Thromboembolic Diseases

Incidence, Risk Factors, and Categories

Deep venous thrombosis (DVT) and pulmonary embolism (PE), together called venous thromboembolism (VTE), remain a serious health care problem. Together it has been estimated that there are more than 900,000 cases per year in this country alone.\(^1\) Approximately 300,000 individuals die of PE every year and deaths from PE are 5 times more common than deaths from breast cancer, motor vehicle accidents, and AIDS combined. Venous thromboembolism is the third most common vascular disease after heart disease and stroke. Additionally, patients with post-thrombotic syndrome (pain and leg swelling after thrombosis) suffer poor quality of life due to chronic symptoms. The incidence of post-thrombotic syndrome is as high as 30% over 8 years.\(^2\)

Acquired risk factors include age, malignancy, surgery and trauma, immobilization, oral contraceptive use, hormone replacement therapy, pregnancy and the puerperium, obesity, neurological disease, cardiac disease, and antiphospholipid antibodies.\(^3\) Genetic causes include deficiencies of antithrombin, proteins C and S, factor V Leiden, prothrombin 20210A, blood group non-O, hyperhomocysteinemia, dysfibrinogenemia, dysplasminogenemia, reduced heparin cofactor II activity, elevated levels of clotting factors such as factors XI, IX, VII, VIII, X, and II, and plasminogen activator inhibitor-1.\(^4\) Hematologic diseases associated with an increased risk of DVT include disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia (HIT), antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and myeloproliferative disorders (polycythemia vera and essential thrombocythemia).\(^5\) For venous thrombosis, indications for screening include venous thrombosis in unusual locations (ie, mesenteric venous, portal venous, etc), idiopathic venous thrombosis, recurrent venous thrombosis, thrombosis on oral contraceptives, and episodes of aggressive superficial thrombophlebitis.
Venous Thrombosis Pathogenesis

Thrombosis in the venous circulation involves a combination of stasis, endothelial perturbations, and hypercoagulabilities. The inciting event involves thrombus formation from local procoagulant events, such as small endothelial disruptions at venous confluences, saccules, and valve pockets. Neutrophils and platelets then adhere to this thrombus and become activated, generating inflammatory and procoagulant mediators. Thrombus is thus amplified. With progression, leukocytes (initially neutrophils and later monocytes) extravasate into the vein wall ultimately resulting in vein wall inflammation (Fig 1). It appears that a balance between proinflammatory and anti-inflammatory cytokines and chemokines determine the ultimate vein wall response. The earliest elevated glycoprotein present on endothelial cells and platelets, P-selectin appears to play an important role in thrombogenesis along with the generation of procoagulant microparticles. These microparticles are tissue factor rich and are released from activated leukocytes, platelets, and endothelium. Additionally, tissue factor released from the vein wall also contributes to thrombosis when direct vein wall injury occurs or when tissue factor becomes exposed to the flowing blood.

Venous Disease Diagnosis

Deep Venous Thrombosis

The diagnosis of DVT must be made with confirmatory laboratory testing, as patients will be asymptomatic at presentation in up to 50% of
cases with DVT. When symptoms are present, patients complain of a dull ache or pain in the calf or leg. The most common physical finding is edema, although Wells and colleagues have classified patients into a scoring system that emphasizes the physical presentation of patients. In their criteria, characteristics that score points include the presence of active cancer, paralysis or paresis, recent plaster immobilization of the lower extremity, being recently bedridden for 3 days or more, localized tenderness along the distribution of the deep venous system, the entire leg being swollen, calf swelling that is at least 3 cm larger on the involved side compared with the noninvolved side, pitting edema in the symptomatic leg, and a history of a previous DVT. With extensive proximal DVT in the iliofemoral system, there may be significant swelling, cyanosis, and dilated superficial collateral veins.

Massive iliofemoral DVT may cause phlegmasia alba dolens (white swollen leg) or phlegmasia cerulea dolens (blue swollen leg). When the capillaries occlude, venous gangrene may occur. This occurs as the arterial inflow becomes obstructed due to the effects of high levels of venous hypertension. Alternatively, arterial emboli or spasm may occur. The skin blisters and the toes on the involved limb may turn black. Venous gangrene must be differentiated from gangrene caused by arterial insufficiency. Such differentiation includes the fact that with arterial gangrene the limb is pale and cold without significant swelling. Venous gangrene is often associated with an underlying malignancy and is always preceded by phlegmasia cerulea dolens. Associated with venous gangrene are amputation rates of 20% to 50%, PE rates of 12% to 40%, and mortality rates of 20% to 40% due to the underlying medical conditions that have been described.

Tests for establishing the diagnosis of DVT of historical interest include indirect flow examinations. Duplex ultrasound imaging has replaced these tests and also contrast phlebography due to its high sensitivity, specificity, and reproducibility. Duplex ultrasound imaging includes a B-mode image and Doppler flow pattern. Duplex imaging carries sensitivity and specificity rates greater than 95%. According to the grade criteria for the strength of medical evidence, duplex ultrasound as the test of choice for the diagnosis of DVT is given a 2C level of evidence (Table 1). Magnetic resonance imaging (MRI) may be helpful to diagnose central pelvic vein and inferior vena cava (IVC) thrombosis, and spiral computed tomography (CT) scanning is also being used more frequently, especially when combined with chest imaging during examination for PE. Even at the calf level, a level in which duplex imaging is felt to be less accurate, duplex imaging is an acceptable technique in symptomatic patients. Other
advantages of duplex imaging include that it is painless, requires no contrast, can be repeated serially, and is safe during pregnancy. This test also identifies other potential causes of a patient’s symptoms.\textsuperscript{14} In the asymptomatic patient, screening venous duplex imaging has been associated with varying levels of sensitivity and specificity.

Combining clinical characteristics with a D-dimer assay may decrease the number of negative duplex scans performed.\textsuperscript{11} Importantly, a single complete technically adequate negative duplex scan is accurate enough to withhold anticoagulation with minimal long-term adverse thromboembolic complications.\textsuperscript{17} However, this means that all segments of the leg have been imaged and evaluated successfully. If the duplex scan is indeterminate, treatment may be based on other factors such as biomarkers, with the duplex scan repeated in 24 to 72 hours. Also, repeat imaging may be necessary if the patient’s symptoms change or worsen. Although the use of clinical characteristics and D-dimer levels is useful to rule out thrombosis, the converse is not true. A positive D-dimer association with a positive risk assessment is associated with thrombosis in only approximately 70\% of cases, and is not felt good enough to base anticoagulant therapy on.\textsuperscript{18} We are attempting to establish a panel of biomarkers that may be used to establish a positive diagnosis of DVT based on the inflammatory response to the thrombotic process and the cross-talk between systems.\textsuperscript{19}

Other conditions may be confused with DVT including lymphedema, muscle strain, and contusion. Iliac vein obstruction in the retroperitoneum leads to unilateral massive leg edema (May-Thurner syndrome), while the presence of a cyst behind the knee may produce unilateral leg pain and

\begin{table}
\centering
\caption{Evidence-based recommendations for the diagnosis and treatment of venous thromboembolism\textsuperscript{15}}
\begin{tabular}{ll}
\hline
Test or intervention & Level of evidence (grade criteria) \\
\hline
Duplex imaging for DVT diagnosis & 2C \\
Spiral CT imaging for PE diagnosis & 1A \\
LMWH for initial treatment of VTE & 1A \\
Criteria for stopping anticoagulation & 1A \\
Alternative agents for treatment of HIT & 1C/2C \\
Use of IVC filters & 2C \\
Nonpharmacological treatment for DVT & 1A \\
Combined pharmacological and mechanical VTE prophylaxis & 2A \\
\hline
\end{tabular}
\end{table}

DVT, deep vein thrombosis; CT, computed tomography; PE, pulmonary embolism; LMWH, low molecular weight heparin; VTE, venous thromboembolism; IVC, inferior vena cava; HIT, heparin-induced thrombocytopenia.
edema. Other causes of leg swelling (usually bilateral) include systemic problems such as cardiac, renal, or hepatic abnormalities.

**Pulmonary Embolism**

The diagnosis of PE involves ventilation-perfusion (V/Q) scanning or pulmonary angiography; newer techniques include spiral CT scanning and MRI. The sensitivity of V/Q scanning is described in a large randomized multicenter study (PIOPED I) to be 98%, but the specificity is low, at 10%.\(^\text{20}\) By combining clinical risk factors with V/Q scan, sensitivity and specificity greater than 95% was achieved. With a high-probability V/Q scan and 2 risk factors for PE, the sensitivity for PE diagnosis was 97%; with 1 risk factor, 84%; and with no risk factors, 82%. Similarly, with a normal V/Q scan, the chance of PE was zero, regardless of the risk factor status.\(^\text{21}\) These results suggest that a normal V/Q scan or a high-probability scan provide good diagnostic information. However, only a small portion of V/Q scans are in 1 of these 2 categories, and thus the majority of patients need further testing. Such further testing includes lower extremity venous duplex ultrasound imaging (venous duplex imaging is positive in approximately 10% of cases in these patients) and spiral CT scanning. Pulmonary angiography is used infrequently today. Indications for pulmonary arteriography include acute massive PE, IVC interruption, and the planning of pulmonary interventional therapy, such as thrombolysis or pulmonary embolectomy.

Spiral CT scanning has demonstrated excellent specificity but relatively low sensitivity (50% to 65%), despite promising initial results. However, as the technology has improved, the sensitivity and specificity have also improved, and now emboli at the subsegmental level can be identified.\(^\text{22}\) A recent study reported that the sensitivity for isolated chest CT imaging was 83%, but increased to more than 90% when clinical analysis was added. Additionally, sensitivity improved when adding a lower extremity imaging study (either CT or ultrasound) to the chest CT scan.\(^\text{16}\) Results from this study (PIOPED II) strongly suggest that if the clinical presentation and spiral CT scan are concordant, therapies can be recommended safely. However, if results are discordant between clinical presentation and spiral CT, then other confirmatory tests are necessary. For the diagnosis of PE, spiral CT imaging is given a 1A level of evidence based on PIOPED II (Table 1). Magnetic resonance imaging has demonstrated excellent promise for PE diagnosis and is currently being investigated in a multicenter randomized study (PIOPED III).
Axillary/Subclavian Vein Thrombosis

Thrombosis of the axillary/subclavian vein accounts for less than 5% of all cases of acute DVT. However, it is associated with PE in up to 10% to 15% of cases and additionally can be the source of significant disability.23 Primary axillary/subclavian vein thrombosis results from obstruction of the vein in the thoracic outlet, the Paget Schrotter syndrome, especially prominent in healthy muscular individuals. It may also occur in patients with hypercoagulable states who have a tendency to thrombosis. Secondary axillary/subclavian vein thrombosis results usually from indwelling catheters or pacemaker wires. Other less common causes include mediastinal tumors, malignancy, and medical conditions such as congestive heart failure and nephrotic syndrome. Patients with axillary-subclavian venous thrombosis often present with pain, edema, and cyanosis of the arm. Due to the venous obstruction, superficial venous distension may be apparent over the arm, forearm, shoulder, and anterior chest wall.

Upper extremity venous duplex ultrasound is used for those patients with suspected axillary-subclavian vein thrombosis. Treatment for documented thrombotic episodes includes anticoagulation. Thrombolysis and phlebography should be considered. If phlebography is performed, it is important that the patient undergo positional phlebography, abducting the arm 120 degrees to confirm extrinsic compression of the subclavian vein at the thoracic outlet. Venous compromise is further evidenced by prominent collateral veins. A chest radiograph should be obtained to exclude the presence of a cervical rib.

Standard Therapy for VTE

The primary treatment of VTE is systemic anticoagulation, which reduces the risk of PE, extension of thrombosis, and recurrence of thrombosis. Immediate systemic anticoagulation should be undertaken, as it has been shown that the recurrence rate for VTE is approximately 4- to 6-fold higher if anticoagulation is not therapeutic in the first 24 hours.24 Adequate anticoagulation has been shown to prevent the development of fatal PE both during the initial treatment and after treatment is complete.25 However, recurrent DVT may still occur in up to one third of patients over an 8-year period after adequate appropriate therapy.26 Traditionally, systemic intravenous unfractionated heparin (UFH) has been undertaken for 5 days, during which time oral anticoagulation with vitamin K antagonists (usually warfarin) is instituted. International normalized ratios (INRs) therapeutic for 2 consecutive days are usually
recommended before stopping heparin. However, due to the need for intravenous administration, the need for frequent monitoring, as well as the bleeding risks of UFH, low molecular weight heparin (LMWH) has been advanced as primary therapy for VTE. Low molecular weight heparins are derived from the lower molecular weight range of standard heparin. They demonstrate less direct thrombin inhibition and more antifactor Xa inhibition. Low molecular weight heparins have significant improvement in bioavailability and less endothelial cell and protein binding compared with standard unfractionated heparin. Low molecular weight heparins are at least equivalent to UFH if not slightly superior regarding thrombus recurrence, with a lower risk for major hemorrhage.

The list of potential advantages of LMWHs compared with standard unfractionated heparin include a lower risk of bleeding, less antiplatelet activity, a lower incidence of HIT, less interference with protein C and complement activation, and a lower risk of osteoporosis. Low molecular weight heparins may be administered subcutaneously weight based, and may be administered in the outpatient setting. They do not require monitoring except in certain circumstances such as renal failure, morbid obesity, and during pregnancy. However, the use in the outpatient settings usually requires a team approach and a coordinated effort of multiple health care providers. There is also mounting evidence that LMWH may decrease the incidence of post-thrombotic syndrome.

Taking all of the evidence together, LMWH is now preferred over standard UFH for the initial treatment of VTE with a level of evidence 1A (Table 1).

Warfarin should be started only after heparinization is therapeutic to prevent warfarin-induced skin necrosis, usually on the first day of therapy. This condition occurs due to transient hypercoagulability that occurs for the first few days after warfarin is administered. Warfarin causes inhibition of protein C and protein S before most coagulation factors are inhibited by warfarin. The goal for warfarin dosing is an INR between 2.0 and 3.0. The recommended duration of anticoagulation after a first episode of VTE is 3 to 6 months. Calf level thrombi may be treated with 6 to 12 weeks of warfarin. After a second episode of VTE, the usual recommendation is prolonged warfarin unless the patient is very young at the time of presentation or there are other mitigating factors. The length of time of warfarin usage in other situations is controversial. Venous thromboembolism recurrence is increased significantly in the presence of homozygous factor V Leiden and prothrombin 20210A mutation, protein C/S deficiency, antithrombin deficiency, antiphospholipid antibodies, and cancer until resolved. In these conditions, most
agree with long-term warfarin therapy especially in circumstances with multiple hypercoagulable states. However, heterozygous factor V Leiden/prothrombin 20210A does not carry the same risk as their homozygous counterparts, and the length of oral anticoagulation is shortened.

Recently, 2 additional criteria have been used to determine the length of anticoagulation. One involves the amount of scar tissue inside the venous circulation leading to stasis. The second and perhaps better validated criterion involves D-dimer testing obtained 1 month after warfarin is completed. If the D-dimer level is elevated above normal, warfarin should be continued, as this result suggests that the patient is still prothrombotic.\(^{33-35}\) One recent study has demonstrated a statistically significant advantage to resuming coumadin if the D-dimer assay is positive compared with remaining off coumadin over an average 1.4-year follow-up period (odds ratio [OR] 4.26, \(P = 0.02\)).\(^{36}\)

Idiopathic DVT is an interesting problem. Most believe that true idiopathic thrombosis requires more than 6 months of warfarin, but the actual length is not known. A recent multicenter trial has suggested that for idiopathic DVT, low dose warfarin (INR 1.5-2.0) is superior to placebo over a 4-year follow-up period with a 64% risk reduction for recurrent DVT after the completion of an initial 6 months of standard warfarin therapy.\(^{37}\) A second study has suggested that full-dose warfarin (INR 2-3) is superior to low-dose warfarin in these same patients without a difference in bleeding.\(^{38}\) Thus, the data together suggest that for idiopathic thrombosis, long-term treatment is desirable and an INR of 2.0 to 3.0 should be achieved. In aggregate, criteria for discontinuation of oral anticoagulation include thrombosis risk, residual thrombus burden, and coagulation system activation (as suggested by D-dimer measurements). These criteria are given a level of evidence of 1A\(^{33-35,37,38}\) (Table 1).

The most common complication of anticoagulation is bleeding. With UFH, bleeding occurs in approximately 10% of cases over the first 5 days. With the addition of warfarin at an INR of 2 to 3, the incidence of major bleeding is approximately 6% per year. In treating patients for DVT and PE, major bleeding has been reported in 0% to 7% of patients, with fatal bleeding in 0% to 2% of patients.\(^{39}\) A meta-analysis showed a rate of hemorrhagic complications estimated at 9.1% for anticoagulation continued beyond 3 months. To decrease bleeding, dose adjustments and use of anticoagulation clinics are emphasized.

Another complication of heparin is HIT. Heparin-induced thrombocytopenia occurs in 0.6% to 30% of patients in whom heparin is administered. While historically morbidity and mortality have been high, early diagnosis and appropriate treatment have decreased the rates.\(^{40}\) Heparin-
induced thrombocytopenia usually begins 3 to 14 days after heparin is begun (earlier if the patient has been exposed to heparin in the past) and is caused by a heparin-dependent antibody immunoglobulin that binds to platelets, activates them, and leads to an increase in thrombocytopenia. Both bovine and porcine UFH as well as LMWH have been associated with HIT, although the incidence with LMWH is less. Arterial and venous thromboses have been reported, and even small exposures to heparin (heparin coating on indwelling catheters) has been known to cause the syndrome. The diagnosis should be suspected in a patient who experiences a 50% or more drop in platelet count, when there is a fall in platelet count below 100,000/µL during heparin therapy, or in the presence of thrombosis during heparin administration. The test of choice for making this diagnosis is an enzyme-linked immunosorbenent assay (ELISA) that detects the antiheparin antibody in the patient’s plasma. This test is highly sensitive but poorly specific. The serotonin release assay is another test that can be used, but this test is more specific but less sensitive than the ELISA test. Cessation of heparin is the most important step in treatment. Warfarin is contraindicated in this condition until an adequate alternative anticoagulant has been established, to prevent paradoxical thrombosis. Low molecular weight heparins demonstrate high cross-reactivity with standard heparin antibodies and therefore cannot be substituted for standard heparin in patients with HIT. The direct thrombin inhibitors hirudin (Lepirudin/Refludan) and argatroban are the treatments now approved by FDA, although other agents such as fondaparinux have been found to treat this syndrome as well. The use of these alternative agents is given a 2C and 1C level of evidence (Table 1).

**Special Features of Low Molecular Weight Heparin**

The safety of LMWH compared with warfarin has led to a consideration of the long-term use of LMWH as a replacement for oral vitamin K antagonists. Rates of recanalization have been reported to be higher in certain venous segments using LMWH versus traditional oral agents. Additionally the use of LMWH has been found to be improved in cancer patients compared with standard heparin or LMWH/warfarin therapy when used for 6 months without differences in major bleeding. They have also been found to provide better DVT prophylaxis compared with placebo for extended 4-week prophylaxis in patients undergoing abdominal/pelvic cancer surgery. The use of once daily compared with twice daily LMWH dosing has been assessed in a meta-analysis. Considering more than 1500 patients...
with VTE, there was a nonsignificant difference in the incidence of recurrent thromboembolism, thrombosis size, hemorrhagic events, and mortality. However, there may be instances when twice daily dosing is still more appropriate. These include patients with marked obesity and those with cancer.

Alternative/Future Medical Treatments for DVT/PE

Two new classes of agents for venous thrombosis treatment include direct thrombin inhibitors and specific factor Xa inhibitors. Ximelagatran is a direct thrombin inhibitor and showed great promise to replace warfarin. However, ximelagatran caused an elevation in liver function tests in up to 6% of patients administered the drug and because of this it was not approved in either the United States or Europe. A relative of this drug, dabigatran etexilate, is currently undergoing phase III studies in the treatment of VTE, and has met a noninflammatory target to enoxaparin in prophylaxis for orthopedic procedures without any elevation in liver enzymes or acute coronary events (Table 2). Other drugs with similar mechanisms of action are currently being evaluated.

Fondaparinux and its relative idraparinux are most like LMWH. They target factor Xa without inhibiting thrombin by potentiating antithrombin III. These drugs are administered subcutaneously and demonstrate a half-life of 17 hours for fondaparinux and 80 to 130 hours for idraparinux (compared with 4 hours for LMWH). These agents exhibit no endothelial

### TABLE 2. Comparison of properties of rivaroxaban, apixaban, and dabigatran etexilate

<table>
<thead>
<tr>
<th>Property</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran etexilate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Thrombin</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>&gt;80</td>
<td>&gt;50</td>
<td>6</td>
</tr>
<tr>
<td>Time to peak drug level, h</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>9</td>
<td>9-14</td>
<td>14-17</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once or twice daily</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Potent CYP3A4 and P-glycoprotein inhibitors</td>
<td>Potent CYP3A4 and P-glycoprotein inhibitors</td>
<td>Proton pump inhibitors</td>
</tr>
<tr>
<td>Renal excretion, %</td>
<td>66</td>
<td>25</td>
<td>80</td>
</tr>
<tr>
<td>Safe in pregnancy</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Antidote</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

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or protein binding. However, no antidote is readily available. Neither of these drugs produces thrombocytopenia. Fondaparinux has been tested for the prophylaxis of major orthopedic surgery. In a meta-analysis involving more than 7000 patients, there was greater than 50% risk reduction using fondaparinux begun 6 hours after surgery compared with LMWH begun 12 to 24 hours after surgery. Although major bleeding was increased, critical bleeding was not different. Fondaparinux has also been effective in prophylaxis of general medical patients, abdominal surgery patients, and for extended prophylaxis after hip fracture. Fondaparinux has also been evaluated in the treatment of both DVT and PE. For DVT it was found equal to LMWH, while for PE it was found equal to standard UFH. This drug is administered based on body weight: 5 mg per body weight <50 kg, 7.5 mg per body weight 50 to 100 kg, and 10 mg per body weight >100 kg. Treatment at least for 5 days with concurrent administration of oral anticoagulation is recommended, until the INR is therapeutic at a level of 2 to 3. It has been approved for the treatment of DVT/PE, thrombosis prophylaxis in total hip, total knee, and hip fracture patients, and in the extended prophylaxis of hip fracture patients. Idraparinux with the longer half-life in an open label, noninferiority trial of 2904 DVT patients and 2215 PE patients was found to meet the noninferiority requirement of DVT, but not for PE. Additionally, in a study of long-term treatment in DVT/PE patients, major bleeding was a significant problem with 3 intracranial bleeding episodes noted. Thus idraparinux development has been halted. However, in an attempt to develop an antidote, idraparinux is being biotinylated (reversal with avidin) in a drug called SSR 126517. Phase III trials are currently under way.

New oral antifactor Xa agents are being developed. Rivaroxaban and apixaban are the 2 agents furthest along in development (Table 2). Rivaroxaban has 66% renal excretion, whereas apixaban has only 25% renal excretion. Rivaroxaban is in phase II trials showing good results in the treatment of DVT regarding symptomatic recurrences and thrombus burden, while apixaban is in phase II trials of patients with proximal DVT and also phase III trials.

Other antithrombotic agents are being evaluated including oral heparins, other direct thrombin inhibitors such as lepirudin, bivalirudin, and argatroban; difibrinating agents such as ancrod; anti-inflammatory agents such as P-selectin inhibitors; factor VIIa inhibitors; tissue factor pathway inhibitor; and activated protein C. Lepirudin and argatroban have been approved for patients with HIT. The use of P-selectin inhibitors is an area of ongoing research in our laboratory. Such an anti-inflammatory approach uses an antithrombotic agent that does not cause direct antico-
agulant activities and thus the possibility of an agent without bleeding potential.

**IVC Filters**

The primary indications for the use of IVC filters includes a complication of anticoagulation, a contraindication to the use of anticoagulation, and/or failure of that anticoagulation. Protection from PE has been greater than 95% using cone-shaped wire-based permanent IVC filters over the past 30 years. The success achieved with filters has expanded the indications. These include a free-floating thrombus longer than 5 cm, when anticoagulation risk is excessive (ie, older patient with DVT or following major trauma), when the risk of PE is felt to be very high (as in certain bone and gastric bypass operations), and to allow for the use of perioperative epidural anesthesia. Filters can be permanent or optional (retrievable). If a retrievable filter is left in to become a permanent filter, its long-term fate has not yet been defined.

Filters are usually placed in an infrarenal location. However, filters may also be placed in either the suprarenal location or in the superior vena cava in special circumstances. Indications for suprarenal placement include high-lying clot, pregnancy, or in a women of childbearing potential, or a previous device that has filled with clot or failed. Sepsis is not a contraindication to the use of wire-based filters since the trapped material can be sterilized with antibiotics. Although traditionally filters have been placed under x-ray guidance, percutaneous techniques for filter insertion using bedside external ultrasound or intravascular ultrasound to reduce exposure to x-rays are now being recommended. Transabdominal external ultrasound is ineffective in the face of morbid obesity, if there is overlying bowel gas, or if there are open abdominal wounds. In these instances, intravascular ultrasound has been found to be more successful. Other than 1 randomized prospective study on the use of filters as treatment of DVT (which is not how filters are traditionally used), the evidence for the use of filters is given a 2C level of evidence (Table 1).

**Nonpharmacological Treatments**

Pain and swelling after an above-the-knee DVT can be decreased by approximately 50% by the use of strong compression stockings. Additionally walking with good compression does not increase the risk of PE, while significantly decreasing the incidence and severity of pain and swelling after DVT. It is recommended that once patients are therapeutic on anticoagulants they ambulate while wearing compression stockings. The use of strong compression and early ambulation after DVT
treatment is initiated can significantly reduce the long-term morbidity of pain and swelling resulting from the DVT and carries a 1A level of evidence.\textsuperscript{68,69} (Table 1).

In addition to the long-term problems related to DVT and PE, there is an increased rate of death. In a study involving 665,248 patients from the Nationwide Inpatient Sample, VTE (DVT or PE) was associated with an increased death rate and unfavorable discharge rate (discharge to rehabilitation facility, nursing home, or another hospital) in those patients originally admitted for myocardial infarction, heart failure, pneumonia, or stroke.\textsuperscript{71} Venous thromboembolism was also associated with increased length of stay and increased cost. Thus, VTE appears to confer a significant risk of death in addition to its adverse effects on the legs and lungs.

**Thrombosis Prophylaxis**

*Introduction and Magnitude of the Problem*

Venous thromboembolism is an enormous and poorly recognized problem that affects thousands of people every year and is associated with more deaths annually than breast cancer, AIDS, and accidental deaths.\textsuperscript{72,73} More than 12 million patients, which represents 31% of US hospital discharges in 2003, were at risk of VTE.\textsuperscript{74} Heit and colleagues have estimated that 296,000 patients die yearly from fatal pulmonary emboli (PE) and one third of these individuals die in a community rather than hospital setting. It is noteworthy that this analysis estimated that one third of the fatal PE events manifested as sudden death, denying any physician-related treatment opportunities.\textsuperscript{75} Venous thromboembolism is the number one preventable cause of death in hospitalized patients.\textsuperscript{76}

It has been estimated that 200,000 nonfatal PE events occur annually and 4% of those patients can be expected to develop chronic pulmonary hypertension.\textsuperscript{77} This problem may pose quality-of-life issues for those affected and is a long-term permanent disability.

Nonfatal DVT represents a serious health issue affecting approximately 375,000 patients per year.\textsuperscript{75} These patients require anticoagulants, which can cause spontaneous bleeding and require frequent blood tests. Patients may need to limit the intake of certain foods and drink while taking the anticoagulants, and avoid contact sports or similar activities where injury may result in excessive bleeding. Many of these patients will require support stockings to control symptoms or leg swelling and to help prevent the post-thrombotic syndrome.\textsuperscript{78} Borow and Goldson studied 500 patients who underwent surgical procedures lasting 1 hour or more, who were over the age of 40 years, and who underwent postoperative fibrinogen
scanning confirmed with contrast venography. They reported that 66% of patients who had a history of venous thrombosis developed thrombosis postoperatively. They observed that 50% of the patients with a significant medical history, including previous abdominal or leg surgery, trauma to the lower abdomen, or leg fracture, developed postoperative venous thrombosis.79,80

One of every 3 patients following a DVT will develop post-thrombotic sequelae within 2 years; these sequelae are severe in approximately 20% of cases and produce considerable socioeconomic consequences.81 Symptoms include aching, pain, or leg swelling that progresses during the day and improves overnight with bedrest. The more severe manifestations of post-thrombotic syndrome in the legs include skin pigmentation, rashes, or open ulcers.82 This represents a permanent disability and necessitates the wearing of life-long compression stockings or bandages.83,84

Another important complication of DVT is a paradoxical embolus that occurs when a clot travels to the right heart, traverses a patent foramen ovale, and travels to the brain resulting in a nonhemorrhagic stroke. It has been documented that 50% of patients presenting with a cryptogenic stroke have a patent foramen ovale.85

The focus of thrombosis prophylaxis should be directed toward prevention of the many faces of VTE seen in Table 3. Too often clinicians focus purely on preventing clinical and fatal events rather than the entire spectrum of the disease. To evaluate all of the complications of VTE, studies must be conducted over extended periods of time to see the full ramifications of the disease.86

### TABLE 3. The many faces of venous thromboembolism

- Prevent fatal pulmonary emboli
  - 1% to 5% incidence in patients with >4 risk factors
  - 16.7% mortality at 3 months
  - 33% of those with pulmonary emboli present as sudden death
- Prevent chronic pulmonary hypertension
  - 4% of patients suffering PE
- Prevent clinical venous thromboembolism
  - Morbidity, drugs, tests, hose, changes in lifestyle
- Prevent silent venous thromboembolism
  - Risk of subsequent event doubles that of control population
- Prevent embolic stroke (20% to 30% PFO rate)
  - 50% disabled; 20% die; 30% recover
- Prevent the post-thrombotic syndrome
  - 33% incidence following DVT and 7% severe
  - May not be evident for 2 to 5 years

PE, pulmonary embolism; PFO, patent foramen ovale; DVT, deep venous thrombosis.
Risk Assessment

Risk assessment as a guide to thrombosis prophylaxis is necessary since there is not only a variety of risk factors but the relative risk of each of these factors is not the same. Heit and colleagues calculated risk estimates for individual factors in a large observational study and found the following results: malignant neoplasm 18%, trauma 12%, congestive heart failure 10%, central venous catheter or pacemaker placement 9%, neurological disease with extremity paresis 7%, and superficial vein thrombosis 5%. Together, 8 risk factors accounted for 74% of all cases of VTE in their study. Borow and Goldson have shown that the incidence of VTE increases dramatically to more than 60% with age, or with the length of surgical procedures. Sugerman and colleagues have observed increasing VTE rates in patients with a body mass index (BMI) greater than 55 and the venous stasis syndrome. Kroger and colleagues have identified risk factors in the cancer patient that are associated with the development of VTE. Hospitalization, past history of VTE, family history of VTE, fever, chemotherapy, and elevated C-reactive protein (CRP) were identified. In the absence of all these factors the predicted VTE risk was 2.3%, increasing to 72% if all were present. Anderson and Spencer have reported that those with 4 risk factors had a 50% incidence of VTE in their population-based studies, and the incidence was 100% in individuals with 5 documented risk factors. We have observed that evidence-based guidelines are applicable only for patients who fit the criteria of the clinical trials. The unique risk pattern of an individual may be such that the prophylaxis appropriate for a particular group may not be appropriate for an individual. A recent Chest consensus document has also expressed this opinion. Kucher and colleagues developed a risk stratification schema that identified a high incidence of imaging-proven symptomatic VTE (8.2%) in patients 90 days after hospital discharge. The VTE incidence was reduced to 4.9% using an electronic alert during hospitalization reminding the physician to consider prophylaxis. We employ a comprehensive risk assessment schema inquiring about a large number of risk factors that have been associated with VTE. A relative score for each of these factors has been calculated based on the results of randomized clinical trials. To simplify the process and maximize compliance, we ask the patient to complete a straightforward medical history form (Fig 2). This is given to the admitting physician, physician assistant, or nurse, and the full risk assessment completed and scored (Fig 3). This information is used to provide a guide to the onset, type, intensity, and
duration of prophylaxis. The document includes an algorithm for selection of prophylaxis for individual patients. We are in the process of refining and validating this document. Zakai and colleagues have shown this system to be valuable in identifying medical patients who are at risk for developing VTE.94

Despite these tools the utilization of prophylaxis is poor, and some feel that until prophylaxis is mandated the percentage of patients that receive appropriate protection will remain suboptimal.

FIG 2. Patient intake risk assessment form.

PATIENT INTAKE RISK ASSESSMENT FORM

1. Personal History of DVT or PE
2. Family History of DVT or PE
3. Malignancy: Current or Previous
4. Personal History of Recent MI or stroke (< 1 month)
5. Recent Major Surgery (< 1 month)
6. Currently on BCP, HRT, or hormonal therapy for Breast or Prostate Cancer
7. Current or recent acute inflammatory or infectious process (< 1 month)
8. Currently immobile (unable to ambulate in the in-patient setting)
10. Swollen legs
11. Varicose Veins
12. Obesity (BMI > 30)
13. Age
Pharmacologic Methods of VTE Prophylaxis

Low-dose unfractionated heparin (UFH) was the first pharmacological agent to be widely investigated for the primary prevention of VTE in patients undergoing surgery. Kakkar demonstrated that LDH significantly reduced the risk for both DVT and PE in general surgical patients, including fatal PE. Thirteen years later another meta-analysis including 16,000 patients has compared UFH versus no prophylaxis in surgery. The results of this review show that UFH significantly reduced the risk of DVT by 56% compared with no prophylaxis (relative risk [RR] = 0.44; 95% confidence interval [CI] 0.37-0.52) and the risk of PE by 30% (RR = 0.70; 95% CI 0.53-0.93) without significantly increasing the risk of bleeding complications. Although no direct comparisons have been made, in general, UFH should be administered twice daily in moderate-risk patients, and 3 times daily in high-risk patients according to evidence presented in the American College of Chest Physicians (ACCP) consensus document that was just released. There is evidence that an increase of wound hematomas from 3.8% to 6.2% could be minimized by avoiding subcutaneous injection of heparin near to the surgical wounds.

Unfractionated heparin is very effective for the prevention of DVT and PE in general surgery, gynecology, and urology, but suffers from one potentially serious complication, namely HIT in up to 5% of patients receiving heparin. This disorder is characterized by the development of antiplatelet antibodies and characterized by a dramatic drop in the platelet count, usually below 100,000/mm³. In 20% of patients suffering from heparin-related thrombocytopenia there is thrombosis that may lead to ischemic complications. One should remember that a 50% drop in the platelet count is presumptive evidence that HIT is present. The short half-life of UFH (0.5-2 hours) is another limitation because it makes more frequent dosing necessary. Yet, this short half-life is an asset when there is a high risk of bleeding complications or in patients with renal impairment. This drug can be measured with the activated partial thromboplastin time (APTT) and neutralized with protamine sulfate. UFH is widely used for cardiac and vascular surgical procedures and most every physician understands the drug and its clinical applications.

Low molecular weight heparins (LMWHs) have been developed over the past 25 years by chemical or enzymatic degradation of UFH resulting in an average molecular weight between 4000 and 8000 D compared with 15,000 D for UFH. These LMWHs have improved bioavailability and longer half-life than UFH, and have a more predictable anticoagulant response than UFH. They have become the standard for prophylaxis and
treatment in a wide variety of clinical settings. As a result, once daily injections can be used for prophylaxis including their use in the outpatient setting. The high and consistent bioavailability coupled with an absence of heparin resistance permit using this drug without routine monitoring. The efficacy of LMWHs for the prevention of postoperative VTE has been demonstrated in several randomized controlled trials and meta-analyses comparing LMWHs with placebo and UFH in general surgery.\textsuperscript{99-101} The comparison between the 2 compounds has revealed similar efficacy, and LMWHs, at appropriate doses, may reduce bleeding complications in general abdominal surgery. A very large study in 23,078 surgical patients demonstrated that either LMWH or UFH was associated with a 0.15% incidence of fatal PE with a bleeding rate of less than 1.5% in either group.\textsuperscript{102} This study coupled with the Kakkar and Collins studies, which total 20,000 patients, demonstrate the value of UFH or LMWH in nearly eliminating fatal PE in surgical patients. We would recommend using one of these drugs in most situations including for very high-risk patients that do not fit the clinical trial criteria but need protection.

Patients having abdominal operations for cancer have been studied in several trials employing 30 days of LMWH compared with 7 days of prophylaxis. The results indicate a statistically significant reduction in VTE in the prolonged prophylaxis groups compared with those receiving the short course of anticoagulants.\textsuperscript{47,103}

Fondaparinux is a synthetic, injectable pentasaccharide that selectively inhibits factor Xa producing a conformational change in the antithrombin molecule. This drug has a high bioavailability and long half-life (17 hours). Only 1 case of HIT has been associated with this drug, and osteoporosis has not been observed. This drug is renally excreted and should not be used in patients with a creatinine clearance of less than 30 mL/min.\textsuperscript{104}

Fondaparinux has been evaluated in high-risk patients undergoing abdominal surgery and showed equivalent efficacy as the LMWH dalteparin with no statistically significant differences in bleeding complications.\textsuperscript{53}

**Physical Methods of VTE Prophylaxis**

Physical and mechanical methods include graduated elastic stockings and intermittent pneumatic compression (IPC) of the calf alone, or calf and thigh and impulse foot.

Elastic compression stockings of the legs reduce the cross-sectional area of the veins and, as a result, increase the velocity of blood flow.
in the limb. It has been demonstrated that graduated compression stockings (GCS) significantly increased the blood velocity around 30% at the femoral vein during recumbence as detected by Doppler ultrasound. The optimal pressure profile according to these authors consisted of 18 mm Hg at the ankle, decreasing to 8 mm Hg in the upper thigh.

It has been shown that endothelial cracking is associated with venous

dilation and can be the beginning of a thrombus. Venous dilation often occurs due to the loss of calf muscle tone with the administration of a muscle relaxant during the induction of general anesthesia. If the leg is also in a dependent position, this aggravates the stasis and can initiate the beginning of the thrombotic process. It has been shown that GCS can
prevent venous distension that occurs in deep veins of the leg during the course of operation.\textsuperscript{108}

The efficacy of GCS for VTE prevention has been studied in a meta-analysis involving 11 studies investigating the efficacy of GCS in 1800 moderate-risk surgery patients. The results showed a significant 68\% reduction in the incidence of postoperative DVT in patients with stockings (OR 0.28; 95\% CI 0.23-0.48; \(P\ < \ 0.0001\)).\textsuperscript{109}

Seven additional randomized controlled trials in general, gynecological, orthopedic, and neurosurgical patients revealed the incidence of postoperative DVT detected by objective diagnostic methods to be significantly reduced from 29\% in the control group to 15\% in the GCS group (OR 0.33; CI 0.26-0.49; \(P\ < \ 0.0001\)).\textsuperscript{110} Finally in another systematic review of the literature in more than 2400 patients, there was a 66\% reduction in the incidence of DVT, from 21\% (133 of 677) in the controls to 8.6\% (57 of 665) in the GCS group (\(P\ < \ 0.001\)).\textsuperscript{111}

Although GCS are as effective for DVT prevention in moderate-risk surgical patients, there is a lack of data in high-risk patients including cancer or orthopedic surgery patients. There is no evidence to suggest that GCS prevents pulmonary emboli.

There is no conclusive evidence regarding the use of thigh versus calf length stockings. Two trials comparing thigh-length and knee-length stockings revealed that the incidence of DVT was 8.7\% (9 of 104) and 8.3\% (9 of 108), respectively. These results are considered inconclusive due to the small number of patients and the low DVT rate.\textsuperscript{112,113}

The main limitations of GCS include the lack of international standardization of their pressure profiles and the difficulty to fit patients with unusual leg sizes or shapes. Patient compliance may be another limiting issue, especially with thigh-length stockings. Common reasons for non-compliance included that stockings were not reapplied after cleaning or bathing, or were removed because patients complained of itching or heat.\textsuperscript{112}

Intermittent pneumatic compression is the most extensively studied of the mechanical methods of prophylaxis and is considered the most effective of the mechanical methods. These devices may be single chamber or multiple chamber, and provide uniform or sequential compression. One of the available devices indirectly estimates the leg venous pressure and adjusts the compression cycle to these changes. These devices can compress the leg up to 3 times per minute.\textsuperscript{114} Another important effect of IPC for VTE prevention is the stimulation of fibrinolysis and coagulation physiological inhibitors by a variety of changes in specific fibrinolytic parameters.\textsuperscript{115-118}
The results of IPC have been variable, but most studies show that IPC reduces the incidence of DVT in a variety of surgical procedures. Roderick and colleagues identified 19 trials assessing IPC in 2255 patients and showed that IPC significantly reduced the incidence of DVT from 23.4% (268 of 1147) in the control group to 10.1% (112 of 1108) in the IPC group, a 66% odds reduction ($P < 0.0001$). There was no evidence that sequential compression devices were more protective than uniform compression machines, as their odds reductions were 65% (6 trials) and 66% (12 trials), respectively. Another report of 15 trials involving 2200 patients also demonstrated the efficacy of IPC for VTE prophylaxis. The issue of whether above-knee IPC devices are more effective than calf-length devices remains unclear in the absence of large-scale trials. The choice between both alternatives should be made on practical grounds, depending on their availability and cost.

As with GCS, another important issue regarding IPC is compliance and adequate implementation. Comerota and colleagues have recorded a poor compliance record for these devices and highlighted an urgent need to improve patient and nursing staff education on the appropriate use of IPC for VTE prophylaxis.

**Combination of Physical and Pharmacologic Methods**

Ever since the first description of the factors leading to the development of a venous thrombosis, we have been searching for methods to prevent venous thromboembolism. The combination of physical and pharmacologic methods appears ideal as a method of thrombosis prophylaxis.

**Combination of Mechanical Methods and Anticoagulants**

There are multiple randomized controlled trials that demonstrate that the combination of GCS in addition to another prophylactic method was significantly more effective than GCS alone. Deep venous thrombosis was encountered in only 2% of the patients in the combined group compared with 15% in the control group. The Pulmonary Embolism Prevention Trial involved a large multinational study that showed that the combination of GCS stockings plus aspirin was effective in lowering the rate of fatal PE in hip fracture patients, whereas aspirin alone did not have the same effect. The combination of heparin and GCS in another Cochrane analysis demonstrated superiority compared with heparin alone following colorectal surgery.

Most studies using combined modalities involve the use of IPC in
conjunction with various anticoagulants. Borow and Goldson showed that using the combination of aspirin, heparin, or coumadin in conjunction with IPC resulted in a 1.5% incidence of DVT in the treated population compared with a 26.8% incidence in the control group.\textsuperscript{123}

In one study patients undergoing total hip replacement (THR) were randomized to IPC alone, IPC plus aspirin, or IPC plus low-dose warfarin. The incidence of ultrasound-detected VTE was 10% in each of the groups.\textsuperscript{124} Woolsen and Watt showed that the combination was not better than IPC although the ultrasonic endpoint and small size of the study (196 patients) make it difficult to conclude that combination prophylaxis is not valuable. The effectiveness of the plantar venous plexus foot pump combined with unfractionated heparin in patients having THR was shown in a study that revealed a 6.6% venographic DVT rate in the combination group compared with 27% in the nonpumped group ($P < 0.025$). The authors conclude that chemical prophylaxis plus the use of GCS stockings and foot pump reduces the incidence of DVT more than chemical prophylaxis alone.\textsuperscript{125} Ramos and colleagues performed a study involving 2551 patients having coronary artery bypass surgery (CABG) over a 10-year period. Patients received either 5000 units of UFH twice daily or in combination with long-leg sequential IPC. The incidence of imaging-proven PE was 4.0% in the heparin group and 1.5% in the combination prophylaxis group ($P < 0.001$).\textsuperscript{126} A study in patients having total joint replacement involving LMWH in combination with IPC showed 0% ultrasound-detected thrombosis compared with the group receiving LMWH and compression stockings where the DVT incidence was 28.6% (40% after total knee replacement [TKR], 14% after THR) ($P < 0.0001$).\textsuperscript{127} A large orthopedic study was done in which patients were randomized prospectively to receive either LMWH alone or in combination with IPC. In the LMWH group, 15 patients (1.7%) had a DVT, compared with 4 patients (0.4%) who had a DVT ($P = 0.007$) in the combined group.\textsuperscript{128} Low molecular weight heparin or aspirin in combination a foot pump was studied in 275 TKR patients and the incidence of ultrasound DVT was 14.1% using LMWH and the foot pump, and 17.8% with the aspirin and the foot pump.\textsuperscript{129} Recently a very large series of general surgical patients was reported that were randomized to receive either a placebo saline injection daily or 2.5 mg of Fondaparinux, a selective inhibitor of factor Xa, daily for 7 days. Bilateral venography on the seventh day revealed a 5.3% DVT incidence in the saline group and 1.7% in the Fondaparinux group.\textsuperscript{130} All of this evidence supports the
concept that combined modalities provide superior DVT prevention compared with any single thrombosis prophylaxis modality.

**Current Recommendations for Combined Prophylaxis**

The newly released 8th ACCP recommends IPC as an option in conjunction with heparin or LMWH in patients in the highest risk category for VTE. The combination of mechanical methods and these anticoagulants is listed as a grade 2A suggestion\(^97\) (Table 1).

Recently Amin and colleagues performed a database review of data from 227 hospitals over a 3.5-year period involving nearly 200,000 patients looking at thrombosis prophylaxis rates in US hospitals. These authors found the thrombosis prophylaxis rate was 66.8%, and only 33.9% received appropriate prophylaxis according to *Chest* guidelines.\(^{131}\) It was observed that 26.8% of the patients received mechanical prophylaxis alone in cases in which there was no contraindication because of bleeding. Inappropriate prophylaxis postdischarge was noted in two thirds of the patients, including 4.7% who received mechanical prophylaxis alone.

**Thrombosis Prophylaxis in the Real World**

Sixteen years ago we surveyed 3500 North American general surgeons and noted that some form of thromboprophylaxis was used 86% of the time. The most frequently used modalities were IPC, low-dose heparin, and elastic stockings. A combination of physical and pharmacologic methods was used by one fourth of respondents, and only 50% started pharmacologic prophylaxis before the surgical procedure. The thrombosis risk factors that are most frequently considered by surgeons when deciding about using prophylaxis are history of VTE, immobility, and length of operation.\(^{132}\) Seven years later a follow-up survey was sent to 10,000 general surgeons and 1145 responses were received. Conventional UFH at fixed doses remains the preferred pharmacological agent for VTE prevention (74%), followed by 2 LMWHs: enoxaparin (34%) and dalteparin (16%). Overall, 52% of surgeons preferred physical methods over pharmacological methods when used separately and 26% of surgeons utilize combined physical-pharmacological modalities. A large multinational cross-sectional study in more than 68,000 patients representing 352 hospitals in 32 countries was recently published. The percentage of patients that received appropriate prophylaxis according to evidence-based guidelines was 40% in medical patients and 59% in surgical patients (Table 4).\(^{133}\) The Global Orthopedic Registry recently published by Warwick and colleagues shows more encouraging results.
There were 15,000 patients in the registry and 95% of these individuals received anticoagulant or mechanical prophylaxis following joint replacement procedures. LMWH prophylaxis was popular outside of the United States and combined with IPC 11% to 17% of the time. This combination was used in nearly 25% of American patients. Warfarin use was rare outside the United States; however, it was combined with IPC approximately 33% of the time in the United States. Amin and colleagues have reported a database review from 227 hospitals involving 200,000 patients looking at thrombosis rates in American hospitals. Overall these investigators found the thrombosis prophylaxis rate was 66.8%, with only 33.9% conforming to Chest guidelines. This study highlights two remaining serious problems regarding thrombosis prophylaxis. There are still very substantial numbers of patients not being protected and even when some form of prophylaxis is used, it does not conform to evidence-based guidelines.

### Aggressive Therapies for Acute DVT and PE

The term “aggressive treatment” gives the connotation that it is out of the ordinary or unusual. For the purpose of this discussion, aggressive is defined as adopting a strategy of thrombus removal before long-term anticoagulation, rather than accepting the existing venous thrombosis or embolic pulmonary occlusion and treating the patient with anticoagulation alone, thereby accepting all of the post-thrombotic or embolic morbidity that accompanies iliofemoral DVT and pulmonary embolism (PE).

Studies have shown that patients with post-thrombotic syndrome have a significant reduction in their quality of life. The severity of the acute venous thrombotic event is predictive of the degree of post-thrombotic morbidity. This is especially true in patients with iliofemoral DVT.

Iliofemoral DVT is a clinically relevant subset of patients with acute venous thrombosis who suffer severe post-thrombotic morbidity. Ninety percent of iliofemoral DVT patients who are treated with

<table>
<thead>
<tr>
<th>TABLE 4. ENDORSE Registry</th>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>37,356</td>
<td>30,827</td>
</tr>
<tr>
<td>At risk for VTE</td>
<td>42%</td>
<td>64%</td>
</tr>
<tr>
<td>Receiving ACCP Tx</td>
<td>40%</td>
<td>59%</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; ACCP, American College of Chest Physicians; Tx, treatment.
anticoagulation alone will have ambulatory venous hypertension, resulting in severe chronic venous insufficiency. Up to 40% will have symptoms of venous claudication, and within 5 years, 15% develop venous ulceration. The adverse impact on quality of life is evident. This discussion reviews the body of evidence demonstrating that a strategy of thrombus removal is the preferred management for patients with iliofemoral DVT and offers the best long-term outcome.140,141

In general, avoiding pathophysiology or minimizing pathophysiologic disturbances offers patients the best chance of a favorable outcome. The pathophysiology of post-thrombotic venous disease is ambulatory venous hypertension, defined as an elevated venous pressure during exercise.142,143 Nicolaides and colleagues143 and Welkie and colleagues144 have demonstrated that ambulatory venous pressure is directly linked to the clinical manifestations observed with chronic venous disease, such as swelling, pigmentation, and lipodermatosclerosis. Long-standing venous hypertension has a significant effect on the microcirculation, which can result in dermal breakdown.

Two pathologic anatomic components contribute to ambulatory venous hypertension: venous valvular incompetence and obstruction of the vein lumen. The most severe post-thrombotic morbidity is associated with the highest venous pressures, which occur in patients with combined valvular incompetence and luminal obstruction.142,143,145 It is intuitive that if thrombus is removed and patency restored, obstruction cannot be part of the underlying pathophysiology. Long-term studies of acute DVT have demonstrated that early thrombus resolution preserves valve function.146 Therefore, early thrombus removal in patients with extensive venous thrombosis eventually eliminates the underlying pathologic conditions leading to ambulatory venous hypertension and has the potential of maintaining normal venous physiology.

**Evidence Supporting an “Aggressive” Approach**

There is a spectrum of evidence supporting a strategy of thrombus removal in patients with acute DVT. Although small segmental thrombi may be well tolerated in many patients without significant post-thrombotic morbidity, typically in the femoral vein of the mid thigh, patients with extensive DVT, especially those with iliofemoral thrombosis, will have severe post-thrombotic morbidity if treated with anticoagulation alone. Data are available from experimental observations in animal models,147,148 long-term follow-up studies in patients with acute DVT treated with anticoagulation alone,146,149,150 clinical reports of large patient series,151-153 and randomized trials.154-157 The aggregate data
overwhelmingly demonstrate that patency can be restored, vein wall and valvular function can be maintained, and post-thrombotic morbidity can be reduced if thrombus is successfully eliminated, intrinsic vein pathology (stenosis) corrected, and long-term therapeutic anticoagulation maintained to avoid rethrombosis.

Strategies of Thrombus Removal

Strategies of thrombus removal have not been widely accepted by the medical community. In large part, this is the result of international guidelines recommending against catheter-directed thrombolysis and operative venous thrombectomy. Unfortunately, authors of these influential guidelines focused on outdated information published many decades earlier and overlooked contemporary randomized trials.

Treatment approaches that have adopted venous thrombectomy and catheter-based thrombolytic therapy have demonstrated significantly better outcomes compared with patients treated with anticoagulation alone.

The underlying principles are similar whether one employs an operative or percutaneous approach. The initial goal is to eliminate all acute thrombus followed by correction of underlying venous pathology and therapeutic anticoagulation to avoid rethrombosis.

Treatment Options and Patient Evaluation

An important part of the initial evaluation of patients with iliofemoral DVT is a CT scan of the head, chest, abdomen, and pelvis. Martinez and Comerota reported their CT scan findings in patients presenting with iliofemoral DVT. In addition to finding asymptomatic pulmonary emboli in 50% of patients and assessing the proximal extent of thrombus, they found an undiagnosed malignancy in 79% of patients with idiopathic iliofemoral DVT. Since iliofemoral DVT is generally the result of an aggressive thrombotic stimulus, it is not surprising that a large proportion of idiopathic patients are found to have an underlying malignancy. Although chest, abdomen, and pelvic CT scans have been a routine part of the evaluation of iliofemoral DVT patients at Jobst Vascular Center for the past several years, a head CT is now added to rule out intracranial pathology.

Contemporary venous thrombectomy is generally available to all patients where vascular surgeons practice. There are few contraindications to operative thrombectomy, especially when the thrombus is less than 10 days old. Treatment goals are straightforward: to remove thrombus in the iliofemoral and infrainguinal venous segments and restore unobstructed venous return into the vena cava. Knowing the full
extent of thrombus preoperatively and having good imaging intraoperatively is imperative for a well-planned and successful procedure.

Catheter-directed thrombolysis is the preferred treatment option for most patients who have no contraindications to thrombolytic therapy. Adjunctive mechanical techniques are becoming increasingly popular and tend to shorten treatment time and reduce the dose of plasminogen activator.

A frequent concern of physicians is the risk of procedure-related PE. The patients at highest risk of procedure-related PE are those with nonocclusive thrombus in their vena cava. Therefore, it is important to image the proximal and distal extent of thrombus and particularly the amount and level of vena caval involvement. This will assist in the decision whether vena caval filtration or other forms of embolic protection (eg, balloon occlusion) are used (Fig 4).

The traditional contraindications to the use of thrombolytic agents are softened by direct intrathrombus infusion and the use of adjunctive mechanical techniques. If the dose of lytic agent can be reduced and the duration of therapy shortened, the risk of a systemic lytic effect is reduced, since circulating plasminogen activator inhibitors and antiplasmins neutralize the effect of plasminogen activators and plasmin that escape into the systemic circulation.

**Operative Venous Thrombectomy**

Contemporary venous thrombectomy for iliofemoral venous thrombosis has been shown to be effective in both the short and the long term. The largest report of operative venous thrombectomy failed to show fatal PE and reported only 1 operative death. The long-term benefits of venous thrombectomy relate to its ability to achieve proximal patency and maintain distal valve competence. Both outcomes are influenced by the initial technical success and the avoidance of recurrent thrombosis. Therefore, attention to operative detail in terms of complete thrombus removal, correcting underlying venous stenoses, and maintaining therapeutic anticoagulation postoperatively are crucial.

Pooled data from a number of contemporary reports on iliofemoral venous thrombectomy (Table 5) demonstrate that early and long-term patency of the iliofemoral venous segment is 70% to 80% compared with 30% of patients treated with anticoagulation alone. Femoropopliteal venous valve function is preserved in the majority of patients. The Scandinavian investigators reported their randomized trial outcomes of operative venous thrombectomy versus anticoagulation alone in patients with iliofemoral venous thrombosis.
underwent complete follow-up evaluation at 6 months, 5 years, and 10 years. They showed that those randomized to venous thrombectomy had improved iliac vein patency ($P < 0.05$), lower venous pressures ($P < 0.05$), less leg edema ($P < 0.05$), and fewer patients with post-thrombotic

FIG 4. A young man with an acute gastrointestinal bleed from Crohn’s colitis developed a painful, swollen left leg with bluish discoloration (phlegmasia cerulea dolens). Venous duplex documented acute thrombus extending from the distal femoral vein into the external iliac vein. A contralateral iliocavagram was performed to evaluate the vena cava, which demonstrated a sizable amount of nonocclusive thrombus extending into the vena cava (A). In preparation for his operative venous thrombectomy, a caval occlusion balloon was positioned under fluoroscopy from the right common femoral vein and was inflated during the iliocaval thrombectomy (B, C). The entire proximal and distal thrombus was removed intact (D, E). (Reprinted with permission from Comerota and Gale.174) (Color version of figure is available online.)
syndrome ($P < 0.05$) compared with patients treated with anticoagulation alone. Table 6 briefly summarizes the general aspects of the contemporary venous thrombectomy. Specific operative detail has been published by Comerota and Gale.$^{174,175}$

**Catheter-Directed Thrombolysis**

Early attempts of pharmacologic clot dissolution of acute venous thrombosis used systemic delivery of plasminogen activators. Although the results demonstrated reduced post-thrombotic morbidity, the high doses of plasminogen activators resulted in higher rates of bleeding complications.$^{176}$ Many patients in these studies were treated for infrain-

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### TABLE 5. Long-term results of venous thrombectomy with arteriovenous fistula: iliac vein patency and femoral-popliteal valve competence

<table>
<thead>
<tr>
<th>No. of reports</th>
<th>Patients</th>
<th>Follow-up (mos) (mean)</th>
<th>Iliac vein patency</th>
<th>Femoral-popliteal valve competence</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{154,162,171}$</td>
<td>702</td>
<td>41</td>
<td>78%</td>
<td>—</td>
</tr>
<tr>
<td>$^{154,163,165,169,170,172,173}$</td>
<td>352</td>
<td>45</td>
<td>—</td>
<td>63%</td>
</tr>
</tbody>
</table>

### TABLE 6. Technique of contemporary venous thrombectomy

1. Identify etiology of extensive venous thromboembolic process
   a. Complete thrombophilia evaluation
   b. Rapid CT scan of head, chest, abdomen, and pelvis
2. Define full extent of thrombus
   a. Venous duplex examination
   b. Contralateral iliocavagram, MRV, or spiral CT
3. Prevent pulmonary embolism (numerous techniques)
   a. Anticoagulation
   b. Vena caval filter (if nonocclusive caval clot)
   c. Balloon occlusion of vena cava during thrombectomy
   d. Positive end-expiratory pressure during thrombectomy
4. Perform complete thrombectomy
   a. Iliofemoral (vena cava) thrombectomy
   b. Infrainguinal venous thrombectomy (if required)
5. Ensure unobstructed venous inflow to and outflow from thrombectomized iliofemoral venous system
   a. Infrainguinal venous thrombectomy (if required)
   b. Correct iliac vein stenosis (if present)
6. Prevent recurrent thrombosis
   a. Construct arteriovenous fistula (3.5-4 mm)
   b. Continuous therapeutic anticoagulation
   c. Catheter-directed postoperative anticoagulation (if infrainguinal venous thrombectomy is required)
   d. Extended oral anticoagulation

MRV, magnetic resonance venography; CT, computerized tomography.
Reprinted with permission from Comerota and Gale.$^{175}$
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Total no. of patients (limbs)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semba et al,180 1994</td>
<td>21 (27)</td>
<td>CDT with UK, angioplasty/stenting for residual stenosis</td>
</tr>
<tr>
<td>Semba et al,181 1996</td>
<td>32 (41)</td>
<td>CDT with UK, angioplasty/stenting for residual stenosis</td>
</tr>
<tr>
<td>Verhaeghe et al,182 1997</td>
<td>24</td>
<td>CDT with rt-PA, stenting for residual stenosis</td>
</tr>
<tr>
<td>Bjarnason et al,151 1997</td>
<td>77 (87)</td>
<td>CDT with UK, angioplasty, stenting, thrombectomy, bypass for residual stenosis</td>
</tr>
<tr>
<td>Mewissen et al,152 1999</td>
<td>287 (312)</td>
<td>CDT with UK, stenting for residual stenosis; systemic lysis (n = 6)</td>
</tr>
<tr>
<td>Comerota et al,153 2000</td>
<td>54</td>
<td>CDT with UK or rt-PA, thrombectomy for residual stenosis</td>
</tr>
<tr>
<td>Horne et al,183 2000</td>
<td>10</td>
<td>CDT with rt-PA</td>
</tr>
<tr>
<td>Kasirajan et al,184 2001</td>
<td>9</td>
<td>CDT with UK, rt-PA, or rPA</td>
</tr>
<tr>
<td>AbuRahma et al,185 2001</td>
<td>51</td>
<td>CDT w/UK or rt-PA, stents/18 Hep/33</td>
</tr>
<tr>
<td>Vedantham et al,186 2002</td>
<td>20 (28)</td>
<td>CDT with UK, rt-PA, or rPA, thrombectomy, stenting</td>
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<td>35</td>
<td>CDT w/SK, angio, stent/18 Hep/17</td>
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<td>Castaneda et al,187 2002</td>
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<td>32</td>
<td>CDT with rt-PA/16 Systemic lysis with rt-PA/16</td>
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<td>Sillesen et al,190 2005</td>
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<td>Jackson et al,191 2005</td>
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<td>Ogawa et al,192 2005</td>
<td>24</td>
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<td>Kim et al,193 2006</td>
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<td>Lin et al,194 2006</td>
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<td>Protack et al,195 2007</td>
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<td>CDT with UK, tPA, retavase, pulse-spray, mechanical thrombectomy, stenting, IVC filters</td>
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<td>CDT and/or systemic lysis with mechanical thrombectomy/9 Anticoagulation alone/13</td>
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CDT, catheter-directed thrombolysis; Hep, heparin; IPC, intermittent pneumatic compression; IVC, inferior vena cava; NR, not reported; rPA, recombinant plasminogen activator; PMT, pharmacomechanical thrombolysis; rt-PA, recombinant tissue plasminogen activator; tPA, tissue plasminogen activator; UK, urokinase.

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guinal DVT; therefore, even when lytic therapy was successful, the clinical benefits were not as apparent as with patients with iliofemoral venous thrombosis.

However, important observations were made in randomized trials. Patients successfully treated with intravenous thrombolytic therapy had a significantly better chance of preserving normal vein valve function and enjoyed reduced post-thrombotic morbidity.\textsuperscript{177-179}

Delivery of thrombolytic agents into the thrombus results in higher rates of clot dissolution, shorter treatment times, and reduced bleeding complications. Many reports have documented good outcomes of catheter-directed thrombolysis for acute DVT. Most of these reports are listed in Table 7,\textsuperscript{151-153,157,180-196} which also includes pharmacomechanical techniques used as adjuncts to catheter-directed thrombolysis. Generally, success rates in the 75% to 90% range can be anticipated. Bleeding complications have been reported in up to 11%; however, in the majority of the reports published within the past 6 years, bleeding complications are 5% or less. Symptomatic PE during thrombolytic infusion is uncommon and fatal PE is a rarity.

The National Venous Registry is the largest report to date of patients treated with lytic therapy for acute DVT. It is hampered with the deficiencies of nonrandomization and the biases of patient selection. However, the authors reported a significant correlation of thrombus-free survival with the results of initial therapy ($P < 0.001$). At 1 year, 78% of patients who initially had complete clot resolution had patent veins compared with only 37% of patients who had less than 50% lysis. In patients with first-time iliofemoral DVT who had initially successful clot lysis, 96% remained patent at 1 year. Initial lytic success also correlated with valve function at 6 months. Sixty-two percent of patients with less than 50% thrombolysis had venous valve incompetence, whereas 72% of patients who had complete lysis had normal valve function ($P < 0.02$).

A quality-of-life (QOL) study was published demonstrating that successful thrombolysis for patients with iliofemoral DVT resulted in a significantly improved quality of life compared with a control cohort of patients treated with anticoagulation alone.\textsuperscript{153} A randomized trial performed by Elshawary and Elzayat\textsuperscript{157} compared catheter-directed thrombolysis with anticoagulation alone in patients with iliofemoral DVT. Patients treated with thrombolysis had considerably better outcomes at 6 months, demonstrating improved patency and vein valve function.

The above data are a compelling argument for catheter-directed thrombolysis. Larger randomized trials are required to establish definitive recommendations for care. Fortunately, 2 large trials are under way that
will randomize patients with acute DVT to catheter-directed thrombolysis versus anticoagulation alone, evaluating anatomic, physiologic, and clinical endpoints.

**Pharmacomechanical Thrombolysis**

Although good results have been reported with catheter-directed thrombolysis, treatment times are often long and doses of plasminogen activators often high to successfully complete a course of therapy. This has dampened the enthusiasm of many physicians. Sillesen and colleagues reported that 93% of their patients were successfully treated with catheter-directed thrombolysis and that 90% of their patients who were discharged with patent veins had normal venous valve function at 1 year. However, they reported an average treatment time for catheter-directed thrombolysis of 71 hours. This duration of acute care is logistically difficult for many practitioners and medical centers. The associated cost of care is high, especially when considering that all patients receiving lytic therapy are monitored in intensive care units.

**FIG 5.** A 32-week pregnant woman presented with left leg pain and swelling of 3 days’ duration. A venous duplex examination suggested external iliac and common iliac vein thrombosis, confirmed with ascending phlebography (A). Isolated segmental pharmacomechanical thrombolysis was performed with a Trellis catheter using 3 mg recombinant tissue plasminogen activator (rt-PA). The thrombus was eliminated, demonstrating stenosis of the left common iliac vein (May-Thurner). The left common iliac vein was dilated and stented (B), resulting in unobstructed venous drainage into the vena cava (C). The patient subsequently delivered a healthy infant boy and was asymptomatic with normal venous function 1 year later.
Management of Iliofemoral DVT

**FIG 6.** Treatment algorithm for patients with iliofemoral deep venous thrombosis. (Color version of figure is available online.)

**TABLE 8.** Evidence-based recommendations for the aggressive treatment of patients with iliofemoral DVT$^{15,201}$

<table>
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<th>Recommendation</th>
<th>Grade</th>
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<tr>
<td>In patients with extensive (iliofemoral) DVT, operative venous thrombectomy may be used to reduce acute symptoms and post-thrombotic morbidity</td>
<td>2B</td>
</tr>
<tr>
<td>Following venous thrombectomy, the same duration and intensity of anticoagulation should be used as in those who do not undergo thrombectomy</td>
<td>1C</td>
</tr>
<tr>
<td>In patients with extensive proximal DVT and low risk for bleeding, CDT can be used to reduce acute symptoms and post-thrombotic morbidity</td>
<td>2B</td>
</tr>
<tr>
<td>Pharmacomechanical thrombolysis should be considered in preference to CDT alone</td>
<td>2C</td>
</tr>
<tr>
<td>Following CDT, underlying venous lesions should be corrected</td>
<td>2C</td>
</tr>
<tr>
<td>Following CDT, the same intensity and duration of anticoagulation should be used as those who are not treated with CDT</td>
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</tr>
<tr>
<td>Patients with acute DVT should be treated with a 30-40 mm Hg compression stocking to reduce post-thrombotic morbidity</td>
<td>1A</td>
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DVT, deep venous thrombosis; CDT, catheter-directed thrombolysis.
FIG 7. Patient being treated for a gastrointestinal bleed with sudden shortness of breath, tachycardia, and drop in blood pressure (A). Pulmonary arteriogram showed large PE of the left main pulmonary artery. Following treatment with pulse-spray infusion of thrombus with 6 mg of recombinant tissue plasminogen activator (rt-PA) and catheter-based fragmentation, patient’s clinical condition improved, oxygenation improved, and subsequent cardiac echo was normal (B).
Percutaneous mechanical techniques alone or in combination with thrombolysis have been developed to more rapidly clear the venous system. Vedantham and colleagues evaluated the effectiveness of mechanical thrombectomy alone or in combination with pharmacologic thrombolysis in 28 limbs of patients with acute DVT. They used a variety of mechanical devices and catheters. They found that mechanical thrombectomy alone was successful for removing thrombus that developed intraprocedurally (which is generally gelatinous and not cross-linked with fibrin). However, in the remaining patients, only 26% of the thrombus was removed by mechanical thrombectomy. The addition of a plasminogen activator solution to the mechanical technique removed 82% of the thrombus. This underestimates the benefit to patients with acute DVT, since these authors included patients with chronic occlusions who did not respond to treatment.

Several reports have recently surfaced documenting the benefits of combined pharmacomechanical thrombolysis. Martinez and colleagues reported the outcome of patients with iliofemoral DVT treated initially with isolated segmental pharmacomechanical thrombolysis (ISPMT) versus catheter-directed thrombolysis. Isolated segmental pharmacomechanical thrombolysis was associated with better success rates, shorter treatment times, and lower doses of plasminogen activators (Figs 4, 5).

Lin and colleagues reported their 8-year experience with rheolytic thrombectomy. Patients treated with the AngioJet catheter had significantly fewer phlebograms, shorter intensive care unit (ICU) stays, shorter hospital stays, and fewer blood transfusions. A smaller group of patients treated by Kasirajan and colleagues reported that rheolytic thrombec-

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</table>

PE, pulmonary embolism; MI, myocardial infarction; CDT, catheter-directed thrombolysis.
tomy alone was less effective than combined pharmacomechanical thrombolysis.

Parikh and colleagues\textsuperscript{200} reported their initial clinical experience with ultrasound-accelerated thrombolysis in both upper and lower extremity DVT. Complete lysis was observed in 70\% of patients and overall lysis in 91\%. The median infusion time was 22 hours and 4\% had major complications. These results, compared with historical controls of catheter-directed thrombolysis, suggest an advantage to ultrasound-accelerated thrombolysis. It is this author’s opinion that each device may have a particular advantage in a given clinical situation and that a combination of techniques may be required in a given patient’s scenario.

\textbf{Summary: Iliofemoral DVT}

The aggregate information on operative venous thrombectomy, catheter-directed thrombolysis, and pharmacomechanical thrombolysis for iliofemoral DVT demonstrate substantial benefits for patients treated with a strategy of thrombus removal. A treatment algorithm for patients with iliofemoral DVT is presented in Fig 6.

The recent ACCP consensus conference on antithrombotic therapy for venous thromboembolic disease has reviewed the existing evidence for the management of patients with iliofemoral DVT and incorporated recommendations for care. These evidence-based recommendations are summarized in Table 8.\textsuperscript{201}

\textbf{Aggressive Treatment for Pulmonary Embolism}

Anticoagulation is the recommended management for the majority of patients with acute PE. However, patients with large pulmonary emboli
causing hemodynamic instability or pulmonary hypertension associated with right heart abnormalities benefit considerably by restoring normal outflow from the right ventricle. Ideally, the goal of therapy in patients with large pulmonary emboli is to improve/restore normal cardiopulmonary hemodynamics, thereby avoiding chronic thromboembolic pulmonary hypertension with its associated morbidity and mortality. Pengo and colleagues reported that within 2 years of a first episode of PE, almost 4% of patients developed chronic thromboembolic pulmonary hypertension. Unquestionably, this percentage will increase in patients with large pulmonary emboli. Chronic thromboembolic pulmonary hypertension is associated with recurrent PE, younger age at onset, large perfusion defects, and idiopathic PE. Pulmonary emboli that cause right ventricular dysfunction are associated with a 6-fold increase in hospital mortality and 2.4-fold increase in 1-year mortality following discharge. Surgical pulmonary embolectomy can reduce thromboembolic pulmonary hypertension. The operative mortality rate for pulmonary thromboembolectomy for massive PE has diminished, with contemporary reports indicating that there remains a definitive role for operative pulmonary embolectomy in patients who do not have other options to open their occluded pulmonary arteries.

Intravenous infusion of thrombolytic agents decreases mortality, improves right ventricular function, improves pulmonary function, and decreases chronic thromboembolic pulmonary hypertension as well as reducing recurrent venous thromboembolic disease (Fig 7). Goldhaber and colleagues showed rapid improvement in right ventricular function, reduction in end diastolic right ventricular area, improved pulmonary perfusion, and reduction in recurrent PE when patients were treated with recombinant tissue plasminogen activator (rt-PA) compared with heparin. Konstantinides and colleagues reported the results of a large international PE registry and showed that 30-day mortality was lower in patients receiving lytic therapy and that primary thrombolysis was the only independent predictor of survival on multivariate analysis. However, not all patients with major pulmonary emboli are candidates for systemic thrombolytic therapy. Several authors have recently reported improved outcomes in patients treated with catheter-based thrombus aspiration, maceration, fragmentation, and power-pulse infusion of plasminogen activators (Table 9).

Improvements in catheter-based techniques, with power-pulse infusion of plasminogen activators into proximally occluding pulmonary emboli with mechanical fragmentation, rapidly reduce pulmonary hypertension, thereby improving patient oxygenation and cardiopulmonary hemody-
Rx of Pulmonary Embolism

Pulmonary Embolism (Diagnosis Confirmed)

ECHO Right Heart

Normal

Abnormal

Lytic Rx

No

Contraindication to Lytic Rx

Yes

Anticoagulation

Catheter-Directed Fragmentation

Pulmonary Embolectomy

FIG 8. Treatment algorithm for patients with pulmonary embolism. (Color version of figure is available online.)

Lower doses of plasminogen activators pulsed into the thrombus promote subsequent lysis of the fragmented thrombus trapped in the proximal pulmonary artery as a result of the plasminogen activator binding to fibrin-bound plasminogen.

Summary: Pulmonary Embolism

Patients with pulmonary emboli that raise pulmonary artery pressures to the point of affecting right ventricular function have a markedly increased early and long-term mortality, increased risk of recurrence, and increased risk of chronic thromboembolic pulmonary hypertension. All patients with PE should undergo cardiac echocardiography to assess pulmonary artery pressure and right heart function. Patients with abnormalities of right heart function should be considered for systemic thrombolytic therapy or catheter-based fragmentation with thrombolysis or operative
pulmonary embolectomy, as suggested by the PE management algorithm (Fig 8).201

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