Initial Treatment of Venous Thromboembolism

Simon J. McRae, MBBS; Jeffrey S. Ginsberg, MD

Abstract—Adequate initial anticoagulant therapy of deep venous thrombosis (DVT) is required to prevent thrombus growth and pulmonary embolism (PE). Intravenous unfractionated heparin (UFH) is being replaced by low-molecular-weight heparin (LMWH) as the anticoagulant of choice for initial treatment of venous thromboembolism (VTE). Both agents are relatively safe and effective when used to treat VTE, with LMWH suitable for outpatient therapy because of improved bioavailability and more predictable anticoagulant response. Serious potential complications of heparin therapy, such as heparin-induced thrombocytopenia (HIT) and osteoporosis, seem less common with LMWH. The potential for fetal harm and changes in maternal physiology complicate the treatment of VTE during pregnancy. Although systemic thrombolysis is used in patients with massive PE and in some patients with proximal DVT, controversy persists with respect to appropriate patient selection for this intervention. (Circulation. 2004;110[suppl I]:I-3-I-9.)

Key Words: venous thromboembolism ■ pulmonary embolism ■ deep venous thrombosis ■ anticoagulants ■ thrombosis ■ heparin

Venous thrombosis (VTE), consisting of deep venous thrombosis (DVT) and pulmonary embolism (PE), is a potentially fatal disease with an estimated annual incidence of 0.1% in white populations. Long-term sequelae, particularly postphlebitic syndrome (PPS), are frequent and often disabling. The initial aim of treatment of DVT is prevention of thrombus extension and PE. Reductions in the incidence of recurrent VTE, PPS, and chronic thromboembolic pulmonary hypertension are longer-term goals.

Anticoagulant therapy has been the mainstay of treatment for VTE since the landmark trial of Barritt and Jordan provided the first convincing evidence for its effectiveness. In this randomized study of 35 patients with clinically diagnosed PE, 25% of those who received no treatment died of recurrent PE proven at autopsy, and another 25% experienced nonfatal recurrent PE. In contrast, none of the patients who received intravenous (IV) heparin therapy died. Because objective testing was not used to establish the diagnosis of nonfatal PE, the risk reduction associated with heparin therapy may have been underestimated.

Treatment of patients with uncomplicated PE or DVT involves similar anticoagulant regimens, in part because asymptomatic PE occurs frequently in patients with symptomatic proximal DVT, and vice versa. This review describes the initial treatment of VTE, including: (1) initiation of anticoagulant therapy with either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH); (2) potential complications of anticoagulant therapy; (3) initiation of warfarin therapy; (4) indications for systemic thrombolytic therapy; and (5) management of VTE in pregnancy.

Initiation of Anticoagulant Therapy

Anticoagulant therapy is the standard of care in patients presenting with acute VTE. Inpatient treatment with IV UFH is being replaced by outpatient therapy with LMWH as the most commonly used anticoagulant regime. Following is a review of the efficacy, safety, and appropriate dosage of both UFH and LMWH.

Initial Treatment With UFH

Discovered in 1916, UFH is a sulfated glycosaminoglycan that exerts its anticoagulant effect primarily by binding to antithrombin (AT) and inducing conformational changes that accelerate the rate at which AT inhibits coagulation enzymes. Commercial UFH is a heterogeneous mixture of carbohydrate chains ranging in molecular weight from 3000 to 30,000 daltons, yet only approximately one-third of UFH molecules contain the unique pentasaccharide sequence required for binding to AT, and hence for anticoagulant activity. This molecular heterogeneity and nonspecific protein binding related to negative charge are responsible for a number of the practical limitations associated with the use of heparin.

Route of Administration

In the initial treatment of VTE, UFH is usually administered by continuous IV infusion, a method shown to reduce extension and recurrence of symptomatic proximal VTE and calf vein DVT and mortality in patients with PE. Overall, ~5% of patients with VTE treated with IV UFH develop VTE during the initial treatment period, and major bleeding occurs in 2% of patients. A meta-analysis of randomized trials has
shown that when given in adequate doses, subcutaneous (SC) UFH is at least as effective and safe as IV heparin for initial treatment of DVT.17 Because the bioavailability of SC UFH is less than that of IV heparin, larger initial doses of SC heparin are needed to achieve a therapeutic anticoagulant effect.13 This point is highlighted by the results of a randomized trial in which recurrent VTE occurred in 19.3% of patients given SC UFH 15 000 U twice daily compared with 5.2% of patients given the same total daily dose of UFH by continuous IV infusion.15 Appropriately designed trials of SC UFH have not been conducted in patients with symptomatic PE.

**Dosage and Coagulation Monitoring**

There is considerable variation in individual anticoagulant responses to UFH.18,19 Current evidence suggests that a minimum threshold dose of heparin is required to achieve therapeutic efficacy.15,20 Monitoring of heparin therapy usually involves measurement of the activated partial thromboplastin time (aPTT).13 A therapeutic range of aPTT ratio (patient/control) of 1.5 to 2.5 is generally recommended, based on animal and prospective human studies in which this range corresponded to a heparin plasma concentration between 0.2 to 0.4 U/mL by protamine titration.13 The relationship of aPTT to heparin levels is dependent on the aPTT reagent and coagulometer used; significant variation is seen.21 It is therefore recommended that individual institutions establish a therapeutic aPTT range specific to the laboratory reagent and coagulometer in use that corresponds to a heparin level of 0.2 to 0.4 U/mL by protamine titration using plasma from patients receiving heparin.22 When this is not possible, a patient/control aPTT ratio ranging from 2.0 to 3.5 with less heparin-responsive reagents has been shown to correspond to therapeutic heparin levels with many modern coagulometers.23

With modern dosage regimens, the relationship between the prolongation of the aPTT with heparin and clinical efficacy is controversial.24–26 Evidence that patients who fail to achieve therapeutic heparin levels, as measured by the aPTT, have a higher rate of subsequent recurrent VTE25 is derived from retrospective subgroup analysis of cohort studies.13 This conflicts with the findings of a randomized trial, in which there was a dissociation between therapeutic effect and aPTT in patients receiving at least 35 000 U per day of UFH.19 This result is supported by 2 subsequent meta-analyses, which found that in patients treated with a 5000-U bolus followed by a continuous IV infusion of at least 30 000 U per day of UFH, there was no association between initial subtherapeutic aPTT results and subsequent recurrence risk.24,26 Furthermore, although the risk of heparin-associated bleeding increases with dose, its association with a particular aPTT threshold is less clear.13 Despite these doubts with regard to the need for aPTT monitoring to maximize either efficacy or safety, dose adjustment guided by the aPTT ratio remains standard practice in the absence of prospective trials evaluating unmonitored UFH therapy.

An initial bolus of 5000 U of UFH is usually given, following which the aPTT should be measured 6 hours later. Because physician-directed heparin therapy often results in inadequate dosing, the use of validated nomograms is recommended (Table 1).20,27 These have been shown to reduce the time required to achieve therapeutic aPTT results20,27 and to improve patient outcomes.20 It may be necessary to adapt published nomograms for local use, depending on the sensitivity of institutional aPTT reagents and measuring devices.

Heparin resistance, defined as a requirement of >35 000 U per day of UFH to achieve a therapeutic aPTT, occurs in up to 25% of patients with VTE.13 In an important randomized trial,19 monitoring therapy by assessing anti–factor Xa levels (targeted range, 0.35 to 0.67 U/mL) in such patients proved as effective and safe as dose adjustments based on aPTT results, and resulted in a lower mean daily dose of UFH. It is therefore recommended that anti-Xa levels be used to guide UFH therapy in patients with heparin resistance. Consideration should be given to checking for AT deficiency when heparin resistance is associated with recurrent or progressive thrombosis. However, in the majority of cases, decreased AT levels are caused by the heparin therapy itself rather than a primary deficiency state.13

**Initial Treatment With LMWH**

LMWH products are produced by controlled enzymatic or chemical depolymerization of UFH. They have a mean molecular weight of ~5000 daltons.9 To catalyze thrombin inhibition, heparin must bind AT and thrombin simultaneously, a process that requires a heparin chain composed of at least 18 saccharide units. In contrast, to catalyze factor Xa inhibition, heparin needs to bind to AT only via the pentasaccharide sequence.28 The reduced molecular size of LMWH therefore results in a decreased ability to inhibit thrombin in comparison to UFH. Because of its reduced size and charge relative to UFH, LMWH exhibits less nonspecific binding to endothelium, macrophages, and heparin-binding plasma proteins other than AT.9 The improved bioavailability, longer half-life, and dose-independent renal clearance of LMWH is associated with a more predictable anticoagulant response, making unmonitored, weight-based SC administration feasible.13

**Comparative Efficacy and Safety of UFH and LMWH**

In 2 meta-analyses, unmonitored, fixed-dose SC LMWH was at least as effective and safe as adjusted-dose IV UFH for

<table>
<thead>
<tr>
<th>Bolus (U)</th>
<th>Hold (min)</th>
<th>Rate Change (mL/h)</th>
<th>Repeat aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>5000</td>
<td>0</td>
<td>+3</td>
</tr>
<tr>
<td>50–59</td>
<td>0</td>
<td>0</td>
<td>+3</td>
</tr>
<tr>
<td>60–85</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>86–95</td>
<td>0</td>
<td>0</td>
<td>−2</td>
</tr>
<tr>
<td>96–120</td>
<td>0</td>
<td>30</td>
<td>−2</td>
</tr>
</tbody>
</table>

\[ \text{aPTT indicates activated partial thromboplastin time.} \]

\[ \text{Heparin infusion based on 20 000 U UFH in 500 mL normal saline, such that} \]

\[ \text{1 mL/h corresponds to 40 U/h. Infusion commenced at 32 mL/h after an initial} \]

\[ \text{5000-U bolus.} \]

\[ \text{The first aPTT measurement is made 6 hours after initiation of anticoagulation.} \]

Adapted from Cruickshank et al. Arch Int Med. 1991;151:333–337.27
treatment of patients with VTE.\textsuperscript{29,30} In both analyses, there was a significant difference in total mortality favoring LMWH. The cause of this difference remains unclear, although the mortality benefit of LMWH appears restricted to the subgroup of patients with VTE associated with malignancy.\textsuperscript{29,30} Subsequent to publication of these meta-analyses, randomized trials confirmed that LMWH is at least as effective and safe as UFH for treatment of VTE,\textsuperscript{31–33} and once-daily LMWH was as effective and safe as UFH for treatment of symptomatic PE.\textsuperscript{34}

The predictable anticoagulant response to weight-based LMWH allows for outpatient therapy of VTE. Secondary analyses of randomized trials found no difference in the rate of recurrent VTE between outpatients and inpatients receiving LMWH therapy,\textsuperscript{30} although patients with symptomatic PE were either excluded or given initial therapy in the inpatient setting. Additional studies have confirmed the safety and effectiveness of outpatient LMWH therapy for the majority of patients with VTE, including those with symptomatic submassive PE.\textsuperscript{35–36} In most health care settings, the higher cost of LMWH relative to UFH is offset by the savings associated with outpatient therapy.\textsuperscript{4} Consequently, outpatient SC LMWH is currently the preferred treatment for the majority of patients with VTE. In those at high risk for bleeding complications, IV UFH may be preferred, however, because of its shorter half-life and the reversibility of the anticoagulant effect by administration of protamine sulfate,\textsuperscript{13} although this perceived advantage has not been examined in a randomized trial.

**Formulation, Dosage, and Monitoring**

LMWH products differ in their method of preparation, mean molecular weight, and anticoagulant effect, as measured by the ratio of anti–factor Xa to anti–IIa (thrombin) activity.\textsuperscript{9} In the absence of trials directly comparing different LMWH preparations, it is unclear whether differences among the various preparations are clinically important.\textsuperscript{37} Standard meta-analysis\textsuperscript{30} and multivariate regression analysis\textsuperscript{38} techniques have been used to compare results obtained with different LMWH preparations in 2 separate studies, both of which failed to draw definite conclusions with regard to comparative efficacy or safety because of the relatively small number of patients available.

For initial treatment of VTE, different dosage regimens are used for the various LMWH preparations; those approved for treatment of VTE in the United States are shown in Table 2. In trials in which they were directly compared, once-daily SC LMWH appeared as effective and safe as a twice-daily regimen for treatment of symptomatic DVT, although the statistical confidence is limited by sample size.\textsuperscript{39}

Because the anticoagulant response to weight-based dosing is predictable, coagulation monitoring is generally unnecessary during treatment with LMWH.\textsuperscript{9} The anti–factor Xa assay is commonly used for monitoring LMWH, despite concerns about the reliability and clinical relevance of anti–factor Xa levels.\textsuperscript{40} Anti–factor Xa levels are usually monitored 4 hours after SC injection, with suggested therapeutic ranges of 0.6 to 1.0 U/mL for twice-daily administration and 1.0 to 2.0 U/mL for once-daily administration.\textsuperscript{13} Monitoring is recommended in patients with renal failure, because of the risk of accumulation of anti–factor Xa activity.\textsuperscript{9} Supporting the use of anti–factor Xa monitoring in patients with renal failure is the different potential for accumulation among the various LMWH preparations and the absence of a clear threshold of creatinine clearance for identification of patients at increased risk for accumulation.\textsuperscript{41} Obese patients have been under-represented in treatment trials using LMWH, and although individual LMWH preparations have shown predictable anti–factor Xa levels in this patient group,\textsuperscript{42,43} measuring levels on at least 1 occasion seems prudent.

**Nonhemorrhagic Complications of Anticoagulant Therapy**

Although bleeding is the most common side effect of anticoagulant therapy, UFH treatment may also be associated with nonhemorrhagic complications. These are caused by the nonspecific protein binding of UFH and are less common with LMWH, likely because of decreased molecular charge.

**Heparin-Induced Thrombocytopenia**

Heparin-induced thrombocytopenia (HIT) is a clinicopathological syndrome;	extsuperscript{44} its diagnosis is based on characteristic clinical events and concurrent laboratory detection of HIT antibodies in the setting of recent heparin therapy. The pathogenic antibodies are directed against multimolecular complexes of platelet factor 4 (PF4) and heparin, and stimulated by neoepitopes expressed on PF4 in response to heparin binding.\textsuperscript{44} Interaction of the antigen/antibody complex with platelets and binding of antibody to platelet Fc receptors result in platelet activation and aggregation.\textsuperscript{45} The end result is increased thrombin generation, which may be associated with arterial or venous thrombosis.\textsuperscript{44}

The central clinical feature of HIT is thrombocytopenia that typically occurs 5 to 10 days after heparin exposure, although it may develop more rapidly in patients previously exposed to heparin within the preceding 100 days.\textsuperscript{44} In 90% of cases, the platelet count decreases to $<150 \cdot 10^9/L$, but a decline of 50% from the baseline platelet count should raise clinical suspicion.\textsuperscript{44} Thrombosis is a common complication and is more frequently venous than arterial. In the absence of alternative anticoagulant therapy, 25% to 50% of patients without thrombosis at the time of HIT subsequently develop thrombotic complications, despite cessation of heparin. Skin

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**TABLE 2. LMWH Preparations Available in the United States**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>SC Treatment Dose for VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>100 anti-Xa U/kg every 12 h\textsuperscript{†} or 150 anti-Xa U/kg every 24 h\textsuperscript{‡}</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>100 anti-Xa U/kg twice daily\textsuperscript{§} or 200 anti-Xa U/kg once daily\textsuperscript{§}</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>175 anti-Xa U/kg once daily\textsuperscript{§}</td>
</tr>
</tbody>
</table>

LMWH indicates low-molecular-weight heparin; VTE, venous thromboembolism.

\textsuperscript{†}For enoxaparin, 100 anti-Xa U/kg corresponds to a dose of 100 mg/kg.

\textsuperscript{‡}Current FDA-approved dose for this indication.

\textsuperscript{§}Current FDA-approved dose for inpatient use.

\textsuperscript{§}Regimen used in other countries, but not currently approved by the FDA.
reactions and systemic reactions to heparin injections are less common manifestations.44

The frequency of HIT depends on the heparin formulation and patient population but appears to range from 0.5% to 5.0% of treated cases.44 In patients receiving heparin for treatment of VTE, both antibody formation and clinical HIT are more common with UFH than LMWH.46 Platelet count monitoring should be performed during therapy with UFH for early detection of HIT. Recent guidelines suggest minimum monitoring of platelet counts every other day between days 4 and 10 of treatment (with day 0 being the first day of treatment).47

Laboratory tests for HIT antibodies involve functional and immunological assays;45 full discussion of these is beyond the scope of this review. Because HIT antibodies may be detected in the absence of clinical features of the syndrome, it is important to establish the clinical pretest probability of HIT in interpreting laboratory results.44

For patients with HIT, even those without VTE at diagnosis, an anticoagulant other than heparin is recommended.44 LMWH is not an optimal alternative to UFH because of a high risk of clinically significant cross-reactivity with the HIT antibodies. Three anticoagulants have been found effective in cohort studies for treatment of HIT, the direct thrombin inhibitors lepirudin and argatroban (Table 3), and danaparoid sodium, a heparinoid, which, however, is no longer available in the United States. There is also anecdotal evidence supporting use of bivalirudin, a hirudin analogue.44 Because of the risk of precipitating venous limb gangrene, warfarin therapy should be delayed until resolution of thrombocytopenia, particularly in patients with VTE at diagnosis.45

**Osteoporosis**

Another complication of long-term UFH or LMWH therapy is osteoporosis.13 This is not a major concern in most patients with VTE, who receive only short-term treatment; however, long-term heparin therapy may be associated with substantial bone loss. This is most likely to occur in patients receiving protracted therapy for VTE associated with malignancy48 or pregnancy.49 Symptomatic vertebral fracture has been reported in 2% to 3% of patients receiving long-term UFH, and up to 30% of patients show a significant reduction in bone density.13 Treatment with LMWH is associated with a lower risk of osteoporosis than UFH.13,50

**Initiation of Oral Anticoagulant Therapy**

After an initial course of treatment with LMWH or UFH, extended anticoagulation is required to prevent recurrent VTE.4 Oral vitamin K antagonist agents in the coumarin class are the most commonly used agents for long-term anticoagulation. Because the onset of anticoagulant activity with these compounds is delayed for several days, however, an initial period of overlap with UFH or LMWH is required. With warfarin commenced on the same day as heparin, a 5-day course of heparin appears as effective as a 10-day course.51,52 A therapeutic international normalized prothrombin time ratio of 2.0 to 3.0 should be achieved for 24 hours before heparin is discontinued.

Large loading doses of warfarin may be associated with an excessive anticoagulant effect without concurrent antithrombotic activity.4 There is conflicting evidence as to the optimal dose with which to initiate warfarin therapy.53,54 An initial randomized trial found a 5-mg initial daily dose of warfarin as effective as 10 mg daily in achieving a therapeutic international normalized prothrombin time ratio within 5 days, with less tendency toward excessive anticoagulation.53 In a more recent trial, involving only outpatients with VTE,54 a 10-mg daily initial dose was more effective than 5 mg daily in achieving therapeutic anticoagulation (international normalized prothrombin time ratio 2.0 to 3.0) by the fifth day of therapy without excessive anticoagulation. It seems reasonable to choose a starting dose of 10 mg daily in fit outpatients with VTE, and 5 mg daily or less in inpatients, particularly those with vitamin K deficiency or impaired hepatic synthetic function.

In patients with VTE associated with an underlying cancer, the recent Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial showed a reduction in recurrent thrombotic events in patients randomized to ongoing LMWH in comparison with those receiving secondary prophylaxis with a vitamin K antagonist.48 Continuation of LMWH therapy rather than conversion to oral anticoagulant therapy, therefore, appears appropriate in this patient subgroup.

**Thrombolytic Therapy for VTE**

By converting plasminogen to plasmin, thrombolytic agents have the potential to accelerate thrombus resolution in patients with VTE. Thrombolytic agents may be administered systemically or locally by intravenous catheter directly into a thrombus; this is discussed elsewhere in this issue. Unlike anticoagulant therapy, both the rationale for thrombolysis and the protocols used differ for patients with symptomatic PE or DVT and will therefore be discussed separately.

**Thrombolytic Therapy for DVT**

Despite standard anticoagulant therapy, up to 30% of patients with DVT have symptomatic PPS,2 and it has been proposed that more rapid and complete thrombus dissolution achieved with thrombolytic therapy could reduce the incidence of this complication. In a recent systematic review, thrombolytic therapy was associated with increased rates of early vein

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**TABLE 3. Alternative Antithrombotic Protocols for Treatment of HIT**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepirudin</td>
<td>Bolus 0.4 mg/kg; then infusion 0.15 mg/kg per h (target aPPT 1.5–2.5 × baseline)</td>
</tr>
<tr>
<td>Argatroban</td>
<td>No bolus; infusion 2 μg/kg per min (target aPPT 1.5–3.0 × baseline)</td>
</tr>
</tbody>
</table>

HIT indicates heparin-induced thrombocytopenia; aPPT, activated partial thromboplastin time.

*In the absence of thrombosis, the bolus dose may be omitted and a target aPPT of 1.5 to 2.0 times baseline may be used. The dose of lepirudin should be reduced in patients with renal failure.†The dose of argatroban should be reduced in patients with hepatic failure. Adapted from Warkentin. Br J Haematol. 2003;121:535–555.44
Treatment of VTE in Pregnancy

Selection of optimum treatment for women in whom VTE develops during pregnancy must take into account alterations in maternal physiology and the potential for fetal harm. Coumarin derivatives cross the placenta and have the potential to cause fetal bleeding and teratogenicity. In contrast, neither UFH nor LMWH cross the placental barrier,\(^\text{49}\) and despite recent precautions from pharmaceutical manufacturers about teratogenicity associated with LMWH, available data support the safety of UFH and LMWH for the developing fetus.\(^\text{60}\) Evidence for the efficacy of this approach is extrapolated largely from trials in nonpregnant patients. Accordingly, either UFH or LMWH may be used for both initial treatment and secondary prophylaxis of VTE during pregnancy.

Despite higher cost, LMWH is generally preferred over UFH because LMWH is associated with a lower incidence of HIT\(^\text{46}\) and probably osteoporosis during long-term use.\(^\text{13}\) LMWH has been found to be at least as effective in preventing recurrence as oral vitamin K antagonists in unselected patients with VTE,\(^\text{61}\) and it appears to be superior with regard to efficacy in patients with underlying malignancy.\(^\text{48,62}\) Because the volume of distribution of LMWH changes over the course of pregnancy and weight gain is common, monitoring of anti–factor Xa levels is recommended to ensure appropriate dosing.\(^\text{60}\) Although the optimal therapeutic range for LMWH during pregnancy based on anti–factor Xa levels is unknown, it seems reasonable to use the target range described earlier for nonpregnant patients. When UFH is given, aPTT monitoring is recommended, although the aPTT response to heparin may be attenuated during pregnancy because of elevated levels of procoagulants such as factor VIII. Anti-Xa monitoring is also appropriate in cases of heparin resistance.\(^\text{19}\) LMWH is normally stopped 24 hours before delivery to reduce the risk of excessive bleeding and to allow for safe epidural anesthesia. In women at high risk for recurrent VTE (eg, proximal DVT or PE within 4 weeks), IV UFH can be initiated and interrupted 4 to 6 hours before induction of labor.\(^\text{60}\)

Novel Antithrombotic Agents for the Initial Treatment of VTE

Increased knowledge of the mechanism of thrombosis has led to the development of novel anticoagulant agents that are designed to target specific clotting factors.\(^\text{63}\) Phase III trials of treatment for acute VTE involving 2 of these agents have been completed. Fondaparinux (Arixtra) is a synthetic polysaccharide, based on the pentasaccharide sequence required to potentiate the anti–factor Xa activity of AT.\(^\text{61}\) It is administered by once-daily SC injection and does not require laboratory monitoring because of a predictable dose response. In phase III trials, fondaparinux has been found to be at least as effective and safe as IV UFH for initial treatment of PE\(^\text{62}\) and as the LMWH enoxaparin for initial treatment of DVT.\(^\text{64}\)

Ximelagatran (Exanta) is an oral, direct thrombin inhibitor, which is metabolized to the active metabolite melagatran once absorbed. Laboratory monitoring of the anticoagulant effect is not needed. A phase III trial comparing ximelagatran with the combination of enoxaparin and warfarin for the

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**TABLE 4. Thrombolytic Protocols for Treatment of PE**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Protocol*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
<td>250 000 U over 30 minutes followed by 100 000 U/h for 4 h</td>
</tr>
<tr>
<td>Urokinase</td>
<td>4400 U/kg over 10 minutes followed by 4400 U/kg for 12 h</td>
</tr>
<tr>
<td>rt-PA</td>
<td>100 mg over 2 h</td>
</tr>
</tbody>
</table>

PE indicates pulmonary embolism; rt-PA, recombinant tissue plasminogen activator complex.

*All agents are administered by intravenous infusion.
†FDA-approved protocols.

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patency, but rates of major hemorrhage also increased in comparison with UFH treatment.\(^\text{55}\) Because of methodological flaws in reported trials, it is not possible to draw definitive conclusions about the effects of thrombolysis on the incidence of PPS. At present, therefore, thrombolysis should be reserved for exceptional circumstances, such as patients with limb-threatening ischemia caused by phlegmasia dolens, an uncommon, severe form of DVT. Surgical thrombectomy may be appropriate in selected patients with extensive limb-threatening venous thrombosis, particularly if contraindications to thrombolysis exist. It is possible that in selected cases, such as young patients with extensive iliofemoral DVT, the benefit-to-risk ratio may be greater, or that outcomes may be more favorable, using catheter-directed rather than systemic thrombolysis, but additional randomized trials are needed that specifically address these issues.

**Thrombolytic Therapy for PE**

In the treatment of patients with PE, the indications for thrombolytic therapy remain controversial. Although thrombolysis is associated with greater initial angiographic resolution of thrombus and lower residual pulmonary vascular resistance than treatment with UFH,\(^\text{4}\) the rate of major hemorrhage is significantly increased. The incidence of intracranial hemorrhage may be as high as 2% to 3% with systemic thrombolytic therapy,\(^\text{56}\) although rates were lower in a recent trial.\(^\text{57}\) Given the increased rate of complications and the low mortality rate in patients with PE treated with conventional therapy, thrombolysis should be reserved for patient subgroups at greatest risk for mortality. Fatality rates in patients with PE presenting in shock may be as high as 30%,\(^\text{58}\) and thrombolytic therapy should be considered in patients with persistent or worsening respiratory failure.

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**TABLE 4. Thrombolytic Protocols for Treatment of PE**

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PE indicates pulmonary embolism; rt-PA, recombinant tissue plasminogen activator complex.

*All agents are administered by intravenous infusion.
†FDA-approved protocols.
treatment of acute VTE was recently published in abstract form, reporting that ximelagatran was not inferior with regard to efficacy and safety.65 Fondaparinux has recently received FDA approval for initial treatment of VTE, whereas ximelagatran is yet to be approved. Other novel agents, including NAPc2 targeting the factor VIIa/tissue factor complex and soluble thrombomodulin, are currently in earlier stages of development.63

Nonpharmacological Management of Acute VTE

In a recent prospective registry of patients treated for acute VTE, absolute bed rest was recommended in the majority of individuals.66 Elevation and rest of an acutely swollen leg may provide initial symptomatic relief. However, bed rest has been shown to be associated with increased thrombus propagation and does not appear to decrease the rate of PE. Early mobilization also may lead to more rapid resolution of pain and swelling.67 Therefore, routine bed rest should not be recommended as part of standard care for patients with DVT. Insufficient studies have been performed with regard to the benefit or harm of mobilization in patients with symptomatic PE.

Conclusions

Over the past decade, LMWH has emerged as an effective alternative to UFH as initial therapy for VTE. Outpatient therapy of VTE is now common, but because the index disorders may arise unpredictably, treatment is best managed under the direction of a team of specialists available around the clock. The emergence of novel antithrombotic agents that target specific factors in the coagulation cascade may modify the initial treatment of VTE in the near future. Further trials, both in selected high-risk subgroups and use of catheter-directed drug delivery, are needed to better define the role of thrombolytic therapy for VTE.

References

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In the article by Huynh et al, “Aspirin, Warfarin, or the Combination for Secondary Prevention of Coronary Events in Patients With Acute Coronary Syndromes and Prior Coronary Artery Bypass Surgery,” which published in the June 26, 2001, issue (Circulation. 2001;103:3069–3074), the authors now realize errors appeared in Tables 3 and 4. The percentages of events and complications were presented on the basis of the number of patients’ visits rather than on the total number of patients.

Overall, the corrected results did not change the implication of the study. There was no benefit of warfarin alone or combined with aspirin in the secondary prevention of ischemic events in this study of patients with previous coronary artery bypass surgery and an acute coronary syndrome; there was a significant excess in minor bleeding compared with the aspirin-alone group.

Corrected versions of Tables 3 and 4 appear below.

### TABLE 3. End-Point Events According to Treatment

<table>
<thead>
<tr>
<th>Events</th>
<th>Warfarin + Placebo (n=45)</th>
<th>Aspirin + Placebo (n=46)</th>
<th>Warfarin + Aspirin (n=44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point, n (%)</td>
<td>18 (40.0)</td>
<td>13 (28.3)</td>
<td>11 (25.0)</td>
<td>0.27</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>4 (8.9)</td>
<td>1 (2.2)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>UA, n (%)</td>
<td>16 (35.6)</td>
<td>13 (28.3)</td>
<td>10 (22.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>PCI, n (%)</td>
<td>6 (13.3)</td>
<td>1 (2.2)</td>
<td>3 (6.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Repeat CABG, n (%)</td>
<td>2 (4.4)</td>
<td>2 (4.4)</td>
<td>2 (4.5)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

UA indicates unstable angina requiring rehospitalization; PCI, percutaneous coronary intervention; and MI, myocardial infarction. Primary end point is any-cause mortality, MI, or UA requiring hospitalization.

### TABLE 4. Complications and Adherence to Protocol by Patients

<table>
<thead>
<tr>
<th>Complications</th>
<th>Warfarin + Placebo (n=45)</th>
<th>Aspirin + Placebo (n=46)</th>
<th>Warfarin + Aspirin (n=44)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding, n (%)</td>
<td>10 (22.2)</td>
<td>2 (4.3)</td>
<td>9 (20.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Major bleeding, n (%)</td>
<td>1 (2.2)</td>
<td>0 (0.0)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Blood transfusions, n (%)</td>
<td>2 (4.4)</td>
<td>0 (0.0)</td>
<td>2 (4.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Compliance, %*</td>
<td>90.1</td>
<td>86.7</td>
<td>86.1</td>
<td>0.66</td>
</tr>
<tr>
<td>Protocol completion, %*</td>
<td>77.6</td>
<td>78.5</td>
<td>69.9</td>
<td>0.22</td>
</tr>
</tbody>
</table>

*Compliance and protocol completion were calculated per visit.

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In the article by Haïssaguerre et al, “Mapping and Ablation of Ventricular Fibrillation Associated With Long-QT and Brugada Syndromes,” which appeared in the August 26, 2003, issue (Circulation. 2003;108:925–928), the authors would like to note the following errors:

1. In the byline, Jerónimo Farré’s name incorrectly appeared as “Gerónimo Farre.”
2. José Angel Cabrera and Jerónimo Farré work at Fundación Jiménez Díaz in Madrid, Spain.
3. The work of Drs Cabrera and Farré was supported by Redes Temáticas de Cooperación, Red Cardiovascular C01/03.

DOI: 10.1161/01.CIR.0000155483.25082.D4

In the article by McRae and Ginsberg, “Initial Treatment of Venous Thromboembolism,” which appeared in the August 31, 2004, supplement sponsored by the Society for Vascular Medicine and Biology (Circulation. 2004;110[suppl I]:I-3–I-9), an error appeared in Table 2. The footnote of the table erroneously states that “For enoxaparin, 100 anti-Xa U/kg corresponds to a dose of 100 mg/kg.” The legend should have read, “For enoxaparin, 100 anti-Xa U/kg corresponds to a dose of 1 mg/kg.”

DOI: 10.1161/01.CIR.0000155484.25082.1A

In the article by Bauer et al, “Acute Improvement in Global and Regional Left Ventricular Systolic Function After Percutaneous Heart Valve Implantation in Patients With Symptomatic Aortic Stenosis,” which appeared in the September 14, 2004, issue (Circulation. 2004;110:1473–1476), two errors of note appeared in the table on page 1474. Under “Endocardiographic data,” the rows for “LV end-systolic volume, mm Hg” and “LV end-diastolic volume, mm Hg” should have appeared as the following:

<table>
<thead>
<tr>
<th>LV end-diastolic volume, mL</th>
<th>102±36 (baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-systolic volume, mL</td>
<td>49±25 (baseline)</td>
</tr>
</tbody>
</table>

DOI: 10.1161/01.CIR.0000155485.32706/1C

Because of a typesetting error, several mathematical symbols appeared incorrectly in the article by Solomon et al, “Effect of Candesartan on Cause-Specific Mortality in Heart Failure Patients: The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) Program,” which appeared in the October 12, 2004, issue (Circulation. 2004;110:2180–2183). On page 2180, in the abstract and in the text of the article, there were several instances in which “LVEF=40%” should have appeared as “LVEF≤40%.” In addition, in the last sentence of the first paragraph of the article, please note that “9% borderline risk” should read “9% borderline significant risk.” The corrected version is available online at http://circ.ahajournals.org/cgi/content/full/110/15/2180. (The previous version can be accessed by selecting the “Previous Version of This Article” link.) We regret these errors.

DOI: 10.1161/01.CIR.0000155486.26868.C9

In the AHA Scientific Statement by Drew et al, “Practice Standards for Electrocardiographic Monitoring in Hospital Settings: An American Heart Association Scientific Statement From the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young,” which appeared in the October 26, 2004, issue (Circulation. 2004;110:2721–2746), Figure 4 contained an error. The text in the figure refers to the “Angle of Lewis.” The correct name is “Angle of Louis.” The Association regrets this error.

DOI: 10.1161/01.CIR.00001155490.19245.B0
In the article by Noujaim et al, “From Mouse to Whale: A Universal Scaling Relation for the PR Interval of the Electrocardiogram of Mammals,” which appeared in the November 2, 2004, issue (Circulation. 2004;110:2802–2808), the name of Ary L. Goldberger, MD, was misspelled as "Goldberg" in reference 12. The authors regret this error.

DOI: 10.1161/01.CIR.0000155482.89456.78

In the article by Spargias et al, “Ascorbic Acid Prevents Contrast-Mediated Nephropathy in Patients With Renal Dysfunction Undergoing Coronary Angiography or Intervention,” which appeared in the November 2, 2004, issue (Circulation. 2004;110:2837–2842), the name of author Panagiotis Iokovis was spelled incorrectly as “Panagiotis Iocovis.” The authors regret this error.

DOI: 10.1161/01.CIR.0000155487.34492.0D

In the article by Francia et al, “Deletion of p66<sup>shc</sup> Gene Protects Against Age-Related Endothelial Dysfunction,” which published in the November 2, 2004, issue (Circulation. 2004;110:2889–2895), the name of author Chiara Delli Gatti incorrectly appeared with a lower case “d” (ie, “delli Gatti”).

DOI: 10.1161/01.CIR.0000155488.34492.E9