylaxis in pregnancy, should start soon after conception. An exception is women who will be undergoing ovulation induction. Because hormone therapy, including clomiphene, increases the risk for thrombosis, these women should begin anticoagulation at the time they start ovulation induction.

Because HIT manifests within the first 5 to 15 days of exposure, platelet counts may be monitored for the first 2 to 3 weeks after initiation of therapy. Although platelet counts usually drop by 10% in pregnancy and thrombocytopenia affects up to 10% of all pregnancies, HIT still must be considered in women who develop thrombocytopenia while taking heparins. If the diagnosis is confirmed, there are few data to guide treatment. Danaparoid has been used most commonly to treat HIT in pregnancy, but it is not available in the United States. The use of recombinant hirudin has been reported in 1 case of HIT and 1 case of heparin allergy in pregnancy. The use of argatroban in pregnancy has not been reported, and there are no published data on placental transfer or fetal effects. Recently, the use of fondaparinux has been reported in 7 cases of heparin allergy in pregnancy.

Anticoagulants that have been used during pregnancy are summarized in Table 3.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Indications</th>
<th>Route of Administration</th>
<th>Placental Transfer</th>
<th>Fetal Risks</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Limited to thromboprophylaxis in women with mechanical heart valves&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Oral</td>
<td>Yes</td>
<td>Miscarriage: 14.6%–56%&lt;sup&gt;50-53,57,84&lt;/sup&gt; Stillbirth: 5%–33%&lt;sup&gt;50-52,53,57&lt;/sup&gt; Congenital anomalies: 0%–30%&lt;sup&gt;49-55&lt;/sup&gt; Fetal or neonatal intracranial hemorrhage: 2%&lt;sup&gt;55,56&lt;/sup&gt; Adverse neurologic outcome: 14%&lt;sup&gt;58&lt;/sup&gt; Low IQ: 4%&lt;sup&gt;58&lt;/sup&gt;</td>
<td>Warfarin &lt;25 ng/ml&lt;sup&gt;85&lt;/sup&gt; Not contraindicated&lt;sup&gt;86&lt;/sup&gt;</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>Treatment or prophylaxis&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Intravenous or subcutaneous</td>
<td>None&lt;sup&gt;59,60,87&lt;/sup&gt;</td>
<td>No increase in adverse fetal outcome in 100 pregnancies&lt;sup&gt;33&lt;/sup&gt; No increase in adverse fetal outcome among 624 pregnancies&lt;sup&gt;34&lt;/sup&gt; No adverse fetal outcome reported in numerous cases Not available in the United States</td>
<td>Presumed not to enter breast milk Presumed not to enter breast milk Presumed not to enter breast milk</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>Treatment or prophylaxis&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Subcutaneous</td>
<td>Low placental permeability&lt;sup&gt;70&lt;/sup&gt; No evidence of anti-Xa activity in placental blood&lt;sup&gt;93&lt;/sup&gt;</td>
<td>Low placental transfer in dogs&lt;sup&gt;94&lt;/sup&gt; &lt;2% of maternal levels detected in plasma of fetal rabbits&lt;sup&gt;93&lt;/sup&gt;</td>
<td>No data</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Heparin allergy&lt;sup&gt;90-92&lt;/sup&gt; or HIT&lt;sup&gt;77-80,91&lt;/sup&gt;</td>
<td>Subcutaneous</td>
<td>No adverse fetal outcome in 100 pregnancies&lt;sup&gt;70&lt;/sup&gt;</td>
<td>Not detected in breast milk&lt;sup&gt;95&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Recombinant hirudin</td>
<td>Heparin allergy&lt;sup&gt;82&lt;/sup&gt; or HIT&lt;sup&gt;70,81&lt;/sup&gt;</td>
<td>Intravenous or subcutaneous</td>
<td>No adverse fetal outcome in 7/7 cases&lt;sup&gt;70,72,83&lt;/sup&gt;</td>
<td>No data</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Heparin allergy&lt;sup&gt;70,72,83,96&lt;/sup&gt; or HIT&lt;sup&gt;96&lt;/sup&gt;</td>
<td>Subcutaneous</td>
<td>No adverse fetal outcome in meta-analyses of large randomized trials&lt;sup&gt;99,100&lt;/sup&gt;</td>
<td>Breast milk concentration is 4%–8% of maternal plasma concentration&lt;sup&gt;101,102&lt;/sup&gt; To be used with caution&lt;sup&gt;86&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Low-dose aspirin</td>
<td>Supplemental therapy in women with mechanical heart valves&lt;sup&gt;98&lt;/sup&gt; or women with the antiphospholipid syndrome&lt;sup&gt;53&lt;/sup&gt;</td>
<td>Oral</td>
<td>Yes</td>
<td>No adverse fetal outcome in meta-analyses of large randomized trials&lt;sup&gt;99,100&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

IQ = intelligence quotient; HIT = heparin-induced thrombocytopenia.

Adapted from <i>Chest</i>,<sup>41</sup> <i>Obstet Gynecol</i>,<sup>43,52,57,100</sup> <i>N Engl J Med</i>,<sup>69,70</sup> <i>BJOG</i>,<sup>50</sup> <i>Arch Intern Med</i>,<sup>51</sup> <i>Int J Gynaecol Obstet</i>,<sup>53</sup> <i>Asian Cardiovasc Thorac Ann</i>,<sup>54</sup> <i>Heart</i>,<sup>55</sup> <i>Q J Med</i>,<sup>56</sup> <i>Thromb Haemost</i>,<sup>58,88</sup> <i>Blood Coagul</i>,<sup>59,88</sup> <i>Am J Obstet Gynecol</i>,<sup>60,87</sup> <i>J Heart Valve Dis</i>,<sup>84</sup> <i>BMJ</i>,<sup>95,99</sup> and <i>Pediatrics</i>.<sup>86</sup>
DIAGNOSIS AND MANAGEMENT OF VENOUS THROMBOEMBOLISM DURING PREGNANCY

When DVT occurs, it is more likely to be proximal and massive and to be located in the left lower extremity. In their meta-analysis, Ray and coworkers reported that 82.2% of DVTs occurred in the left lower extremity. This left-sided predominance is associated with proximal thromboses. Although distal thromboses are as likely to occur on the right as on the left, proximal thromboses occurring under the influence of estrogen are more likely to occur on the left. The predominance of left-sided proximal or iliofemoral thrombosis is thought to be due to a relative stenosis of the left common iliac vein where it lies between the lumbar vertebral body and the right common iliac artery, but the true mechanism is unknown. Pelvic vein thrombosis, which accounts for <1% of all cases of DVT, accounted for 11% in a series of cases among pregnant or postpartum patients.

The 2 most common initial symptoms, present in >80% of women with pregnancy-related DVT, are pain and swelling. When DVT is suspected, the first test recommended is compression ultrasonography of the proximal veins. When results are equivocal or an iliac vein thrombosis is suspected, magnetic resonance venography (MRV) may be used. MRV does not carry the radiation risk of contrast venography. The diagnosis of PE is similar to that in the nonpregnant individual. Ventilation/perfusion (V/Q) scanning gives relatively low radiation exposure to the fetus.

With an indeterminate study in a woman without a DVT, a confirmatory test, such as angiography or spiral computed tomography, is necessary to prevent the woman from unnecessary exposure to anticoagulation during pregnancy, at delivery, or in future pregnancies.

The initial management of VTE in pregnancy is with intravenous unfractionated heparin or subcutaneous LMWH. Pregnant women are generally admitted to the hospital. Those started on intravenous unfractionated heparin are converted to LMWH before discharge. LMWH is administered twice daily, as the half-life of LMWH is shorter in pregnancy. The shorter half-life may be due to the higher glomerular filtration rate, greater volume of distribution, or placental heparinase that accompanies pregnancy. Due to the shorter half-life, dosing requirements increase during pregnancy. Monitoring with monthly anti–factor Xa levels is recommended with doses adjusted accordingly. Thrombolysis, associated with a 6% rate of fetal loss, an 8% rate of maternal hemorrhage, and a 1% risk of maternal mortality, is reserved for cases of life- or limb-threatening VTE.

POSTPARTUM MANAGEMENT

Pneumatic compression devices are left in place until the patient is ambulatory and until anticoagulation is restarted after delivery. To minimize bleeding complications, resumption of anticoagulation should be postponed until 12 hours after vaginal delivery, 12 hours after epidural removal, or 24 hours after cesarean delivery. After the risk of postpartum hemorrhage has subsided, unless a woman prefers to remain on unfractionated heparin or LMWH, she may be bridged to warfarin for the remainder of the 6-week postpartum period. Women who had a thrombotic event during pregnancy should be continued on warfarin for at least another 3 to 6 months after delivery. Women on lifelong anticoagulation will be continued indefinitely. Although warfarin is contraindicated during pregnancy, it is not contraindicated during breastfeeding. In a study of the transfer of warfarin into breast milk, <25 ng/mL of warfarin was detected. The American Academy of Pediatrics (AAP) Committee on Drugs supports breastfeeding for women who take warfarin.

Since there are no data about whether fondaparinux enters breast milk, at the present time it should not be used routinely in women who are breastfeeding. It is an option, however, for women who are not breastfeeding. Fondaparinux may be used until a woman is bridged to warfarin. For women who have to be fully anticoagulated for only 6 weeks postpartum, an advantage of fondaparinux over warfarin is that it does not require monitoring. An advantage of fondaparinux over LMWH is that it requires only daily, as opposed to twice-daily, dosing.
SUMMARY
During pregnancy and the postpartum period, women are 4 times more likely to suffer from VTE than when they are not pregnant. Relative to pregnancy, the risk is even higher postpartum. The overall risk of VTE is approximately 2 per 1,000 births. The most important risk factors during pregnancy are thrombophilia and a history of thrombosis. Despite the increased risk for thrombosis during pregnancy and postpartum, most women do not require anticoagulation. Those who do include women with a current VTE, women on lifelong anticoagulation, and many women with thrombophilia or a history of thrombosis. Warfarin crosses the placenta and is associated with miscarriage, congenital anomalies, stillbirth, fetal bleeding, and poor neurologic outcome. Therefore, recommended options for anticoagulation in pregnancy are limited to heparins, which do not cross the placenta. LMWH is preferred over unfractionated heparin because LMWH has a longer half-life and is presumed to have fewer side effects. The longer half-life is a disadvantage around the time of delivery when unfractionated heparin, with its shorter half-life, is easier to manage. For women who develop HIT or severe cutaneous reactions, fondaparinux is probably the agent of choice. Women who do not require lifelong anticoagulation, but do require anticoagulation during pregnancy, will still require anticoagulation for the first 6 weeks postpartum.

CONFLICT OF INTEREST
Andra H. James, MD, MPH, reports no conflict of interest with the sponsor of this supplement article or products discussed in this article.

References


73. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the...


The Pharmacoeconomics of Deep Vein Thrombosis Treatment

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ABSTRACT

Venous thromboembolism (VTE), encompassing both deep vein thrombosis (DVT) and pulmonary embolism, remains a common and costly condition that is associated with significant morbidity and mortality. Treatment options for initial management of DVT include unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), and fondaparinux, which is the first of a new class of pentasaccharide antithrombotic agents with anti-factor Xa activity. LMWHs are an important tool in DVT management, offering advantages over UFH such as ease of dosing, lack of need for coagulation monitoring, and reduced risk for heparin-induced thrombocytopenia (HIT). Fondaparinux is also characterized by a simple dosing regimen, no need for coagulation monitoring, and potentially a lower risk of HIT compared with LMWH. In a recent clinical trial of DVT management, efficacy and bleeding rates with fondaparinux appeared similar to those observed with LMWH. In contrast to LMWH, fondaparinux is generally given as a fixed dose across a range of patient weights rather than calculated per individual patient weight. Given the increasing economic burden of VTE, particularly due to its increased rate among the elderly, pharmacoeconomic analyses have become a particularly useful tool to aid in selecting among similarly effective and safe agents for VTE treatment. A recent cost-effective analysis demonstrated that fondaparinux use offers an attractive economic alternative to other agents for initial DVT therapy that could yield cost savings without compromising clinical outcomes or patient safety. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Anticoagulation; Deep vein thrombosis; Pharmacoeconomics; Venous thromboembolism

Venous thromboembolism (VTE), encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a common condition in the United States. More important, VTE is associated with significant morbidity and mortality. Reflecting this, VTE is responsible for approximately 250,000 hospitalizations in the United States each year. Of the >200,000 new cases of VTE that occur annually, 20% of persons with an acute PE present with sudden death and 30% of those with other VTE syndromes die within the subsequent 30 days. Survivors face an approximately 30% risk for recurrent VTE over the next 10 years.

Limited data exist regarding the economic burden of VTE. Published estimates suggest that the direct costs of VTE approach $3 to $4 billion annually. These estimates do not reflect the additional indirect cost of lost workdays and productivity that often accompany a VTE diagnosis. Furthermore, a number of other so-called “hidden” cost considerations arise in relation to VTE and its treatment. Depending on the anticoagulant agent used for VTE therapy, there are additional costs potentially associated with therapeutic monitoring and with the agents used to reverse the pharmacologic effect in the event of overanticoagulation (e.g., protamine for overanticoagulation with unfractionated heparin [UFH]). Furthermore, management of potential side effects of anticoagulants, including bleeding and heparin-induced thrombocytopenia (HIT) are expensive. Finally, the costs related to long-term complications of VTE, including clot recurrence and postthrombotic syndrome, can ac-
count for up to approximately 75% of the overall costs of treating the primary event.6  

Although there have been many advances in VTE diagnosis and management, the primary goals of anticoagulation therapy in the treatment of DVT remain the same: to prevent clot propagation and recurrence.7 Presently, treatment options for initial management of DVT include UFH, low-molecular-weight heparins (LMWHs), and fondaparinux, which is the first of a new class of pentasaccharide antithrombotic agents with anti–factor Xa activity. Since their advent in the 1980s, LMWHs have evolved as an important tool in DVT management. LMWHs offer advantages over UFH, which include ease of dosing, no need for coagulation monitoring, and a reduced risk for HIT.4,5,7,8 In addition, clinical trials and various meta-analyses indicate that LMWHs are either equivalent or superior to UFH with respect to efficacy for initial treatment of VTE.9,10 LMWHs may also reduce bleeding complications when compared with UFH. Because of these attributes, LMWHs have been shown to be cost-effective for DVT therapy when compared with UFH.11,12  

Similar to LMWHs, fondaparinux use is characterized by a simple dosing regimen and does not require coagulation monitoring.9 In addition, the risk of HIT is potentially lower with fondaparinux compared with both UFH and LMWH.13 Fondaparinux prevents thrombus formation by selectively binding to the pentasaccharide binding site on antithrombin III and enhancing its inactivation of factor Xa, with a resultant decrease in thrombin generation.14 In a recent clinical trial of DVT management, efficacy and bleeding rates with fondaparinux appeared similar to those observed with LMWH.15 In contrast to LMWHs, fondaparinux is generally given as a fixed dose across a range of patient weights rather than calculated per individual patient weight.  

When selecting an anticoagulant for use either in an individual patient or adoption in a healthcare system, clinicians and healthcare policy makers must consider a number of factors. In the absence of data indicating that a particular agent is superior to others in terms of efficacy, cost and implementation concerns become important. Economic analyses, therefore, are particularly useful when weighing anticoagulant options for DVT management.  

To facilitate this process, it is necessary to review recent clinical and pharmacoeconomic data comparing fondaparinux with enoxaparin for the treatment of VTE and DVT. Additionally, it is important to evaluate factors that may affect the relative financial consequences of different approaches to DVT therapy.  

**EFFICACY OF FONDAPARINUX VERSUS ENOXAPARIN FOR DEEP VEIN THROMBOSIS TREATMENT**  

In a recent randomized, multicenter, double-blind clinical trial Mondial Assessment of Thromboembolism Treatment Initiated by Synthetic Pentasaccharide With Symptomatic Endpoints—Deep Vein Thrombosis (MATISSE-DVT), Buller and associates15 determined that once-daily subcutaneous fondaparinux was at least as effective and as safe as twice-daily, body-weight–adjusted enoxaparin in the initial treatment of patients with symptomatic DVT. A total of 2,205 patients with acute symptomatic DVT were randomized to treatment with either fondaparinux once-daily subcutaneously dosed by weight category: 5.0 mg (body weight <50 kg), 7.5 mg (body weight 50–100 kg), and 10 mg (body weight >100 kg), or enoxaparin 1 mg/kg of body weight, subcutaneously dosed twice daily. Treatment was continued for >5 days and until vitamin K antagonists induced an international normalized ratio >2.0 for 2 consecutive days. Patients excluded from this study included those with symptomatic PE, a contraindication for anticoagulation, or elevated serum creatinine levels (>2 mg/dL).  

A total of 43 (3.9%) patients randomly assigned to fondaparinux and 45 (4.1%) patients randomly assigned to enoxaparin experienced symptomatic recurrent VTE during the 3-month study period (absolute difference, −0.15 percentage points [95% confidence interval (CI), −1.8 to 1.5]), indicating comparable efficacy between the 2 agents (Figure 1).15 The incidence of major bleeding during initial treatment was also similar between the treatment groups, occurring in 12 (1.1%) patients receiving fondaparinux and 13 (1.2%) patients receiving enoxaparin (absolute difference, −0.1 percentage points [95% CI, −1.0 to 0.8]) (Figure 1). Bleeding contributed to death in 2 patients in the fondaparinux group. Mortality rates during the 3-month study period were 3.8% and 3.0% in the fondaparinux and enoxaparin groups, respectively (absolute difference, 0.8 percentage points [95% CI, −0.8 to 2.3]). Subgroup analysis indicated that both treatment groups had similar efficacy and safety independent of body weight. Also, among the approximately 33% of patients in each group who received some or all of their initial treatment at home, the incidence of clinical outcomes was low and similar in each group.  

**COST-EFFECTIVENESS OF FONDAPARINUX VERSUS ENOXAPARIN FOR DEEP VEIN THROMBOSIS TREATMENT**  

A recent cost-effective analysis determined that use of fondaparinux for initial DVT therapy may offer substantial cost savings relative to enoxaparin from a healthcare system perspective.16 The researchers created a decision model that evaluated a cohort of 1,000 hypothetical subjects with acute DVT who required injectable DVT treatment for 5 days (with once-daily enoxaparin 1.5 mg/kg or once-daily fondaparinux 7.5 mg). Estimates for model inputs were created based on values identified in a review of the literature and a meta-analysis of bleeding rates across the VTE trials with fondaparinux (Table 1).13,15–22 Incremental costs for DVT therapy and the economic outcomes of the complications associated with DVT management served as the primary end point. The authors purposefully biased the model against fondaparinux. This was achieved through
several major assumptions underlying the analysis: (1) the agent chosen for therapy did not alter the duration of therapy, hospital length of stay if admitted, probability of suffering a subsequent PE, quality of life, or the risk for mortality; (2) the population had essentially normal renal function; (3) the prevalence of obesity was low; (4) once-daily enoxaparin dosing was used to minimize related costs, even though twice-daily dosing may be recommended\textsuperscript{23}; and (5) neither pharmacy administration costs nor costs associated with drug waste were included (both would be higher for enoxaparin versus fondaparinux owing to weight-based dosing and the need to create patient-specific syringes.

Figure 1  Clinical outcomes of fondaparinux versus enoxaparin for the treatment of deep vein thrombosis. No differences were observed between fondaparinux and low-molecular-weight heparin. In the fondaparinux group, causes of death were pulmonary embolism, including unexplained death (n = 5), bleeding (n = 5), cancer (n = 24), and other (n = 7). Of the 5 fatal bleeding episodes, 2 occurred during treatment with fondaparinux; the others occurred during long-term therapy with vitamin K antagonists. In the enoxaparin group, causes of death were pulmonary embolism, including unexplained death (n = 5), cancer (n = 19), and other (n = 9). (Adapted from Ann Intern Med.\textsuperscript{15})

Table 1  Model inputs for rates of venous thromboembolism (VTE) recurrence, major bleeding, and heparin-induced thrombocytopenia (HIT), and associated costs per event

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case</th>
<th>Ranges Tested</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Rate with enoxaparin</td>
<td>4.1%</td>
<td>3.0%–5.4%</td>
<td>Buller et al., 2004\textsuperscript{15}</td>
</tr>
<tr>
<td>— OR with fondaparinux</td>
<td>0.96</td>
<td>0.63–1.43</td>
<td>Buller et al., 2004\textsuperscript{15}</td>
</tr>
<tr>
<td>— Cost per recurrence</td>
<td>$4,318</td>
<td>$3,239–$5,398</td>
<td>Gould et al., 1999\textsuperscript{12}</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Rate with enoxaparin</td>
<td>1.2%</td>
<td>0.6%–2.0%</td>
<td>Buller et al., 2004\textsuperscript{15}</td>
</tr>
<tr>
<td>— OR with fondaparinux</td>
<td>1.05</td>
<td>0.60–1.82</td>
<td>Buller et al., 2003\textsuperscript{18}</td>
</tr>
<tr>
<td>— Cost per major bleed</td>
<td>$5,355</td>
<td>$4,016–$6,694</td>
<td>Aujesky et al., 2005\textsuperscript{17}</td>
</tr>
<tr>
<td>HIT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Rate with enoxaparin</td>
<td>0.5%</td>
<td>0.3%–1.3%</td>
<td>Prandoni et al., 2005\textsuperscript{21}</td>
</tr>
<tr>
<td>— OR with fondaparinux</td>
<td>0.10</td>
<td>0.01–0.50</td>
<td>Savi et al., 2005\textsuperscript{13}</td>
</tr>
<tr>
<td>— Cost per case of HIT</td>
<td>$10,081</td>
<td>$7,561–$12,601</td>
<td>McGarry et al., 2004\textsuperscript{20}</td>
</tr>
</tbody>
</table>

OR = odds ratio.

Adapted from Shorr AF, Jackson WL, Moores LK, Warkentin TE. Minimizing costs for treating deep vein thrombosis: the role for fondaparinux. J Thromb Thrombolysis. 2007, Volume 23, Table 1, page 231, with permission from Springer Science and Business Media.\textsuperscript{16}
of enoxaparin). In addition, it was assumed that the development of HIT did not increase the risk for death or significantly decrease quality of life. By limiting the potential clinical consequences of HIT and because HIT should not occur with fondaparinux,13 the model favored enoxaparin.16

Multiple sensitivity analyses were conducted to assess the impact of the assumptions. To evaluate the overall uncertainty in the model and to generate 95% CIs around the estimated cost differential, the authors performed a Monte Carlo simulation.16 The analysis made 2 additional assumptions: (1) the base-case patient weight was 80 kg and (2) the base-case cost of acquisition was $96 and $50 for enoxaparin and fondaparinux, respectively. Model inputs for rates of VTE recurrence, major bleeding, and HIT, as well as the costs associated with these events are listed in Table 1.

Results of the base-case analysis are summarized in Table 2. Total costs per patient treated associated with the use of fondaparinux were $472 compared with $769 with use of enoxaparin.16 This difference resulted in a 40% reduction in composite system costs. Drug acquisition cost was the major driver of overall costs. Univariate sensitivity analysis indicated that the model was mildly sensitive to the costs of the agents, particularly enoxaparin, and to patient weight (Figure 2). The 95% CI around the overall cost difference per patient ranged from $48 to $401, favoring cost savings with fondaparinux. Break-even analysis indicated the findings to be robust over a wide range of likely clinical scenarios.

**DOSING AND OTHER CONSIDERATIONS: POTENTIAL COST IMPACT ON CHOICE OF DEEP VEIN THROMBOSIS THERAPY**

Several considerations, in addition to those addressed in this cost analysis, can substantially affect the relative costs associated with different approaches to DVT therapy. One important consideration is dosing regimen differences between agents. For VTE treatment fondaparinux is dosed once daily by subcutaneous injection based on patient weight category: 5 mg (body weight <50 kg), 7.5 mg (body weight 50–100 kg), or 10 mg (body weight >100 kg).24 Data from the MATISSE-DVT trial and a post-hoc analysis of data from obese and nonobese patients in both the MATISSE-DVT and MATISSE-PE trials demonstrate that efficacy and safety outcomes remained comparable between fondaparinux dosed once daily based on weight category versus either LMWH or UFH regardless of body weight (up to 217 kg) or body mass index (BMI; up to 80).25

Enoxaparin dosing for VTE treatment is based directly on the patient’s weight and, unlike fondaparinux, is indicated for inhospital treatment for patients with acute DVT (with or without PE) and outpatient treatment for acute DVT only (without PE).26 The approved enoxaparin regimens are: 1 mg/kg twice daily or 1.5 mg/kg once daily for inpatients, and 1 mg/kg twice daily for outpatient treatment of DVT. Notably, results of a controlled trial of enoxaparin versus UFH for treatment of VTE suggested reduced efficacy in obese patients (BMI >27) with a once-daily (1.5 mg/kg) versus twice-daily (1 mg/kg) enoxaparin regimen (VTE recurrence rates: 7.3% vs. 3.4%, respectively).23 Like enoxaparin, the LMWH tinzaparin is dosed by specific patient weight: 175 IU/kg subcutaneously once daily.27 The following calculation is required to determine the correct volume to be withdrawn from the 20,000 IU/mL vial with an appropriately calibrated syringe for the correct dose: patient weight (in kilograms) × 0.00875 mL/kg = volume (milliliters) to be administered.

These dose regimen differences among the various anticoagulant agents have significant cost implications for VTE management. Since fondaparinux is dosed based on weight category with prefilled syringes available in the exact doses needed (5 mg, 7.5 mg, and 10 mg doses), drug waste is avoided. Furthermore, pharmacy administration costs are minimized because dosing is once daily and no pharmacist time is needed for syringe preparation. A simplified regimen and once-daily dosing also promote outpatient therapy with fondaparinux, which can drastically reduce costs from a healthcare system perspective. This nearly 1-size-fits-all aspect of fondaparinux also enhances patient safety as it minimizes the chance that a patient will receive an overdose because of an error made during syringe preparation. In contrast, enoxaparin dosing is subject to drug waste and higher pharmacy administration costs relative to fondaparinux because it is dosed based on patient weight. For example, doses for odd weights do not readily fall within the range for prefilled enoxaparin syringes, resulting in waste of part of the premeasured dose and requiring additional pharmacy time to prepare the syringe. Also, doses >150 mg must be prepared from a multidose vial. Twice-daily dosing (indicated for outpatients and, possibly, obese patients) also increases pharmacy administration costs. These issues may also complicate outpatient treatment with enoxaparin or tinzaparin because many patients may have limited capability to titrate prefilled syringes or drawdown dosages from multidose vials.15

As the investigators of the abovementioned cost analysis observed, their analysis likely underplayed the cost implications of enoxaparin’s weight-based dosing, given their assumptions of no drug waste, little obesity, and once-daily enoxaparin dosing.16 Particularly noteworthy is the rising incidence of obesity in the United States, which currently affects approximately 33% of the adult population and has a direct impact on the cost of specific weight-based medications such as enoxaparin.16,28

While playing only a minor role in determining the overall financial outcomes of DVT management, the difference in risk of HIT between fondaparinux and enoxaparin is potentially clinically meaningful. LMWH is associated with a much lower prevalence of HIT versus UFH (0% to 0.8% vs. 1% to 5%, respectively).29 Use of fondaparinux, however, should theoretically be completely devoid of a risk for HIT. The absence of HIT with fondaparinux relates to its
limited or absent cross-reactivity in vitro with HIT antibod-
ies. Furthermore, fondaparinux has been successfully
used for the treatment of HIT.

OTHER PHARMACOECONOMIC ANALYSES
No other pharmacoeconomic analyses to date have ad-
dressed the relative cost-effectiveness of fondaparinux
versus enoxaparin for the treatment of VTE. In the area of VTE
prophylaxis, however, several studies have explored
fondaparinux’s cost-effectiveness. These reports reveal that
fondaparinux yields total economic savings with similar or
improved clinical outcomes over enoxaparin in orthopedic
patients. For example, Spruill and colleagues performed an incremental cost analysis from an institutional
perspective using efficacy and safety data from a random-
ized clinical trial of fondaparinux versus enoxaparin for
DVT prophylaxis in total knee replacement surgery. They
calculated a $1,081 cost savings with fondaparinux over
enoxaparin per VTE event avoided. Sullivan and col-
leagues used a cohort simulation model to perform a
trial-based analysis and a label-based analysis from the
healthcare payer perspective to determine the cost-effective-
ness of fondaparinux compared with enoxaparin for VTE
prophylaxis in patients undergoing major orthopedic sur-
gery. In the trial-based analysis, fondaparinux was esti-
mated to prevent 15.1 symptomatic VTE events per 1,000
patients at 3 months after surgery, and was associated with
a cost savings of $89 per patient. In the label-based analysis,
fondaparinux was estimated to prevent 17.8 symptomatic
VTE events per 1,000 patients at 3 months after surgery,
and was associated with a cost savings of $141 per patient.

A recent study addressed the cost-effectiveness of
LMWH versus UFH for the prevention of VTE in medical
patients. Using a decision model approach, the authors

Table 2 Results of base-case cost-effective analysis of fondaparinux
versus enoxaparin for treatment of deep vein thrombosis (DVT)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enoxaparin</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug costs</td>
<td>$480,000</td>
<td>$250,000</td>
</tr>
<tr>
<td>Recurrences (n)</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Bleeds (n)</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Cases of HIT (n)</td>
<td>5</td>
<td>&lt;1*</td>
</tr>
<tr>
<td>Per patient cost</td>
<td>$769</td>
<td>$472</td>
</tr>
</tbody>
</table>

HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight hepa-
rin.

*Although in vitro antibody studies suggested that the risk for HIT is eliminated
in patients receiving fondaparinux, the current model conservatively estimated that
fondaparinux reduced the risk for HIT by 90% relative to LMWH.

Adapted from J Thromb Thrombolysis.
concluded that despite higher acquisition costs, the use of LMWH in hospitalized patients was cost-saving, primarily due to the lower rate of HIT associated with the use of LMWH. According to this analysis, routine use of LMWH would save approximately $89 per patient (95% CI, $7 to $373). No cost-effective analyses evaluating the use of fondaparinux for VTE prevention in medically ill patients have been reported.

No studies have directly addressed the cost-effectiveness of fondaparinux versus UFH for the management of VTE. However, a number of cost-effective analyses, including one based on a meta-analysis of randomized trials of LMWH versus UFH for the treatment of DVT, have demonstrated the economic superiority of LMWH over UFH for this indication. Based on available pharmacoeconomic and clinical data, therefore, it would seem reasonable to conclude that fondaparinux for VTE management would likely result in significant cost savings over UFH as well. Furthermore, most economic comparisons have used enoxaparin as the representative LMWH. Given the varying cost of different LMWHs, it is unclear how the findings from cost studies evaluating enoxaparin might differ if a less expensive LMWH were used as the alternative strategy.

SUMMARY
VTE and its subsequent management remain costly irrespective of whether it arises de novo or as a complication of surgery or hospitalization. New options for VTE therapy and prevention are available that offer at least comparable efficacy and safety to standard agents, as well as dosing and convenience advantages that may translate into enhanced savings. Given the increasing economic burden of VTE, particularly due to its increased rate among the elderly, pharmacoeconomic analyses have become a particularly useful tool to aid in selecting among similarly effective and safe agents for VTE treatment. A recent cost-effective analysis demonstrated that fondaparinux use offers an attractive economic alternative to other agents for initial DVT therapy that could yield cost savings without compromising clinical outcomes or patient safety.

CONFLICT OF INTEREST
The author reports the following conflicts of interest with the sponsor of this supplement article or products discussed in this article. Andrew F. Shorr, MD, MPH, has served as a member of the Speakers’ Bureau for GlaxoSmithKline and sanofi-aventis; has served as a consultant/advisory board member for GlaxoSmithKline and sanofi-aventis; and has received research/grant support from GlaxoSmithKline and sanofi-aventis.

References


Management of Venous Thromboembolism

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