Venous thromboembolism: Highlights of recent studies

Deep venous thrombosis (DVT) and pulmonary embolism (PE) are responsible for significant morbidity and mortality, particularly in critically ill patients.[1-3] Silent PE is a major cause for concern—without warning, patients can die within a few hours of the event. Clearly, several factors are essential; these include risk assessment, prompt and accurate diagnosis, aggressive prophylaxis, and treatment with the most effective agents available.

Pulmonary angiography has long been considered the gold standard for the diagnosis of PE. In recent years, though, increased attention has focused on the role of noninvasive studies, such as CT scanning and the D-dimer assay. In addition, a major development has occurred in the treatment of venous thromboembolism (VTE)—the availability of low molecular weight heparin (LMWH).

These advances in treatment and diagnosis are reflected in the recent VTE literature. This Clinical Update will present the highlights of some of the relevant studies within the past year.

How useful is a negative CT scan?

Swensen and associates[4] retrospectively studied 1512 patients who had clinically suspected acute PE. CT results were interpreted as being negative for acute PE in 67% of patients. During 3 months' follow-up, DVT or PE occurred in 8 of the patients with negative CT findings; the cumulative 3-month incidence of DVT or PE was 0.5%.

The authors conclude that it is generally safe to withhold anticoagulant therapy in patients with negative CT findings, assuming there is no other evidence of VTE. Compared with lung scanning, CT is less expensive and less time-consuming and has less interobserver variability.

Is there a role for magnetic resonance angiography?

According to a study from the Netherlands, magnetic resonance angiography (MRA) may have a promising role in the evaluation of PE. Oudkerk and associates[5] found that this study was sensitive and specific for segmental or larger PE. They studied 118 patients who had suspected PE and abnormal perfusion scan findings. The patients underwent MRA before conventional angiography. Two reviewers, who were blinded to the results of conventional pulmonary angiography, independently assessed the MRA images.

PE was documented by pulmonary angiography in 35 patients (30%). MRA detected PE in 27 of the 35 patients, yielding a sensitivity of 77% (Figure 1). The sensitivity of MRA for subsegmental, segmental, and central or lobar PE was 40%, 84%, and 100%, respectively. The results of MRA were false-positive in 2 patients (specificity, 98%).

The authors note that the accuracy of MRA is comparable to that of helical CT, but MRA involves safer contrast agents and does not involve ionizing radiation.

How sensitive is the D-dimer assay?

Bates and colleagues[6] found that a latex agglutination assay is very sensitive to the presence of VTE. A negative result may reliably rule out the diagnosis in patients who have a low or moderate pretest probability of VTE. They studied 595 patients who had suspected DVT or PE. The D-dimer assay had a sensitivity of 96%, a specificity of 45%, and a negative predictive value of 98%. In patients with a low or moderate pretest probability of VTE, the sensitivity and negative predictive value were 97% and 99%, respectively.

de Monye and associates[7] found that the accuracy of the D-dimer assay depends on the location of the PE. The assay is accurate in excluding segmental and large emboli (sensitivity, 93%), but it may miss the smaller, subsegmental emboli (sensitivity, 50%).

While the D-dimer test has proved to be useful in the evaluation of suspected DVT, one disadvantage is that results are frequently abnormal, especially in certain patient groups. Schutgens and colleagues[8] retrospectively studied 704 outpatients (mean age, 59 years) in whom DVT was suspected. The patients underwent a semi-quantitative D-dimer test and ultrasonography (US). DVT was detected in 36% of the patients.

The accuracy of the D-dimer test

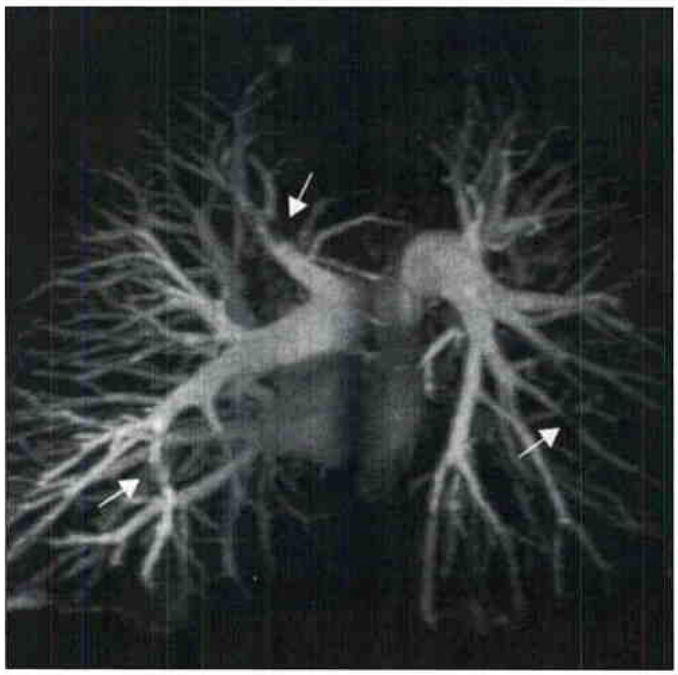


Figure 1 – ***Multiple pulmonary emboli*** *are clearly visible in this magnetic resonance angiogram (arrows). (From Oudkerk M et al.* Lancet. *2002.*[5]*)*

was evaluated in 61 patients who were receiving anticoagulants, 127 patients who had previous thrombosis, and 47 patients with malignancy (39 patients had more than 1 of these features). The 508 remaining patients were the reference group.

In the reference group, the D-dimer test had a sensitivity of 99% and a negative predictive value of 98%. The sensitivity was 75% in the group taking anticoagulants, 96% in those with previous thrombosis, and 100% in patients with malignancy. However, D-dimer results were abnormal in 91% of the patients with malignancy. The prevalence of positive results increased with age.

The authors concluded that the D-dimer test generally has good sensitivity and negative predictive value, but its sensitivity is notably diminished in persons who are taking anticoagulants. In addition, the D-dimer test may not be particularly useful in elderly patients who have cancer, because of the high rate of positive results observed in these patients.

Using the D-dimer test in conjunction with clinical pretest probability

The standard approach to the workup of suspected DVT is compression US; if the results are normal, the test usually is repeated 1 week later. Kraaijenhagen and associates[9] found that a normal D-dimer result can obviate the need for repeating US in patients who have a low clinical pretest probability of DVT.

In this study, 1756 patients with suspected DVT underwent US and whole-blood D-dimer assay. Those patients with normal US findings but abnormal D-dimer results underwent another US. The prevalence of DVT was 22%. The results of US and D-dimer testing were normal in 828 patients (47%). Six of these patients returned with confirmed symptomatic VTE. Repeated US was avoided in 61% of the patients who had an initially normal test result.

The complication rate was 1.6% in patients who had both a low clinical pretest probability of DVT and normal US results at referral. It was 1.8% in those who had a low pretest probability and normal D-dimer result.

The authors conclude that it is not necessary to repeat US if the initial findings were normal and the patient's D-dimer results were normal. In patients with a low clinical pretest probability of DVT, a normal D-dimer result appears to be as reliable as normal US results with respect to ruling out DVT.

The combination of low pretest probability of DVT and negative D-dimer results rules out DVT in most symptomatic patients, according to a study by Kearon and associates.[10] It appears to be safe to withhold further testing and anticoagulant therapy in these patients.

They studied 445 outpatients with a suspected first episode of DVT. Patients were categorized as having low, moderate, or high pretest probability of DVT and underwent whole-blood D-dimer testing. Patients who had low pretest probability and negative D-dimer results did not undergo further diagnostic testing. The remaining patients underwent additional testing for DVT.

The authors found that 40% of patients had a low pretest probability and negative D-dimer results. These patients were followed for 3 months. One of these patients had DVT during follow-up. The negative predictive value was 99.4%.

Among the 268 patients who had moderate or high pretest probability or positive D-dimer results, 63 had DVT detected on the day of presentation or during the subsequent additional testing. None of the patients in this group had an episode of DVT or PE during 3-month follow-up.

The use of D-dimer testing in conjunction with clinical pretest probability can also facilitate the workup of suspected PE. This ap-

proach can reduce the need for diagnostic imaging. Wells and associates[11] studied 930 patients in whom PE was suspected. Patients' pretest probability of PE was determined, and the patients underwent D-dimer testing. Those with a low pretest probability and normal D-dimer results did not undergo further testing. The remaining patients underwent ventilation-perfusion lung scanning. If the scan was nondiagnostic, bilateral deep venous US was performed. Further tests were done as needed.

The negative predictive value for the combined strategy of using pretest probability and D-dimer was 99.5% in patients with low pretest probability and negative D-dimer results. Variables included in the assessment of clinical pretest probability of PE are shown in the Table. An algorithmic approach to the workup of suspected PE is shown in Figures 2 and 3.

Table – Variables included in the assessment of clinical pretest probability of PE

Clinical signs and symptoms of DVT (leg swelling and pain with palpation in the deep venous region)
Heart rate higher than 100 beats per minute
Immobilization (bed rest for 3 or more consecutive days)
Surgery in the previous 4 weeks
Previously diagnosed DVT or PE
Hemoptysis
Malignancy
PE is likely or more likely than an alternative diagnosis

PE, pulmonary embolism; DVT, deep venous thrombosis.

Compliance with treatment guidelines

Arnold and associates[12] found that two thirds of VTE cases for which prophylaxis had been indicated might have been prevented if physicians had followed the American College of Chest Physicians guidelines for the prevention of VTE. In some cases, the wrong type of prophylaxis was given or the duration of prophylaxis was inadequate; but in most cases, prophylaxis was omitted altogether. Missed opportunities occurred most often in the setting of nonorthopedic surgery, pneumonia, and stroke.

Recurrence of VTE during warfarin therapy

Luk and associates[13] found that recurrent VTE is more likely to develop in cancer patients during treatment with warfarin. Long-term treatment with LMWH may be effective in this setting.

They studied patients at 3 tertiary care teaching hospitals who were receiving warfarin therapy. Of 887 patients, VTE recurred in 32. The incidence of recurrence was higher in patients with cancer than in those who did not have cancer. Patients with recurrent VTE were treated with an LMWH. Symptomatic recurrence developed during LMWH therapy in 3 patients. Most of the patients who died during the study died of malignancy; none died of PE or bleeding.

Further evidence of the benefits of LMWH

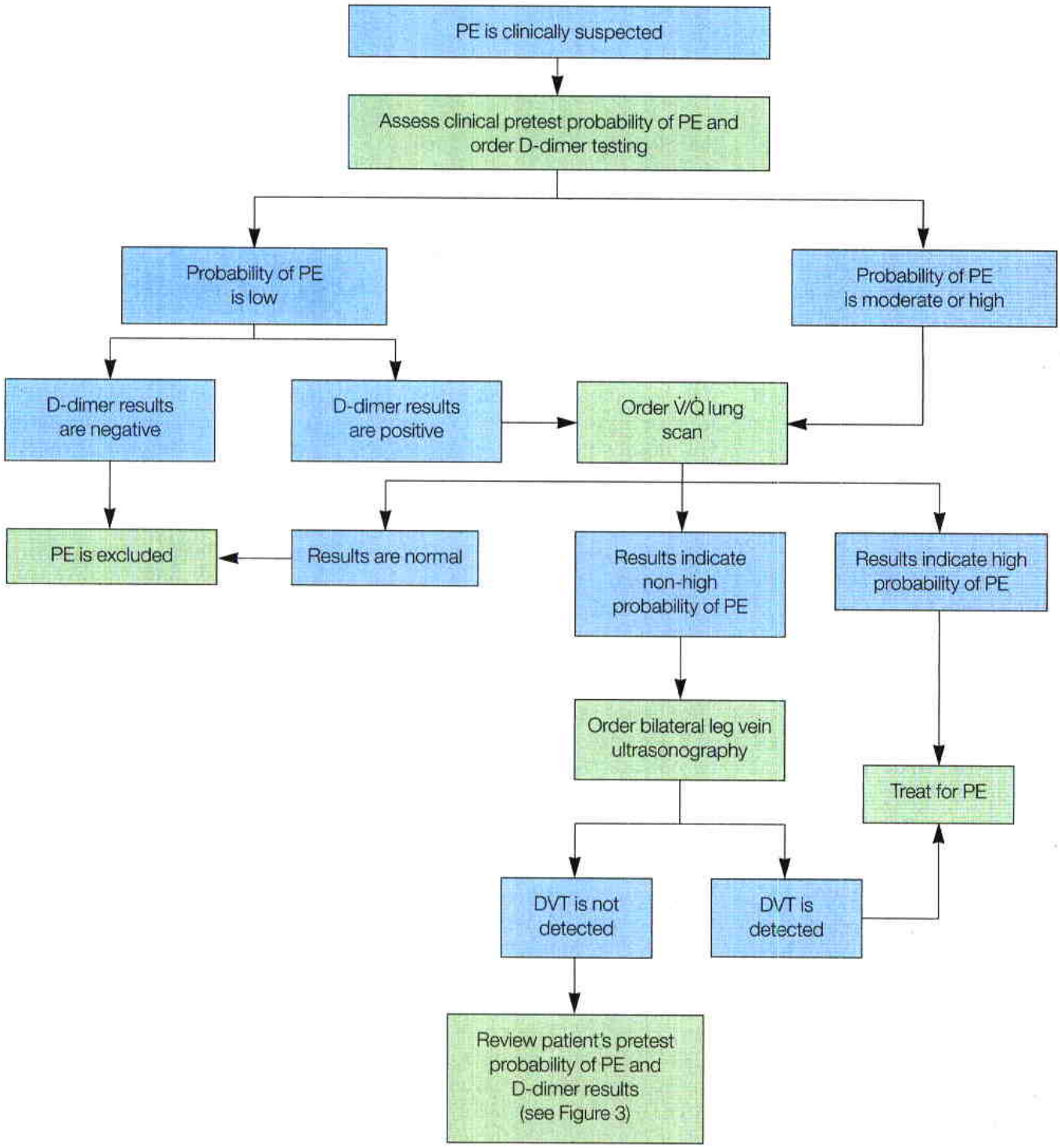
In the past, the conventional approach to preventing and treating VTE was to give intravenous unfractionated heparin (UH) in the hospital before discharging the patient on a regimen of oral warfarin. However, LMWH is now available and is a safe and effective alternative to UH. According to a meta-analysis by Dolovich and associates,[14] LMWH is at least as effective as UH in the treatment of VTE.

LMWH has a number of advantages over UH in the treatment of VTE. It offers better safety and efficacy, improved pharmacokinetics, and a longer half-life, and it can be given subcutaneously once or twice daily without the need for laboratory monitoring. LMWH has the potential for reducing the costs associated with VTE prophylaxis and treatment, without compromising patient care.

The development of LMWH has made it possible to shift the management of DVT from inpatient to outpatient settings, thus reducing costs. The 4 following studies provide convincing support:

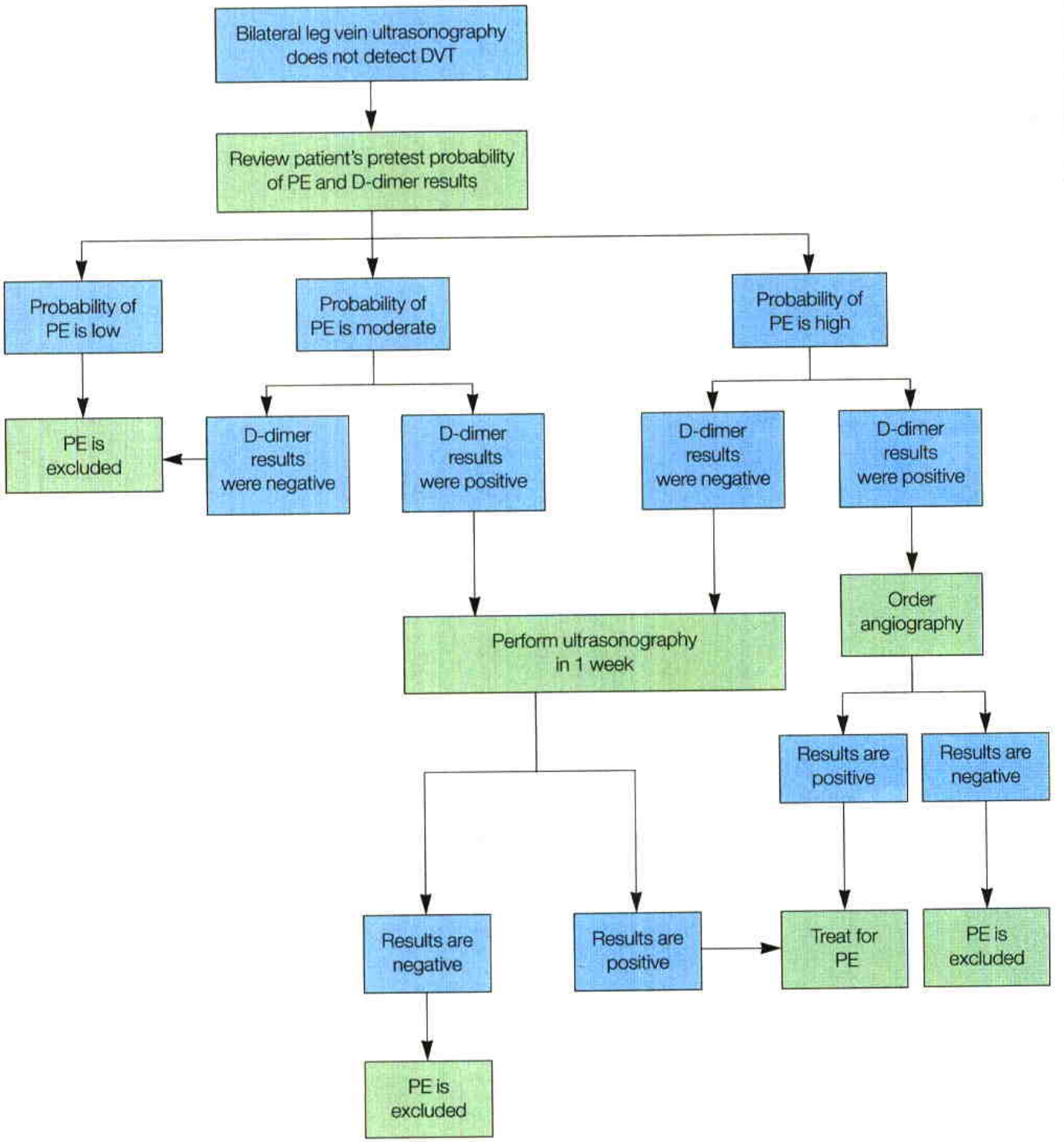
- Spyropoulos and associates[15] studied patients with acute, proximal DVT. As initial anticoagulant therapy, 64 patients received intravenous UH in the hospital, and 65 received subcutaneous enoxaparin (an LMWH) primarily at home. This treatment was followed by warfarin therapy. The authors found no significant differences in the incidence of recurrent VTE events or bleeding events. The mean cost per patient was $9347 in the enoxaparin group, compared with $11,930 in the UH group.
- Rymes and associates[16] found that outpatient management of DVT with LMWH is as safe as hospital treatment with continuous infusion of UH. For patients treated at home, there was a lower incidence of recurrence and a lower complication rate.
- Huse and coworkers[17] found that outpatient therapy for DVT with LMWH and warfarin was associated with earlier hospital discharge, fewer readmissions, and lower to-

Figure 2 – Algorithm for evaluating suspected PE: The initial steps



PE, pulmonary embolism; V̇/Q̇, ventilation-perfusion; DVT, deep venous thrombosis.
From Wells PS et al. *Ann Intern Med.* 2001.[11]

Figure 3 – Algorithm for evaluating suspected PE: The steps after ultrasonography



PE, pulmonary embolism; DVT, deep venous thrombosis.
From Wells PS et al. *Ann Intern Med.* 2001.[11]

tal DVT-related costs, compared with warfarin monotherapy. They compared the outcomes and costs associated with enoxaparin therapy plus warfarin with those of warfarin alone in outpatients with DVT. They analyzed data from medical and pharmacy claims paid by 37 US health plans.

The mean costs of outpatient therapy were higher in the enoxaparin/warfarin group, but the rate of readmission was significantly lower (6.7% vs 9.0%, $P < .05$). As a result, the subsequent inpatient costs were reduced by $140 per patient. The total cost savings (net of higher outpatient costs) were $1151 per patient.

• In an Australian study, Smith and associates[18] analyzed the costs associated with at-home treatment with enoxaparin compared with standard inpatient care in patients with uncomplicated DVT. They found that at-home LMWH treatment was cost-effective and patient satisfaction was high.

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