Initial treatment of venous thromboembolism

Cecilia Becattini1, Giancarlo Agnelli1, Joseph Emmerich2, Alessandra Bura2, Jeffrey I. Weitz3

1Division of Internal and Cardiovascular Medicine, Department of Internal Medicine, University of Perugia, Perugia, Italy; 2Service de Médecine Vasculaire-HTA, Hôpital Européen Georges Pompidou, Paris, France; 3Departments of Medicine and Biochemistry, McMaster University and Henderson Research Center, Hamilton, Ontario, Canada

Summary
Immediate anticoagulant treatment is essential to reduce morbidity and mortality in patients with acute venous thromboembolism (VTE). Currently, rapid anticoagulation can only be achieved with parenteral anticoagulants, such as heparin or low-molecular-weight heparin (LMWH). Weight-adjusted LMWH is the treatment of choice, because it produces predictable anticoagulation and does not require coagulation monitoring. If heparin is used, the activated partial thromboplastin time must be monitored and the heparin dose adjusted to ensure a therapeutic level of anticoagulation. Heparin is recommended for patients with renal impairment and for those at high risk of bleeding. The selective factor Xa inhibitor fondaparinux is a recently introduced alternative to heparin or LMWH for initial VTE treatment. Heparin, LMWH, or fondaparinux should be given for at least five to seven days. Vitamin K antagonists should be initiated on the first day, or as soon as possible, in patients who are candidates for an oral anticoagulant. An oral anticoagulant agent to be used without laboratory monitoring for both acute and long-term treatment of VTE remains an unsolved clinical need in the treatment of VTE.

Keywords
Venous thromboembolism, deep vein thrombosis, pulmonary embolism, heparin, low-molecular-weight heparin, anticoagulants

Introduction
Venous thromboembolism (VTE) is a common disease associated with substantial morbidity and mortality. The incidence of VTE, estimated in a Minnesota cohort followed from 1966 to 1990 was 117.0 per 100 000 person-years (1). A follow-up cohort study from the same area showed an almost identical incidence in 1991 to 1997, suggesting that the incidence is not changing over time (1).

Deep vein thrombosis and pulmonary embolism are two clinical manifestations of VTE. About 60% of patients with symptomatic proximal deep vein thrombosis have concomitant asymptomatic pulmonary embolism (2), whereas at least 40% of patients with symptomatic pulmonary embolism have associated asymptomatic deep vein thrombosis (3). The treatment of deep vein thrombosis or pulmonary embolism is identical in the majority of patients, although differences in short-term outcomes may justify targeted initial treatment in selected patients with deep vein thrombosis or pulmonary embolism.

We revised the literature on the treatment of venous thromboembolism by searching in Medline and Embase for the terms ‘venous thromboembolism’, ‘deep venous thrombosis’ and ‘pulmonary embolism’. For the purpose of this manuscript, we reviewed papers focusing on the initial treatment of venous thromboembolism.

Objectives of initial treatment of VTE
The clinical objectives of the initial treatment of VTE are to prevent fatal pulmonary embolism and recurrent VTE, with an acceptable rate of bleeding complications. Because recurrent pulmonary embolism is the main cause of death in patients with acute VTE, reduction in mortality can only be achieved by preventing recurrent VTE (4–6). Conceptually, reducing VTE recurrence depends on preventing thrombus extension and, if possible, promoting thrombus regression.

A number of studies evaluated thrombus regression to assess the efficacy of anticoagulants in the initial treatment of VTE. In patients with deep vein thrombosis, thrombus regression was assessed by repeated venography with quantitative assessment of thrombus-filled venous segments using Marder score (7). More recently, quantitative compression ultrasonography has been
used instead of venography to assess thrombus regression. In patients with pulmonary embolism, thrombus regression can be assessed based on improvement of pulmonary perfusion determined by Miller index at pulmonary angiography or by perfusion at lung scanning.

Using thrombus regression after initial VTE treatment as a surrogate efficacy end-point, several studies have examined its correlation with the risk of recurrent VTE (8–11). In one of these studies, 170 patients with symptomatic proximal deep vein thrombosis underwent repeated venography and perfusion lung scanning after 10 days of treatment with low-molecular-weight heparin (LMWH) or heparin (8). Symptomatic VTE occurred in 4%, 10% and 29% of patients with reduced, unchanged or increased thrombus burden, respectively (p < 0.005). In a larger study, venography repeated at day 21 showed thrombus regression in 40.2, 53.4 and 53.5% of patients randomized to intravenous heparin, twice-daily subcutaneous LMWH or once-daily subcutaneous LMWH, respectively (9). Consistently, the incidence of recurrent VTE was higher in patients randomized to heparin than in those given LMWH. The correlation between thrombus regression and recurrent VTE was evaluated in a meta-analysis of randomized trials comparing LMWH with heparin for initial treatment of patients with deep vein thrombosis (10). There was an inverse correlation between thrombus regression and recurrent VTE at two months. Consistently, a correlation has been found between thrombus regression and clinical events in patients with pulmonary embolism.

In conclusion, individual studies and a meta-analysis suggest a relationship between thrombus burden change and the risk of recurrent VTE. These findings support the concept that prevention of thrombus extension or enhancement of thrombus resolution should be goals of initial anticoagulant treatment of VTE.

Deep vein thrombosis and pulmonary embolism: the same disease, the same initial treatment? Mortality is four- to five-fold higher in patients hospitalized for pulmonary embolism than it is in those hospitalized for deep vein thrombosis (5–6). In the ICOPER registry, mortality was 11.4% at two weeks and 17.4% at three months in patients with pulmonary embolism, with 45% of deaths at two weeks due to
pulmonary embolism may benefit from thrombolytic treatment. In the other hand, patients with pulmonary embolism, normal blood pressure and no evidence of right ventricular overload can be managed as patients with deep vein thrombosis (Fig. 1).

**Heparin treatment in VTE**

A heparin derivative, either heparin or LMWH, in association with vitamin K antagonists, forms the basis of currently recommended initial treatment for the majority of patients with VTE (Table 1) (18). In a landmark trial in patients with acute pulmonary embolism, none of 54 patients randomized to receive heparin died, in contrast to five of 19 patients (26%) given placebo (19).

Provided there are no contraindications to anticoagulant therapy, heparin or LMWH should be given to patients with suspected VTE while awaiting definitive diagnostic testing (18). In patients with confirmed VTE, heparin or LMWH should be continued for at least five days while waiting for the therapeutic effect of concomitant vitamin K antagonists. Heparin or LMWH treatment should only be stopped when the international normalized ratio (INR) is $>2$ for at least two consecutive days. Vitamin K antagonists should always be overlapped with heparin or LMWH. A three-fold higher rate of recurrent VTE was observed in patients randomized to vitamin K antagonists alone as compared with those given both a vitamin K antagonist and heparin (20).

Heparin is usually given as a continuous intravenous infusion, but can be given subcutaneously. If it is given subcutaneously, higher doses of heparin are often needed to overcome its poor bioavailability after subcutaneous injection. Heparin produces an unpredictable anticoagulant response because of its non-specific binding to plasma proteins, the levels of which vary from patient to patient. Therefore, anticoagulation monitoring is mandatory to ensure that a therapeutic response is achieved (18). The activated partial thromboplastin time (aPTT) is the test most often used to monitor heparin although anti-factor Xa levels also can be used (21).

The importance of achieving adequate anticoagulation early in the course of VTE treatment is highlighted by the results of cumulated analyses of randomized trials evaluating various initial heparin regimens for treatment of proximal deep venous thrombosis (22–26). Logistic regression analysis showed that inadequate anticoagulation in the first 24 hours of treatment, as determined by a subtherapeutic activated partial thromboplastin time, was associated with a high rate of recurrent VTE (26). The rate of recurrent VTE was 23.3% in patients who failed to achieve an early adequate anticoagulation, whereas it was about 5% in those whose aPTT was therapeutic by 24 hours ($p=0.02$). The importance of a therapeutic aPTT as a predictor of recurrent VTE was not confirmed in a following analysis (23). In a recent randomized study, recurrent thromboembolism occurred in 7 (2.7%) of the 263 patients who achieved a therapeutic aPTT within 24 hours, as compared with eight (8.2%) of the 97 patients who did not achieve therapeutic levels within 24 hours ($p=0.02$) (24); and in 13 (4.1%) of the 317 patients who achieved the APTT therapeutic threshold within 48 hours, as compared with two (4.7%) of the 43 patients who did not achieve therapeutic levels within 48 hours ($p=0.86$).

### Table 1: Levels of evidence/grades of recommendation for heparin treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), according to recent recommendations of the American College of Chest Physicians (17).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Condition</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td>Treatment of objectively confirmed DVT and non-massive PE</td>
<td>IA</td>
</tr>
<tr>
<td></td>
<td>Treatment of suspected VTE</td>
<td>IC</td>
</tr>
<tr>
<td></td>
<td>Initial VTE treatment of at least 5 days</td>
<td>IC</td>
</tr>
<tr>
<td></td>
<td>Start oral anticoagulants on the first day</td>
<td>IA</td>
</tr>
<tr>
<td></td>
<td>Discontinuation when INR is stable $&gt;2$</td>
<td>IA</td>
</tr>
<tr>
<td></td>
<td>Therapeutic anti-Xa levels (0.3–0.7 UI/ml) for continuous infusion in VTE</td>
<td>IC+</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous administration in DVT</td>
<td>IA</td>
</tr>
<tr>
<td></td>
<td>Subcutaneous dosing in DVT</td>
<td>IC</td>
</tr>
<tr>
<td></td>
<td>VTE treatment in severe renal failure</td>
<td>2C</td>
</tr>
<tr>
<td><strong>LMWH</strong></td>
<td>In-patient treatment of DVT and non-massive PE</td>
<td>IA</td>
</tr>
<tr>
<td></td>
<td>Effectiveness for DVT outpatients</td>
<td>IC</td>
</tr>
<tr>
<td></td>
<td>No laboratory monitoring</td>
<td>IA</td>
</tr>
<tr>
<td></td>
<td>Non-massive PE</td>
<td>IA</td>
</tr>
</tbody>
</table>

DVT, deep vein thrombosis; PE, pulmonary embolism.

In contrast, in patients with deep vein thrombosis, the mortality rate was 2.5% per month in the first three months and 1.9% in the subsequent nine months after the index event (12).

Analysis of the early clinical course of patients treated for acute VTE showed a similar incidence of non fatal recurrent VTE in the first three months in patients with deep vein thrombosis or pulmonary embolism (13). However, fatal pulmonary embolism was more common in patients who presented with pulmonary embolism than it was in those whose index event was deep vein thrombosis. These findings were confirmed in a cohort study of patients with a first episode of deep vein thrombosis or pulmonary embolism (14). The 7- and 30-day survival rates were higher in patients with deep vein thrombosis than they were in those with pulmonary embolism.

The spectrum of clinical presentations and the range of outcomes are wider in patients with pulmonary embolism than they are in those with deep vein thrombosis. Massive pulmonary embolism associated with cardiogenic shock carries an in-hospital mortality rate of up to 30% (6). In contrast, pulmonary embolism patients who are hemodynamically stable and have no evidence of right ventricular dysfunction have in-hospital mortality rates similar to those of patients with deep vein thrombosis. Echocardiographic right ventricular dysfunction and increased levels of troponin and/or brain natriuretic peptide have been proposed as markers of high risk pulmonary embolism patients (15–17).

These data highlight the need for more aggressive management of patients with massive pulmonary embolism and raise the possibility that even patients with less massive pulmonary embolism may benefit from thrombolytic treatment. In the other hand, patients with pulmonary embolism, normal blood pressure and no evidence of right ventricular overload can be managed as patients with deep vein thrombosis (Fig. 1).
If heparin is given for initial VTE treatment, use of heparin nomograms is recommended to optimize treatment (27–28). These involve an initial intravenous heparin bolus of 80 U/kg or 5,000 U followed by a continuous intravenous infusion of 18 U/kg/hour or 30,000 U over 24 hours. The aPTT time should be measured three or six hours after the bolus and then three hours after each dose adjustment or daily if no adjustment is necessary. Weight-adjusted nomograms have advantages over fixed-dose nomograms.

A review of eight clinical studies compared the efficacy and safety of dose-adjusted intravenous or subcutaneous heparin for initial treatment of deep vein thrombosis (29). These studies suggest that dose-adjusted heparin given subcutaneously twice daily is as effective and safe as continuous intravenous heparin. An open, multicenter clinical trial, included 720 consecutive patients with acute symptomatic VTE, of which 119 patients (16.5%) with non critical pulmonary embolism (24). Patients were randomly assigned to treatment with subcutaneous heparin with dose adjusted by aPTT by means of a weight-based algorithm, or fixed-dose (adjusted to body weight) subcutaneous LMWH. Fifteen (4.2%) of the 360 patients assigned to heparin had recurrent thromboembolic events, as compared with 14 (3.9%) of the 360 patients assigned to LMWH. Four patients assigned to heparin (1.1%) and three patients assigned to LMWH (0.8%) had major bleeding. Overall mortality was 3.3% in each group.

The concept that subcutaneous heparin requires laboratory monitoring has been challenged by a recent randomized open-label study that showed that fixed weight-adjusted doses of subcutaneous heparin are effective for initial treatment of deep vein thrombosis (30). In this study, fixed dose of heparin (333 U/Kg followed by twice-daily doses of 250 U/Kg) were compared to fixed doses of LMWH. Overall, 708 patients presenting with acute deep vein thrombosis (81%) or pulmonary embolism (19%) were included in the study. Three-month recurrence of VTE occurred in 3.8% of patients given heparin and in 3.4% of patients given LMWH. Major bleeding occurred in the first 10 days of treatment in 1.1% and 1.4% of patients in the two treatment groups, respectively.

Vitamin K antagonists should be initiated as soon as possible. The efficacy and safety of this approach has been documented by two studies (31–32). If warfarin is used, starting doses of 5 or 7.5 mg are preferred over higher doses.

<p>| Table 2: LMWH versus heparin in initial VTE treatment: results of meta-analyses. |</p>
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Qualifying VTE</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
</tr>
<tr>
<td>Leizorovicz et al. 1994</td>
<td>DVT</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>Lensing et al. 1995</td>
<td>DVT</td>
<td>47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Leizorovicz et al. 1996</td>
<td>DVT</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.035</td>
</tr>
<tr>
<td>Siragusa et al. 1996</td>
<td>DVT</td>
<td>49%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Rocha et al. 2000</td>
<td>DVT</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Dolovich et al. 2000</td>
<td>DVT</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Quinlan et al. 2004</td>
<td>PE</td>
<td>+20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ns</td>
</tr>
</tbody>
</table>

* at the end of treatment. DVT, deep vein thrombosis; PE, pulmonary embolism; na, not available; ns, not significant.

<p>| Table 3: Randomized studies comparing LMWH with heparin including patients with pulmonary embolism (PE). *Symptomatic PE excluded. |</p>
<table>
<thead>
<tr>
<th>Study, year</th>
<th>Number of patients</th>
<th>Qualifying VTE</th>
<th>Symptomatic PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>European MS,1991</td>
<td>108</td>
<td>Symptomatic p-DVT</td>
<td>na</td>
</tr>
<tr>
<td>Hull et al.,1992</td>
<td>200</td>
<td>Symptomatic p-DVT</td>
<td>14%</td>
</tr>
<tr>
<td>Prandoni et al. 1992</td>
<td>91</td>
<td>Symptomatic p-DVT</td>
<td>0%</td>
</tr>
<tr>
<td>Thery et al. 1992</td>
<td>68</td>
<td>Symptomatic PE</td>
<td>100%</td>
</tr>
<tr>
<td>Kuier et al. 1995</td>
<td>67</td>
<td>Symptomatic PE</td>
<td>100%</td>
</tr>
<tr>
<td>Meyer et al. 1995</td>
<td>60</td>
<td>Symptomatic PE</td>
<td>100%</td>
</tr>
<tr>
<td>Columbus Trial 1997</td>
<td>271</td>
<td>Symptomatic VTE</td>
<td>27%</td>
</tr>
<tr>
<td>Simonneau et al. 1997</td>
<td>608</td>
<td>Symptomatic PE</td>
<td>100%</td>
</tr>
<tr>
<td>Campbell et al. 1998</td>
<td>16</td>
<td>Symptomatic PE</td>
<td>100%</td>
</tr>
<tr>
<td>Decousus et al. 1998</td>
<td>95</td>
<td>Symptomatic p-DVT</td>
<td>35%</td>
</tr>
<tr>
<td>Kirchmaier et al. 1998</td>
<td>80</td>
<td>Symptomatic DVT</td>
<td>na</td>
</tr>
<tr>
<td>Merli et al. 2001</td>
<td>287</td>
<td>Symptomatic DVT</td>
<td>30%</td>
</tr>
</tbody>
</table>

For personal or educational use only. No other uses without permission. All rights reserved. Downloaded from www.thrombosis-online.com on 2017-06-27 | IP: 54.191.40.80
Unfractionated heparin or LMWH for initial VTE treatment?

LMWH, which is produced by depolymerization of heparin, has improved pharmacokinetic properties compared with heparin (33). This allows subcutaneous LMWH administration in fixed doses without the need for coagulation monitoring.

Many studies have compared the efficacy and safety of unmonitored subcutaneous LMWH with those of heparin given by continuous intravenous infusion with monitoring. In the initial studies, patients underwent repeated venography to assess thrombus regression. A meta-analysis of these studies (10) showed greater reduction of thrombus extension with LMWH than with heparin (OR 0.51, 95% CI 0.32 to 0.83; p = 0.006).

While early clinical outcome-based trials reported lower rates of recurrent VTE and bleeding with LMWH than with heparin, more recent studies have shown comparable outcomes. Recent meta-analyses of randomized trials comparing LMWH with heparin for initial VTE treatment show a trend toward an advantage of LMWH (Table 2). Overall, LMWH and heparin appear to have similar efficacy and safety (34). However, LMWH is more convenient to administer. An intriguing finding is a reduction in mortality with LMWH that is confined to patients with cancer. The mechanism responsible for this reduction is unknown but ongoing trials are exploring potential anti-tumor effects of LMWH.

Although patients with symptomatic pulmonary embolism were excluded from initial trials with LMWH, the efficacy and safety of LMWH patients with pulmonary embolism has been investigated in more recent trials (Table 3). A meta-analysis of trials comparing LMWH with heparin for initial treatment of pulmonary embolism showed similar efficacy and safety with a non-significant trend for lower rates of recurrent VTE and major bleeding with LMWH (35).

A meta-analysis of individual patient data from three randomized controlled trials comparing the efficacy and safety of enoxaparin with those of heparin in patients with proximal deep vein thrombosis with or without symptomatic pulmonary embolism showed no difference in the rates of recurrent VTE in patients with or without symptomatic pulmonary embolism (36). A trend in favour of enoxaparin was shown for mortality and major bleeding. The in-hospital mortality of 1.2% observed in patients with pulmonary embolism suggests that most were low risk patients. Therefore, it is not clear whether the results can be translated to patients with more extensive pulmonary embolism. Patients with massive pulmonary embolism should not be given LMWH. LMWH should be used in patients without signs of right ventricular overload. LMWH should be considered cautiously in patients with normal blood pressure but signs of right ventricular overload.

Bleeding risk with heparin and LMWH

A cumulative analysis of clinical trials of VTE treatment showed that 46% of bleeding complications (13 of 28) occurred within the first week of anticoagulant treatment. The three-month incidence was reported to be 3% and 2% in patients with deep vein thrombosis and pulmonary embolism, respectively (37).

Bleeding complications with heparin are related to its dose and anticoagulant effect as determined by the aPTT (38). Continuous intravenous heparin infusion was associated with fewer bleeding complications than intermittent intravenous bolus administration (39). There appears to be no significant difference in bleeding rates between continuous intravenous heparin and subcutaneous heparin, but the numbers of patients treated are relatively small (28).

Once- versus twice-daily LMWH for VTE treatment

Five studies compared the efficacy and safety of once- versus twice-daily LMWH for initial treatment of deep vein thrombosis.

A systematic review of the five studies showed no difference in the rate of recurrent VTE in the two treatment regimens (OR 0.82, 0.49 to 1.39) (40). Rates of major bleeding and mortality were not statistically different between the two treatment regimens. Assessment of thrombus regression performed in two of these studies showed no difference between the once- and twice-daily administration. A subgroup analysis in cancer patients receiving one specific LMWH suggested superior efficacy of the twice-daily regimen (40).

Treatment for specific subgroups of VTE patients

Obese patients, pregnant women, and patients with severe renal insufficiency were excluded from the majority of the clinical trials evaluating LMWH for VTE treatment. The doses of LMWH used in clinical practice derive from estimates of volumes of distribution and plasma half-life, which is affected by renal function. Certain clinical conditions complicate estimates of distribution volume. For example, because the relationship between intravascular volume and body weight is not linear, to estimate the optimal dose of LMWH in obese patients is difficult. Likewise, changes in intravascular volume late in pregnancy also complicate LMWH dosing. Finally, because LMWH is cleared via the kidneys, its half-life is prolonged in patients with impaired renal function (41–42).

LMWH dosing in obese patients has been clarified by recent studies that showed a linear relationship between the LMWH dose based on body weight and plasma anti-Xa activity (43–45). No excessive bleeding was observed when LMWH was given in a weight-adjusted fashion to patients weighing up to 150 kg. However, few patients with a BMI over 50 were included. Therefore, LMWH dosing in morbidly obese patients remains problematic.

Heparin or LMWH are the anticoagulants of choice for VTE treatment during pregnancy. There is no consensus regarding the optimal dosing of LMWH in pregnancy (46). Although small studies suggest that only minimal dose adjustments are necessary during pregnancy, anti-factor Xa levels should be measured periodically to ensure that administered doses are therapeutic.

The use of LMWH should be considered with caution in patients whose creatinine is less than 30 ml/min; these patients should receive heparin (47–48). Anti-Xa levels should be moni-
tored if LMWH is given to patients with renal impairment. The dose should be reduced if there is drug accumulation to minimize the risk of bleeding.

Anti-Xa levels are usually measured in blood samples collected about four hours after the subcutaneous injection. A value between 0.6 to 1.0 UI/ml is considered therapeutic (49).

The prolongation of phospholipid-dependent assays commonly seen in patients with antiphospholipid-antibody syndrome may complicate monitoring anticoagulant treatment (50, 51). Whether a different therapeutic range of aPTT is needed for heparin treatment in patients with lupus anticoagulant is undefined. LMWH should be preferred in these patients. A practical treatment approach involves patient-specific screening for a reagent insensitive to lupus anticoagulant and determination of a reagent-specific therapeutic range in seconds that corresponds to heparin serum concentrations of 0.2–0.4 U/ml. Other monitoring methods, such as using the patient’s baseline activated partial thromboplastin time or using an antifactor Xa activity assay, may offer an alternative for heparin monitoring in patients with anti-phospholipid antibody syndrome (52).

A number of studies evaluated the optimal INR intensity for patients with lupus anticoagulants. A randomized study showed that an INR of 2.0 to 3.0 was as effective and safe as higher-intensity warfarin therapy (53). No difference was found in the incidence of recurrent thromboembolism between the two groups of patients.

Heparin induced thrombocytopenia (HIT) is a rare, but serious, antibody mediated complication of heparin treatment associated with a high risk for venous and arterial thromboembolic complications (54). Nearly 8% of heparin treated patients develop auto-antibodies while 1 to 5% of patients will progress to a clinically overt HIT.

The short duration of heparin treatment for the acute VTE treatment reduced the incidence of HIT. However, treatment of VTE in patients with a history of HIT is a real challenge. As LMWH may present cross-reactivity with antiplatelet antibodies, alternative treatment strategies have been evaluated (55). Hirudin has been approved for the treatment of VTE patients with HIT. Treatment starts with or without an intravenous bolus dose (0.4 mg/kg) followed by intravenous continuous infusion (initial 0.15 mg/kg/h) targeted to obtain 1.5–2.5 baseline aPTT. Danaparoid is also approved for VTE treatment in patients with HIT (initial bolus dose of 2,250 U; continuous intravenous infusion of 400 U/h for 4 h, then 300 U/h for 4 h, then 200 U/h, adjusted by anti-Xa levels).

### Fondaparinux for initial VTE treatment

Fondaparinux is a synthetic analogue of the pentasaccharide sequence of heparin that, after binding to antithrombin, catalyzes factor Xa inhibition (56). Fondaparinux has no direct effect on thrombin as thrombin inhibition requires a chain of at least 18 saccharides. After binding with fondaparinux, antithrombin dissociates from the complex antithrombin/factor Xa and is free to bind other molecules of antithrombin while antithrombin remains permanently bound to factor Xa. Fondaparinux has 100% bioavailability after subcutaneous injection. The half-life of fondaparinux (about 15–20 hours) allows a once-a-day administration either for prophylaxis or treatment of venous thromboembolism. Therefore, it is given subcutaneously once daily. The drug is excreted unchanged in urine. Efficacy and safety of fondaparinux have been shown in several phase II and phase III clinical trials for the prophylaxis and treatment of venous thromboembolism and for the acute treatment of unstable angina. Fondaparinux is approved in Europe and the United States for the initial treatment of acute VTE, including both deep vein thrombosis and pulmonary embolism. Fondaparinux was compared with LMWH for initial treatment of symptomatic deep vein thrombosis and with heparin for initial treatment of pulmonary embolism (57, 58).

In two phase III studies, both designed for non-inferiority analysis, 2,205 patients with deep vein thrombosis and 2,213 patients with pulmonary embolism were randomized to receive fondaparinux at fixed doses (5.0, 7.5, or 10.0 mg in patients weighing less than 50, 50 to 100, or more than 100 kg, respectively), or standard anticoagulant treatment (58, 59).

Patients with objectively confirmed deep vein thrombosis included in the first study were randomly assigned to fondaparinux or to LMWH (given subcutaneously twice daily) for at least five days. Recurrent VTE occurred in 43 (3.9%) patients given fondaparinux compared with 45 (4.1%) patients given enoxaparin (95% CI 1.8 – 1.5). Rates of major bleeding were similar in the two groups (1.1 and 1.2%, respectively). Mortality rates were 3.8% and 3.0% in patients given fondaparinux and LMWH, respectively (Table 4).

### Table 4: Fondaparinux vs. LMWH or heparin in initial VTE treatment: results of clinical trials.

*At the end of treatment.

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Qualifying VTE</th>
<th>Comparator</th>
<th>Study phase</th>
<th>Primary end-point</th>
<th>Patients</th>
<th>Mortality</th>
<th>Recurrent VTE</th>
<th>Major bleeding</th>
<th>Thrombus regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rembrandt, 2000</td>
<td>DVT</td>
<td>Dalteparin</td>
<td>Phase II, DB</td>
<td>Thrombus regression</td>
<td>438</td>
<td>0.41</td>
<td>0.52</td>
<td>−1.14</td>
<td>0.10 (−0.24–0.47)</td>
</tr>
<tr>
<td>Matisse DVT, 2004</td>
<td>DVT</td>
<td>Enoxaparin</td>
<td>Phase III, DB</td>
<td>Symptomatic VTE</td>
<td>2205</td>
<td>−0.25</td>
<td>0.04</td>
<td>0.07</td>
<td>0.07 (−0.73–0.88)</td>
</tr>
<tr>
<td>Matisse PE, 2003</td>
<td>PE</td>
<td>Heparin</td>
<td>Phase III, Open</td>
<td>Symptomatic VTE</td>
<td>2213</td>
<td>−0.19</td>
<td>0.24</td>
<td>−0.17</td>
<td>Na</td>
</tr>
</tbody>
</table>

Relative risk reduction at 3 months (95% Confidence interval)

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Recurrent VTE</th>
<th>Major bleeding</th>
<th>Thrombus regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>−0.37–0.44</td>
<td>0.04</td>
<td>0.07</td>
<td>(−0.73–0.88)</td>
</tr>
<tr>
<td>−0.77–0.26</td>
<td>0.04</td>
<td>0.07</td>
<td>(−0.73–0.88)</td>
</tr>
<tr>
<td>−0.61–0.22</td>
<td>0.24</td>
<td>−0.17</td>
<td>(−1.02–0.70%)</td>
</tr>
</tbody>
</table>

DVT: Deep Vein Thrombosis.
Patients with objectively confirmed pulmonary embolism included in the second study were randomly assigned to fondaparinux or heparin (given intravenously, target aPTT ratio 1.5–2.5). Recurrent VTE occurred in 42 (3.8%) patients receiving fondaparinux, as compared with 56 (5.0%) of the patients receiving unfractionated heparin, (95% CI 3.0 – 0.5). Major bleeding and mortality were similar in the two groups. Overall, 2,201 patients received fondaparinux as acute treatment of VTE. No statistically significant difference in efficacy or safety was observed with fondaparinux as compared to standard anticoagulant treatment. No difference was observed regarding time to achieve a therapeutic INR in patients given fondaparinux or standard anticoagulant treatment.

Fondaparinux is more convenient to administer than heparin. Its only advantage over LMWH, is a lower risk of heparin induced thrombocytopenia.

Outpatient VTE treatment

Out-of-hospital treatment of VTE is feasible for most patients. This approach reduces health care costs and improves patient satisfaction.

Several studies have compared out-of-hospital LMWH with in hospital treatment with heparin. In the first study, 400 patients with acute deep vein thrombosis were randomized to in-hospital treatment with unfractionated heparin or to outpatient treatment with LMWH (60). Rates of recurrent VTE with heparin and LMWH were 8.6% and 6.9%, respectively (95% CI 3.6–6.9), and bleedings were observed in 2.0 and 0.5% of the patients, respectively. These findings suggest that home-treatment of deep vein thrombosis with LMWH is feasible, effective and safe. These data were confirmed in a large additional randomized studies with a similar experimental design (61).

Recent surveys indicate that about 80% of patients presenting to the emergency room for deep vein thrombosis are suitable for home treatment. However, concerns remain that a simplified home treatment of VTE could be translated in a trivial management of a disease with important clinical implications. Thus, patient selection and risk stratification criteria for patients considered for home therapy deserve careful consideration. A number of factors can influence the choice for home or in-hospital treatment as co-morbidity, bleeding risk, home care, concomitant symptomatic pulmonary embolism. Hospital admission and early discharge may be an alternative strategy in medium or high risk patients. Home treatment seems a promising opportunity also in cancer patients.

Patients with symptoms of pulmonary embolism were excluded from most of the studies on home treatment of VTE. Data on patients with pulmonary embolism managed at home have been published (62). However, there is no consensus regarding the home treatment of patients with symptomatic pulmonary embolism. It is conceivable that this procedure should be reserved to very selected patients with pulmonary embolism and no signs of right heart overload.

Thrombolysis and vena cava filter for the initial treatment of VTE

The role of thrombolysis in patients with massive pulmonary embolism is clinically sound while its value in patients with normal blood pressure and right ventricular dysfunction remain to be defined. Thrombolysis has a reduced role, if any, in the treatment of deep vein thrombosis and should be however reserved to individual cases.

The insertion of a vena cava filter should be considered for patients with confirmed VTE and absolute contraindications to anticoagulant treatment or for patients experiencing recurrences of VTE despite adequate anticoagulation (18). In a randomized controlled trial, patients with deep vein thrombosis were randomized in a two-by-two factorial design to the insertion of a vena cava filter and to receive unfractioned heparin or LMWH (63). This study showed that vena cava filter is effective in reducing pulmonary embolism, although no reduction in mortality was achieved by vena cava filter insertion. Moreover, a higher rate of extension of venous thrombosis was observed in patients randomized to vena cava filter insertion. Thus, heparin treatment is recommended as soon as possible after the procedure to avoid thrombotic filter occlusion (14).

New anticoagulant agents

Several new anticoagulant agents with a potential role in the treatment of venous thromboembolism are currently in different phases of clinical development. Based on the mechanism of action, these new agents can be distinguished in factor Xa inhibitors and thrombin inhibitors. These new agents are given orally once or twice daily, except for idraparinux that is given subcutaneously. All these new agents can be administered at fixed doses without laboratory monitoring.

Ximelagatran is an oral direct thrombin inhibitor (64). The optimal dose of ximelagatran to be used for treatment of venous thromboembolism was firstly assessed in a phase II randomized, dose-ranging study (65). In this study ximelagatran (doses ranging from 24 to 60 mg twice daily) was compared with subcutaneous dalteparin followed by warfarin. Similar rates of thrombus regression and clinically overt recurrence were observed in the two treatment groups. Ximelagatran (36 mg twice daily) was compared with enoxaparin (1 mg/kg twice daily) followed by warfarin (target INR between 2.0 to 3.0) in a randomized, double blind study in 2,498 patients with deep venous thrombosis with or without pulmonary embolism (66). The incidence of objectively confirmed recurrent venous thromboembolism during the three months following the index event was similar in the two treatment groups (2.1% and 2.0% in patients receiving ximelagatran or enoxaparin/warfarin, respectively). No difference was observed concerning major bleedings (1.3% and 2.2%, respectively, in patients receiving ximelagatran or enoxaparin followed by warfarin) and mortality (2.3% and 3.4%, respectively, in patients receiving ximelagatran and enoxaparin followed by warfarin).

The clinical development of ximelagatran has been recently interrupted due to a 6–10% incidence of increased levels of liver
enzymes and in particular of alanine aminotransferase. The increase occurred between three weeks and four months after starting treatment, either for treatment of venous thromboembolism or for prevention of thromboembolic complications in atrial fibrillation.

Idraparinux is a pentasaccharide derivative of fondaparinux that, due to a prolonged half-life (130 hours) can be administered once a week. Idraparinux was evaluated for the treatment of proximal deep vein thrombosis in a randomized trial in 659 patients (67). All patients received enoxaparin for 5–7 days in the acute phase and then were randomized to weight-adjusted idraparinux (2.5 mg, 5 mg, 7.5 mg or 10 mg once a week) or INR-adjusted warfarin. Patients receiving idraparinux or warfarin had a similar incidence of changes in compression ultrasound and perfusion lung scan. Bleeding complications were significantly lower in patients receiving idraparinux 2.5 mg in comparison to warfarin. Two fatal bleeding complications occurred in patients receiving idraparinux at the dose of 5.0 mg. Two large clinical trials on the efficacy and safety of idraparinux 2.5 mg given subcutaneously once a week are currently ongoing in patients with deep venous thrombosis or pulmonary embolism, respectively.

Several oral anti-Xa inhibitors and the oral thrombin inhibitor dabigatran are under evaluation in the treatment of venous thromboembolism. The real advantage of these agents over warfarin is the potential use at fixed daily doses without laboratory monitoring.

Unmet clinical needs

An anticoagulant agent with improved ease of use, but with at least the same efficacy and safety of LMWH and vitamin K antagonists, is currently needed. Rapid acting oral anticoagulants could replace parenteral agents for initial VTE treatment. A number of new oral anticoagulants are currently under clinical development as agents that do not require laboratory monitoring. An improvement in terms of efficacy is currently needed in the treatment of severe pulmonary embolism. In these patients, treatment could be optimized by thrombotic agents with improved safety profile.

Acknowledgements

This manuscript has been developed as part of the Thrombosis Quorum initiative, under the direction of the Thrombosis Quorum Steering Group [G. Agnelli (Chairman), P. Bath, J. Emmerich, B. Gersh, M. Ogren, S. Schulman, and J. Weitz]. Thrombosis Quorum is supported by an unrestricted educational grant from AstraZeneca.

References

29. Hommes DW, Bura A, Mazzolai L, et al. Subcutaneous heparin compared with continuous intravenous