Subcutaneous Adjusted-Dose Unfractionated Heparin vs Fixed-Dose Low-Molecular-Weight Heparin in the Initial Treatment of Venous Thromboembolism

Writing Committee for the Galilei Investigators*

Background: Few reports have addressed the value of unfractionated heparin (UFH) or low-molecular-weight heparin in treating the full spectrum of patients with venous thromboembolism (VTE), including recurrent VTE and pulmonary embolism.

Methods: In an open, multicenter clinical trial, 720 consecutive patients with acute symptomatic VTE, including 119 noncritically ill patients (16.5%) with pulmonary embolism and 102 (14.2%) with recurrent VTE, were randomly assigned to treatment with subcutaneous UFH with dose adjusted by activated partial thromboplastin time by means of a weight-based algorithm (preceded by an intravenous loading dose), or fixed-dose (adjusted only to body weight) subcutaneous nadroparin calcium. Oral anticoagulant therapy was started concomitantly and continued for at least 3 months. We recorded the incidence of major bleeding during the initial heparin treatment and that of recurrent VTE and death during 3 months of follow-up.

Results: Fifteen (4.2%) of the 360 patients assigned to UFH had recurrent thromboembolic events, as compared with 14 (3.9%) of the 360 patients assigned to nadroparin (absolute difference between rates, 0.3%; 95% confidence interval, −2.5% to 3.1%). Four patients assigned to UFH (1.1%) and 3 patients assigned to nadroparin (0.8%) had episodes of major bleeding (absolute difference between rates, 0.3%; 95% confidence interval, −1.2% to 1.7%). Overall mortality was 3.3% in each group.

Conclusions: Subcutaneous UFH with dose adjusted by activated partial thromboplastin time by means of a weight-based algorithm is as effective and safe as fixed-dose nadroparin for the initial treatment of patients with VTE, including those with pulmonary embolism and recurrent VTE.

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Since the demonstration that heparin is necessary for the initial treatment of venous thromboembolic (VTE) disorders,1,2 numerous prospective randomized clinical trials have convincingly shown that fixed-dose low-molecular-weight heparins (LMWHs) are at least as effective and safe as adjusted-dose unfractionated heparin (UFH) for the treatment of symptomatic VTE.3,4 Most of these studies were confined to patients with symptomatic proximal deep venous thrombosis (DVT) of the lower extremities, largely at their first episode of DVT. Few reports have compared the efficacy and safety of these agents in treating the full spectrum of patients with VTE, including calf vein thrombosis, recurrent VTE, and pulmonary embolism (PE).5,6

In all of the above-mentioned studies but one,7 UFH was administered intravenously with the use of a loading dose followed by the continuous infusion of doses capable of prolonging the activated partial thromboplastin time (APTT) within the targeted therapeutic range, either empirically or according to appropriate nomograms.8 Recently, Prandoni et al9 showed that the use of a weight-based algorithm allows the rapid achievement of correct anticoagulation in most patients treated with subcutaneous UFH after an initial intravenous loading dose. As this strategy enables the early mobilization and discharge of suitable patients with DVT, the subcutaneous administration of UFH might still represent a valuable tool for the initial treatment of thromboembolic disorders.

We performed an open, multicenter clinical trial in 720 consecutive patients with acute symptomatic VTE, of whom 119 (16.5%) had PE and 102 (14.2%) had recurrent VTE. They were randomly assigned to treatment with subcutaneous UFH with dose adjusted by APTT by means of a weight-based algorithm (pre-
cended by an intravenous loading dose), or to fixed-dose (adjusted only to body weight) subcutaneous LMWH (nadroparin calcium). Oral anticoagulant therapy with a coumarin derivative was started concomitantly and continued for at least 3 months. We recorded the incidence of major bleeding during the initial heparin treatment and that of recurrent VTE and death during 3 months of follow-up, with blinded validation of outcome events by a central adjudication committee.

### METHODS

#### STUDY PATIENTS

All consecutive inpatients and outpatients referred to 19 Italian participating centers from October 1, 1998, to April 30, 2001, with the clinical suspicion of an acute (less than 3 weeks old) DVT of the lower extremities and/or PE were eligible for the study, provided that the suspicion was objectively confirmed. A positive result of at least 1 of the following tests was accepted for APTT greater than 120 seconds.

<table>
<thead>
<tr>
<th>APTT, s</th>
<th>Heparin Regimen</th>
<th>Next APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤120</td>
<td>Fixd 0.35-0.70</td>
<td>After 6 h</td>
</tr>
<tr>
<td>&lt;50</td>
<td>One step† up</td>
<td>After 6 h</td>
</tr>
<tr>
<td>50-90</td>
<td>Same step</td>
<td>After 6 h</td>
</tr>
<tr>
<td>&gt;91-120</td>
<td>One step down</td>
<td>After 6 h</td>
</tr>
<tr>
<td>&gt;120</td>
<td>Withhold hep.</td>
<td>After 3 h †</td>
</tr>
</tbody>
</table>

Abbreviations: APTT, activated partial thromboplastin time; IV, intravenous; SC, subcutaneous.

*Doses: weight less than 50 kg, 4000 U IV + 12500 U SC; 50-70 kg, 5000 U IV + 15000 U SC; more than 70 kg, 6000 U IV + 17500 U SC.
†Steps: 10000, 12500, 15000, 17500, 20250, 25000, and 30000 U. ‡Repeat APTT until a value less than 120 seconds is obtained, then adjust hep. dosage according to the schedule given for APTT greater than 120 seconds.

All patients meeting the inclusion criteria were enrolled in the study provided they gave written informed consent. The study was approved by the ethical board of all participating centers.

### TREATMENT REGIMENS

Randomization to UFH or LMWH treatment (stratified according to whether the patients presented with DVT only or with PE, and also stratified according to clinical center) was performed with a computer algorithm and the use of a 24-hour telephone service that recorded patient information before disclosure of the treatment assigned.

Patients randomized to UFH were administered an intravenous bolus of heparin sodium (Roche, Basel, Switzerland) and a subcutaneous injection of heparin calcium (Genentium SpA, Como, Italy) in doses adjusted to body weight (4000 U intravenously plus 12500 U subcutaneously in patients weighing less than 50 kg; 5000 U plus 15000 U, respectively, in those weighing 50 to 70 kg; and 6000 U plus 17500 U, respectively, in patients weighing more than 70 kg). The first APTT was measured after 6 hours, and subsequent dose adjustments during the first 48 hours were scheduled twice daily according to the algorithm shown in Table 1, with the APTT performed in the midinterval. They were arranged in “steps” to be taken up or down according to APTT values, irrespective of body weight. The targeted APTT range (50-90 seconds) was calibrated to correspond to a plasma heparin level, as expressed by aXa activity, of 0.35 to 0.70 U/mL. After the first 48 hours, UFH administration was managed on the basis of daily APTT determinations.

Patients randomized to LMWH received subcutaneous administration of nadroparin, 85 U/kg twice daily.

Oral anticoagulant treatment with warfarin sodium was started within the first 2 days and continued for a total of 12 weeks. During initial combined heparin and warfarin treatment, in both patient groups, prothrombin time was measured at least every other day, with the dose adjusted to achieve an international normalized ratio (INR) of 2.0 to 3.0, by adopting an identical approach. Heparin was discontinued when the INR was greater than 2.0 for 2 consecutive days and the patient had received the study drug for at least 5 days.

### SURVEILLANCE AND FOLLOW-UP

During the initial treatment with the study drugs, patients were examined daily for signs and symptoms of recurrent thromboembolism, bleeding, or the occurrence of heparin-induced thrombocytopenia.

Follow-up visits were scheduled after 1 and 3 months. Patients were asked to return to the study center if clinical manifestations of recurrent thromboembolism occurred. Information on all suspected outcome events and deaths was reviewed and classified by a central adjudication committee blinded to treatment assignment.

### CLINICAL OUTCOME ASSESSMENT

We evaluated the rate of recurrent thromboembolism and mortality during heparin treatment and follow-up, as well as the rate of major bleeding occurring during the period of heparin treatment and the subsequent 48 hours.

Recurrent DVT was diagnosed as follows: a new intraluminal filling defect on a venogram that was seen on at least 2 projections; abnormal results of compression ultrasound in an area where compression had been normal, or a substantial increase in the diameter of the thrombus during full compression at the popliteal or femoral vein; or a new defect in the calf vein system on color Doppler testing. Recurrent PE was diag-
nosed as follows: a new intraluminal filling defect on pulmo-
nary angiography or computed tomographic scan; a new de-
fect of at least 75% of a segment on the perfusion scan, with
normal ventilation; or autopsy demonstration.

Bleeding was defined as major if it was clinically overt and
associated with a fall in the hemoglobin level of at least 2 g/dL;
or a need for transfusion of 2 or more units of red blood cells;
if it was intracranial or retroperitoneal; or if it warranted the
permanent discontinuation of treatment. Heparin-induced
thrombocytopenia was defined as a platelet drop below
100 × 103/µL and/or a fall greater than 50% below baseline.

Deaths were classified as due to PE, bleeding, another iden-
tifiable cause, or unexplained. Autopsy was intended for all pa-
tients who died and in whom PE could not be excluded.

STUDY OUTCOMES AND ANALYSIS

The main aim of the study was to compare the efficacy of the 2
treatment strategies by assessing the incidence of symptomatic
recurrent VTE during the 3-month study period. The sec-
ondary analysis dealt with the incidence of major bleeding dur-
ing the initial LMWH treatment and additional 48 hours. Both
analyses were performed on an intention-to-treat basis and in-
cluded all patients who were randomly assigned to either strat-
egy. Results were reported as a difference in incidence be-
tween treatment groups and the 95% confidence interval.

On the basis of previous observations, the incidence of re-
current VTE during the 3-month period of follow-up was
assumed to be 4% to 5% in the LMWH group.34 To exclude a
ture increase of 3.3% or more in the incidence of recurrent VTE
among the UFH-treated patients, we calculated a sample size
of approximately 350 patients per group, allowing for a type I
error of 0.05 (1 sided) and a type II error of 0.20. For the com-
parison between treatment groups and within the 95% confidence interval.

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated
heparin.

The mean ± SD heparin dose administered during the
first and the second days in patients allocated to the UFH
group was 36 500 ± 5300 U and 30 500 ± 10 800 U, respec-
tively. The proportion of patients who reached the therapeu-
tic APTT threshold (≥50 seconds) was 73.1% (263/
360) and 88.1% (317/360) after 24 and 48 hours,
respectively. During the course of initial UFH treatment,
only 23 patients (6.4%) required no dosing changes, while
the remaining 337 required at least 1 change (1 change in
35 patients, 2 changes in 58, and more than 2 dosing changes in the remaining 244). On average, 3 dosing changes were needed to monitor heparin in patients allo-
cated to the UFH group.

Compliance with treatment and with the study pro-
tocol was high, and no patients were lost to follow-up.
The quality of oral anticoagulant treatment was similar
in both groups; an INR within or above the targeted therapeu-
tic range (INR, 2.0-3.0) in more than 70% of determina-
tions.

RESULTS

STUDY PATIENTS

Between October 1998 and April 2001, 845 patients were
referred to the study centers with an episode of clinically
symptomatic VTE. Of these patients, 112 were excluded for
the following reasons: full-dose anticoagulants for more than
24 hours (36 patients); geographic inaccessibility for follow-
up (18 patients); contraindications to anticoagulant treat-
ment (16 patients); previous (within 1 year) episode of VTE
(14 patients); life expectancy less than 3 months (13 pa-
tients); poor compliance (6 patients); hemodynamic insta-
bility (5 patients); pregnancy (3 patients); and age less than
18 years (1 patient). Of the remaining 733 patients, 720 gave
informed consent and were randomly assigned to receive
UFH or LMWH (360 patients in each group). The baseline
characteristics of the patients in the 2 treatment groups were
similar (Table 2).

INITIAL TREATMENT AND FOLLOW-UP

The median duration of heparin treatment was 6.5
days in each group (range, 3–12 days). All patients
completed their initial treatment while remaining in the
hospital.

Table 2. Baseline Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>UFH (n = 360)</th>
<th>LMWH (n = 360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>65.7 ± 15.6</td>
<td>67.0 ± 14.8</td>
</tr>
<tr>
<td>Sex, No. M/F</td>
<td>158/202</td>
<td>167/193</td>
</tr>
<tr>
<td>Risk factors for thrombosis, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous thromboembolism (&gt;1 y)</td>
<td>54 (15.0)</td>
<td>48 (13.3)</td>
</tr>
<tr>
<td>Cancer</td>
<td>80 (22.2)</td>
<td>76 (21.1)</td>
</tr>
<tr>
<td>Recent trauma/fracture</td>
<td>61 (16.9)</td>
<td>63 (17.5)</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>56 (15.6)</td>
<td>46 (12.8)</td>
</tr>
<tr>
<td>Prolonged immobilization</td>
<td>55 (15.3)</td>
<td>61 (16.9)</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td>23 (6.4)</td>
<td>12 (3.3)</td>
</tr>
<tr>
<td>Known thrombophilia</td>
<td>30 (8.3)</td>
<td>23 (6.4)</td>
</tr>
<tr>
<td>Diagnosis at presentation, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep venous thrombosis only</td>
<td>301 (83.6)</td>
<td>300 (83.3)</td>
</tr>
<tr>
<td>Proximal ± distal</td>
<td>234</td>
<td>235</td>
</tr>
<tr>
<td>Isolated distal</td>
<td>67</td>
<td>65</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>59 (16.4)</td>
<td>60 (16.7)</td>
</tr>
<tr>
<td>Associated with deep-vein thrombosis</td>
<td>16</td>
<td>17</td>
</tr>
</tbody>
</table>

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated
heparin.
5 episodes occurred in the initial 2 weeks, 4 in the following month, and 6 in the remaining 6 weeks; the corresponding figures in the LMWH recipients were 4, 5, and 5, respectively.

Among the 119 patients with PE, 3 had symptomatic recurrent VTE (1 in the group of 59 patients allocated to UFH and 2 in the group of 60 LMWH recipients).

**BLEEDING COMPLICATIONS**

Among the 360 patients treated with UFH, 4 (1.1%) developed a major bleeding complication during the initial treatment, which was fatal in 1. A major bleeding event was also recorded in 3 (0.8%) of the 360 patients treated with LMWH (absolute difference between rates, 0.3%; 95% confidence interval, −1.2% to 1.7%) (Table 3).

During the subsequent period, 5 additional patients developed major bleeding while receiving warfarin (fatal in 1 patient); 1 was in the UFH group, and the remaining 4 were initially allocated to LMWH.

**Mortality**

During the 12 weeks of follow-up, 24 patients died, 12 (3.3%) in each group. Among the 12 deaths of patients treated with UFH, 3 were classified as due to PE and 1 to major bleeding; the respective figures in the LMWH group were 4 and none.

**ADDITIONAL OBSERVATIONS**

Overall, recurrent thromboembolism was more frequent among patients with proximal than isolated calf DVT (25/469 [5.3%] vs 1/132 [0.8%; *P* = .02], and among patients with cancer than those free of malignancy (11/156 [7.1%] vs 17/564 [3.0%; *P* = .03), whereas the rate of recurrent events did not differ between patients with a history of previous thromboembolism and those with a first episode of thrombosis (5/102 [4.9%] vs 24/618 [3.9%; *P* = .63]. Subgroup analysis failed to display differences between UFH and LMWH recipients in this regard.

Among patients allocated to UFH, recurrent thromboembolism occurred in 7 (2.7%) of the 263 patients who reached the APTT therapeutic threshold within 24 hours, as compared with 8 (8.2%) of the 97 patients who did not (*P* = .02); and in 13 (4.1%) of the 317 patients who reached the APTT therapeutic threshold within 48 hours, as compared with 2 (4.7%) of the 43 patients who did not (*P* = .86).

During the study period, immune heparin-induced thrombocytopenia was observed in 1 patient in each group. Two patients per group developed a malignancy that was not apparent at the time of inclusion into the current investigation.

**COMMENT**

Despite the increasing availability of LMWHs, UFH still represents a widely used antithrombotic drug for the initial management of venous thromboembolic disorders, especially in the United States. In clinical practice, UFH is commonly administered intravenously, either empirically or with the use of nomograms, which allows the prompt achievement of adequate levels of anticoagulation in most patients. However, the continuous intravenous administration requires costly facilities, makes early mobilization and discharge of patients with venous thrombosis problematic, and generally is not well tolerated by either patients or hospital staff. The subcutaneous administration of adjusted-dose UFH has the potential to shorten the duration of patients' hospitalization as compared with the intravenous route. The equivalence between the 2 drugs was seen in all categories of enrolled patients, including those with noncritical PE and recurrent VTE. The distribution of recurrent thromboembolic events during the study period was similar, as was the mode of presentation of recurrent events and the case-fatality rate. The rate of major bleeding during the initial treatment and subsequent 48 hours was similarly low, as was the mortality due to reasons other than recurrent thromboembolism and bleeding. Our results are consistent with those obtained in a study of similar characteristics where patients treated with UFH received intravenous administration of heparin, and suggest that whenever UFH is considered for the initial treatment of VTE disorders, subcutaneous heparin is an attractive alternative.

Bentley et al randomized 100 patients with calf vein thrombosis, as shown by phlebography, to receive either subcutaneous or intravenous heparin for 7 days, and noted a 48% rate of thrombus resolution in the subcutaneous group compared with 18% in the intravenous group, suggesting an effect of heparin that was related to the route of administration. A meta-analysis of 8 trials comparing

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**Table 3. Primary Study Results**

<table>
<thead>
<tr>
<th></th>
<th>UFH (n = 360)</th>
<th>LMWH (n = 360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent thromboembolism*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral thrombosis</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Contralateral thrombosis</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>15 (4.2)</strong></td>
<td><strong>14 (3.9)</strong></td>
</tr>
<tr>
<td>Major bleeding†</td>
<td>4 (1.1)</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>

*During the initial treatment and follow-up. †During the initial treatment.

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.
subcutaneous with intravenous administration in patients with DVT concluded that both thrombus propagation and symptomatic recurrences were less likely in patients receiving subcutaneous therapy. In addition, in the only available comparative study between subcutaneous adjusted-dose UFH and fixed-dose LMWH in patients with DVT, the 2 strategies were associated with a similar reduction of the thrombotic burden, as shown by repeated phlebography, which contrasts with the distinct advantage of LMWH over intravenous UFH consistently shown in all comparative studies between the 2 strategies. According to the results of recent investigations, continuous intravenous heparin might deplete stores of intravascular tissue factor pathway inhibitor and reduce levels of the natural anticoagulant antithrombin III to a greater extent than subcutaneous UFH.

Prescribing an intravenous loading dose was chosen because of the poor bioavailability of subcutaneous heparin, and weight-adjusted heparin doses were used because body weight is the single best predictor of individual heparin requirements. Owing to the use of APTT-adjusted doses according to a weight-based algorithm, an adequate level of anticoagulation was reached within 24 hours in 73% of patients and within 48 hours in 88%. Not surprisingly, these rates were slightly lower than those (87% and 99%, respectively) observed in the primary clinical study performed a few years ago with the aim of identifying and validating this algorithm. Mitigation of benefit is likely to occur whenever guidelines are moved from the realm of efficacy research into clinical practice. Nevertheless, the weight-based algorithm was well accepted by all clinicians participating in this trial, leading to a more aggressive heparin dosage than that used in the single institutions, and most likely accounts for the favorable outcome achieved by UFH in this clinical trial.

Whether the adequacy of anticoagulation, as expressed by an APTT level above the lower limit of the therapeutic range within the first 24 to 48 hours, is an important component of the success of UFH therapy is controversial. In the present investigation, failure to promptly achieve a therapeutic APTT level in patients treated with UFH was associated with a statistically significant and clinically important increase in the risk of subsequent recurrent thromboembolism. The rate of recurrence was indeed 3 times lower in patients who did achieve the therapeutic APTT threshold within the first 24 hours of therapy than in those who did not. The results of our study are fully consistent with those obtained by Hull and coworkers and suggest that, irrespective of administration route, prompt achievement of therapeutic APTT level considerably improves the long-term clinical outcome of patients treated with UFH.

Despite the large number of patients treated with both heparin compounds, immune thrombocytopenia was observed in only 1 patient in each group during the study period. As the duration of initial heparin treatment is the main determinant of this threatening complication that especially affects patients treated with UFH, we think that the low rate of heparin-induced thrombocytopenia throughout the whole study period is likely to be explained by the early overlap with coumarin derivatives adopted in the present investigation and the consequent short duration of heparin treatment (on average, 6.5 days).

In keeping with findings from other investigations, irrespective of the study arm, recurrent thromboembolism was considerably more frequent among patients with proximal than isolated calf DVT. Furthermore, patients with cancer exhibited a significantly higher risk of recurrent events than did cancer-free patients. This observation is fully consistent with that reported by others and suggests that anticoagulant therapy needs further improvement in cancer patients with thrombosis.

A few methodologic aspects deserve proper comment. Because of the need for laboratory monitoring of patients treated with UFH, no attempt was made to blind the treatment. Since this was an open trial, care was taken to minimize the potential for bias. We included consecutive patients, used central randomization by telephone, and ensured that follow-up was complete for all randomized patients. Furthermore, all clinically suspected outcome events were assessed by an independent, blinded central adjudication committee on the basis of predetermined criteria. Because the rate of eligible patients who were actually excluded from the current investigation was negligible, our results are likely to be applicable to the vast majority of patients with VTE.

We conclude that treatment with subcutaneous UFH with doses adjusted by APTT by means of a weight-based algorithm is as effective and safe as fixed-dose (adjusted only for body weight) nadroparin for the initial treatment of patients with VTE, including those with PE and recurrent VTE. The use of LMWHs for VTE treatment has clear advantages over UFH, as they do not require laboratory monitoring, are associated with a lower incidence of immune thrombocytopenia, and make home treatment of selected patients feasible. If for any reason (such as mode of clinical presentation, drug availability, anticipated prolonged hospitalization for comorbidities other than VTE, or patient’s choice) UFH is deemed to be the proper choice, the subcutaneous administration of this drug is an attractive option.

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