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Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism

The Matisse Investigators*

ABSTRACT

BACKGROUND
The standard initial treatment of hemodynamically stable patients with pulmonary embolism is intravenous unfractionated heparin, requiring laboratory monitoring and hospitalization.

METHODS
We conducted a randomized, open-label trial involving 2213 patients with acute symptomatic pulmonary embolism to compare the efficacy and safety of the synthetic antithrombotic agent fondaparinux with those of unfractionated heparin and to document noninferiority in terms of efficacy. Patients received either fondaparinux (5.0, 7.5, or 10.0 mg in patients weighing less than 50, 50 to 100, or more than 100 kg, respectively) subcutaneously once daily or a continuous intravenous infusion of unfractionated heparin (ratio of the activated partial-thromboplastin time to a control value, 1.5 to 2.5), both given for at least five days and until the use of vitamin K antagonists resulted in an international normalized ratio above 2.0. The primary efficacy outcome was the three-month incidence of the composite end point of symptomatic, recurrent pulmonary embolism (nonfatal or fatal) and new or recurrent deep-vein thrombosis.

RESULTS
Forty-two of the 1103 patients randomly assigned to receive fondaparinux (3.8 percent) had recurrent thromboembolic events, as compared with 56 of the 1110 patients randomly assigned to receive unfractionated heparin (5.0 percent), for an absolute difference of −1.2 percent in favor of fondaparinux (95 percent confidence interval, −3.0 to 0.5). Major bleeding occurred in 1.3 percent of the patients treated with fondaparinux and 1.1 percent of those treated with unfractionated heparin. Mortality rates at three months were similar in the two groups. Of the patients in the fondaparinux group, 14.5 percent received the drug in part on an outpatient basis.

CONCLUSIONS
Once-daily, subcutaneous administration of fondaparinux without monitoring is at least as effective and is as safe as adjusted-dose, intravenous administration of unfractionated heparin in the initial treatment of hemodynamically stable patients with pulmonary embolism.

The writing committee of the Matisse Study (H.R. Büller, B.L. Davidson, H. Decousus, A. Gallus, M. Gent, F. Piovella, M.H. Prins, G. Raskob, A.E.M. van den Berg-Segers, R. Cariou, O. Leeuwenkamp, and A.W.A. Lensing) takes responsibility for the content of this article. Address reprint requests to Dr. Büller at the Academic Medical Center, Department of Vascular Medicine, F4-211, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, or at m.m.veendorp@amc.uva.nl.

*The institutions and investigators participating in the study are listed in the Appendix.

PULMONARY EMBOLISM IS A FREQUENT and often life-threatening event that contributes to 5 to 10 percent of deaths among hospitalized patients. The goals of antithrombotic therapy for this disease are to minimize early morbidity and mortality and to prevent recurrence without provoking excessive bleeding. In hemodynamically stable patients, unfractionated heparin is effective and remains the reference therapy for initial anticoagulation. Because unfractionated heparin requires continuous intravenous infusion with regular laboratory monitoring and dose titration, patients remain hospitalized even when their clinical condition permits discharge. A less complex and resource-intensive but equally efficacious and safe treatment, allowing earlier discharge, would be desirable.

Low-molecular-weight heparins have replaced unfractionated heparin for the treatment of most patients with deep-vein thrombosis, but in patients with symptomatic acute pulmonary embolism they have been less extensively evaluated. As a result, use of low-molecular-weight heparins for this indication varies, and in many countries they have not been approved by regulatory authorities for the initial treatment of patients with pulmonary embolism.

Fondaparinux is a synthetic antithrombotic agent with specific anti–factor Xa activity. Its pharmacokinetic properties allow for a simple, fixed-dose, once-daily regimen of subcutaneous injection, without the need for monitoring. In a dose-ranging trial involving patients with symptomatic proximal deep-vein thrombosis, 7.5 mg of fondaparinux appeared to have efficacy and safety similar to those of a low-molecular-weight heparin (dalteparin). Given the practical advantages of a simple fondaparinux regimen, this study was designed to determine whether fixed-dose, once-daily, subcutaneous administration of fondaparinux is at least as effective as unfractionated heparin for the initial treatment of symptomatic pulmonary embolism. This randomized trial, with blinded adjudication of outcome events, was conducted on an open-label basis, permitting early discharge in the fondaparinux group.

METHODS

PATIENTS

Consecutive patients 18 years of age or older who presented with acute symptomatic pulmonary embolism and who required antithrombotic therapy were potentially eligible for the study. Diagnostic criteria were an intraluminal filling defect on spiral computed tomography (CT) or pulmonary angiography, a high-probability ventilation–perfusion lung scan, or a nondiagnostic lung scan with documentation of deep-vein thrombosis either by compression ultrasonography or by venography.

Patients were ineligible for the study if they had received therapeutic doses of low-molecular-weight heparin or oral anticoagulants for more than 24 hours; if they required thrombolysis, embolectomy, or a vena cava filter; or if anticoagulant therapy was contraindicated — for example, because of active bleeding or thrombocytopenia (a platelet count below 100,000 per cubic millimeter). Patients were also ineligible if they had a serum creatinine level above 2.0 mg per deciliter (177 µmol per liter) or uncontrolled hypertension (systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg); if they were pregnant; or if a physician had estimated the life expectancy to be less than three months.

After written informed consent had been obtained, randomization was performed at a central location with the use of a computerized, interactive voice-response system that recorded information about the patient before his or her treatment assignment. The protocol was approved by the institutional review board at each of the study centers. The study was monitored by an independent data and safety monitoring board. The data were collected and held by the two sponsors, NV Organon and Sanofi-Synthélabo. The statistical-analysis plan was approved by the steering committee, which also checked the final analysis.

TREATMENT REGIMENS

The patients assigned to fondaparinux (Arixtra, NV Organon and Sanofi-Synthélabo) received a single daily subcutaneous injection of 5.0 mg (if their body weight was less than 50 kg), 7.5 mg (if their body weight was 50 to 100 kg), or 10.0 mg (if their body weight was greater than 100 kg). The patients assigned to unfractionated heparin received an initial intravenous bolus of at least 5000 IU, followed by at least 1250 IU per hour, administered as a continuous intravenous infusion. The infusion dose was adjusted to maintain the activated partial-thromboplastin time at 1.5 to 2.5 times a control value. The activated partial-thromboplastin time was measured approximately six hours after the start of heparin treatment, about six hours after.
each measurement of the activated partial-thromboplastin time that was subtherapeutic or supra-
therapeutic, and otherwise daily. Heparin was pro-
vided by American Pharmaceutical Partners for all
centers except those in France, where it was sup-
plied by Laboratoires Choay.

In both groups, treatment with a vitamin K an-
tagont was begun as soon as possible and within
72 hours after initiation of the study treatment. Ini-
tially, the prothrombin time was measured at least
every other day, and the dose of vitamin K antagonist
was adjusted to maintain the international normal-
ized ratio (INR) at a value between 2.0 and 3.0. Ad-
ministration of heparin or fondaparinux was con-
tinued for at least five days and until the INR had
been greater than 2.0 for two consecutive days.
Treatment with a vitamin K antagonist was con-
tinued for three months, and the INR was determined
at least once per month.

SURVEILLANCE AND FOLLOW-UP
All the patients were contacted daily during the ini-
tial treatment period and at one and three months
after the start of the study. At each contact, the pa-
tient was evaluated for symptoms and signs of re-
current venous thromboembolism and bleeding. All
the patients were informed about the symptoms and
signs of recurrent pulmonary embolism and deep-
vein thrombosis and about the potential for bleed-
ing. They were instructed to report to the study cen-
ter immediately if any of these conditions occurred.
The protocol required objective testing in cases of
suspected recurrent pulmonary embolism or deep-
vein thrombosis.

ASSESSMENT OF OUTCOMES
The primary efficacy outcome was symptomatic re-
current venous thromboembolism during the three-
month study period. Symptomatic recurrent venous
thromboembolism was considered to have occurred
if recurrent pulmonary embolism or deep-vein
thrombosis was documented objectively or if there
was a death in which pulmonary embolism was a
contributing cause or could not be ruled out. In the
absence of objective test results that adequately con-
formed or ruled out recurrent venous thromboem-
bolism, the diagnosis was accepted if the condition
was managed with therapeutic dosages of low-
molecular-weight heparin for more than two days,
thrombolysis, a vena caval filter, or thrombectomy.

The objective criterion for the diagnosis of recur-
rent pulmonary embolism was a new intraluminal
filling defect on spiral CT or pulmonary angiogra-
phy; cutoff of contrast material in a vessel more than
2.5 mm in diameter on pulmonary angiography; a
new perfusion defect involving at least 75 percent of
a segment, with corresponding normal ventilation
(i.e., a high-probability lung scan); a new nondiag-
nostic lung scan accompanied by documentation
of deep-vein thrombosis by ultrasonography or ve-
nography; or confirmation of a new pulmonary em-
bolism at autopsy.\textsuperscript{5,12} The objective criterion for the
diagnosis of new deep-vein thrombosis was a new,
noncompressible venous segment or a substantial
increase (4 mm or more) in the diameter of the
thrombus during full compression in a previously
abnormal segment on ultrasonography or a new in-
traluminal filling defect on venography.\textsuperscript{13,14}

The main safety outcomes were major bleeding
during the initial treatment period and death during
the three-month study period. Bleeding was consid-
ered major if it was clinically overt and associated
with a decrease of 2 g per deciliter or more in the he-
moglobin level, led to the transfusion of 2 or more
units of red cells or whole blood, was retroperito-
neal or intracranial, occurred in a critical organ, or
contributed to death. Bleeding episodes that were
clinically relevant but did not qualify as major (e.g.,
epistaxis that required intervention, formation of a
large hematoma visible on the skin, or spontaneous
macroscopic hematuria) were an additional safety
outcome and were classified as clinically relevant
nonmajor bleeding. All other hemorrhages were
categorized as trivial. The cause of death was classi-
fied as pulmonary embolism, bleeding, cancer, or
another established diagnosis or was considered to
be unexplained. All suspected outcome events were
reviewed and classified by a central adjudication
committee whose members were unaware of the
treatment assignments.

Platelet counts were assessed at base line, on
day 4, and at the end of initial treatment. Antiplate-
let antibodies were measured at base line and at the
end of initial treatment and also were measured if
heparin-induced thrombocytopenia was suspected
because the platelet count was confirmed on retest-
ing to be below 100,000 per cubic millimeter or to
have decreased by more than 40 percent from the
base line count.\textsuperscript{15}

STATISTICAL ANALYSIS
We assumed a 5 percent incidence of the primary ef-
cicacy outcome in the unfractionated-heparin group
and hypothesized that fondaparinux would be as
effective as unfractionated heparin. Studies in patients with pulmonary embolism or deep-vein thrombosis who received no treatment or inadequate treatment have found recurrence rates of approximately 20 percent.\textsuperscript{2,16,17} On the basis of previous studies, we chose a fixed noninferiority margin of 3.5 percent for the absolute difference between the two treatment groups in the rates of venous thromboembolism.\textsuperscript{4,5,7,12,16,17} From these assumptions, we calculated that a study with 1100 patients per group would have 95 percent power, with a one-sided type I error of 0.025, to reject the hypothesis that the rate of recurrence with fondaparinux would be 3.5 percent higher than that with unfractionated heparin.

The primary efficacy analysis was based on the incidence of symptomatic recurrent venous thromboembolism during the entire three-month study period. Analyses of bleeding events included events during the initial treatment period plus three, four, or nine days, according to the creatinine clearance (more than 50, 30 to 50, or less than 30 ml per minute, respectively).\textsuperscript{18} Efficacy analyses were based on data from all the patients who had been randomly assigned to a study group, whereas safety analyses were based on data from all the patients who actually received treatment. The 95 percent confidence interval for the absolute difference between the treatment groups in the rates of outcomes were calculated with use of the normal approximation.

The steering committee had the final responsibility for the study protocol, statistical analysis plan, progress of the study and analysis, and reporting of the data.

\textbf{RESULTS}

\textbf{PATIENTS AND BASE-LINE CHARACTERISTICS}

Between May 2000 and March 2002, 5993 patients with pulmonary embolism were screened in the 235 participating centers. Of these patients, 2948 (49 percent) were ineligible because they met one or more of the predefined exclusion criteria. The most common reasons for exclusion were the use of therapeutic anticoagulation for more than 24 hours (1237 patients), contraindications to anticoagulant therapy (470), a life expectancy of less than three months (205), and the use of thrombolytic therapy or a vena cava filter (128). In addition, 832 patients chose not to participate.

In total, 2213 patients were randomly assigned to receive either fondaparinux (1103) or unfractionated heparin (1110). The base-line characteristics of the patients in the two treatment groups were similar (Table 1). Follow-up with respect to the primary efficacy outcome was incomplete for six of the patients assigned to the fondaparinux group (0.5 percent) and seven of those assigned to the unfractionated-heparin group (0.6 percent), either because of withdrawal of informed consent (six patients) or loss to follow-up (seven).
Table 2 presents data on the initial treatment and vitamin K–antagonist therapy in the 1092 patients in each group who received treatment. The duration of initial treatment was similar in the two groups. An adequate anticoagulation response to unfractionated heparin (i.e., an activated partial-thromboplastin time above the lower limit) was achieved in a high proportion of patients.

Of the 158 patients in the fondaparinux group (14.5 percent) who received fondaparinux in part on an outpatient basis, 37 did so for one day, 29 for two days, and 92 for three or more days. In both groups, more than 90 percent of the patients had an INR of 2.0 or more at the end of the initial treatment. The intensity of treatment with vitamin K antagonists was similar in the two groups.

**Recurrent Venous Thromboembolism**

Of the 1103 patients assigned to receive fondaparinux, 140 had one or more episodes of clinically suspected recurrent venous thromboembolism, and the diagnosis was confirmed in 42 patients (Table 3). Among the 1110 patients assigned to receive unfractionated heparin, 122 had one or more episodes of clinically suspected recurrent venous thromboembolism, and the diagnosis was confirmed in 56 patients. Thus, the incidence of recurrence was 3.8 percent in the fondaparinux group and 5.0 percent in the unfractionated-heparin group, for an absolute difference in favor of fondaparinux of −1.2 percent (95 percent confidence interval, −3.0 to 0.5). The upper limit of this confidence interval indicates that a true difference of more than 0.5 percent in favor of unfractionated heparin was unlikely (probability of such a difference, 2.5 percent). Hence, the noninferiority of fondaparinux was clearly demonstrated.

**Bleeding Complications**

As shown in Table 3, major bleeding during initial treatment occurred in 14 of the patients who received fondaparinux (1.3 percent) and in 12 of those who received unfractionated heparin (1.1 percent) (absolute difference, 0.2 percent; 95 percent confidence interval, −0.7 to 1.1). Bleeding contributed to death in one patient in each treatment group. Among the patients whose creatinine clearance was below 30 ml per minute, major bleeding occurred in 2 of 26 (7.7 percent) in the fondaparinux group and in 1 of 28 (3.6 percent) in the unfractionated-heparin group.

Major or clinically relevant nonmajor bleeding during initial treatment occurred in 49 of the patients treated with fondaparinux (4.5 percent) and in 69 of those treated with unfractionated heparin (6.3 percent) (absolute difference, −1.8 percent; 95 percent confidence interval, −3.7 to 0.1). A total of 58 patients treated with fondaparinux and 67 of those treated with unfractionated heparin were considered to have had a trivial hemorrhage. The incidence of bleeding during treatment with a vitamin K antagonist was low and was similar in the two groups (Table 3).

**Mortality**

During the three-month study period, 57 patients who received fondaparinux (5.2 percent) died, as compared with 48 who received unfractionated heparin (4.4 percent) (absolute difference, 0.8 percent; 95 percent confidence interval, −1.0 to 2.6). In the fondaparinux group, the causes of death were pulmonary embolism (in 14 patients), bleeding (in 3), cancer (in 28), and other causes (in 12). In the
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unfractionated-heparin group, the corresponding numbers were 15, 1, 22, and 10.

Additional Observations

Of the 158 patients who received some fondaparinux on an outpatient basis, 5 (3.2 percent; 95 percent confidence interval, 1.0 to 7.2) had recurrent venous thromboembolism, and none (95 percent confidence interval, 0.0 to 2.4) had major bleeding or died during the initial treatment. Among patients with active cancer at the time of enrollment, recurrent venous thromboembolism occurred in 10 of 112 patients in the fondaparinux group (8.9 percent) and in 22 of 128 patients in the unfractionated-heparin group (17.2 percent). Major bleeding occurred in two patients with cancer who received fondaparinux (1.8 percent) and in three patients with cancer who received unfractionated heparin (2.3 percent). The incidences of recurrent venous thromboembolism and major bleeding according to body weight are shown in Table 4.

In the fondaparinux group, thrombocytopenia occurred in 10 patients (0.9 percent), 1 of whom had associated thromboembolism (myocardial infarction) and 1 of whom had major bleeding. Neither of these patients had antiplatelet antibodies. In the unfractionated-heparin group, thrombocytopenia occurred in 13 patients (1.2 percent). Two of these 13 patients had recurrent pulmonary embolism without antiplatelet antibodies.

Discussion

In this clinical trial of initial antithrombotic therapy for acute symptomatic pulmonary embolism, therapy with fondaparinux, a selective inhibitor of factor Xa, was not inferior to therapy with unfractionated heparin. The two therapies were associated with a similar incidence of adverse effects.

Optimal administration of intravenous unfractionated heparin requires reliable, frequent, and timely blood sampling and laboratory testing with reporting of the activated partial-thromboplastin time to a clinician, who then adjusts the dosage as needed. The minimal duration of treatment is five to seven days. Deviations in clinical practice from these complex, resource-intensive requirements are well documented, and abandoning heparin for an equally safe and effective but simpler therapy could be considered advantageous.

In our study, care was taken to recruit a representative sample of patients with pulmonary embolism. The demographic features, range of risk factors, and spectrum of disease severity at enrollment and the observed rates of recurrent and fatal venous thromboembolic events were consistent with those reported in previous investigations. Hence, our findings regarding the efficacy and safety of fondaparinux apply to a broad range of patients with hemodynamically stable pulmonary embolism and have the potential to simplify care.

Some methodologic aspects of this open-label trial require comment. The procedures used to minimize bias included strict requirements to verify the qualifying pulmonary embolism and any suspected recurrent venous thromboembolic or bleeding events, as well as randomization at a central location, nearly complete follow-up, and masked adjudication of each suspected outcome event. Success at minimizing bias due to unmasked treatment assignment is supported by our finding that the diagnostic procedures at enrollment and at the time of recurrence were similar and that the incidences of a workup for and confirmation of suspected recurrence and bleeding in the two groups were similar. Three considerations dictated the choice of unfractionated heparin rather than a low-molecular-weight heparin as the comparator drug. Unfractionated heparin is easier to use, more affordable, and more widely available.

Table 3. Clinical Outcomes during the Study Period.

<table>
<thead>
<tr>
<th>Population</th>
<th>Fondaparinux</th>
<th>Unfractionated Heparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients randomly assigned to a study group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>1103</td>
<td>1110</td>
</tr>
<tr>
<td>Recurrent venous thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— no. (%)</td>
<td>14 (1.3)</td>
<td>19 (1.7)</td>
</tr>
<tr>
<td>— Entire study</td>
<td>42 (3.8)</td>
<td>56 (5.0)</td>
</tr>
<tr>
<td>Type of recurrence — no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal pulmonary embolism</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Nonfatal pulmonary embolism</td>
<td>14</td>
<td>24</td>
</tr>
<tr>
<td>Deep-vein thrombosis only</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>Patients as treated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>1092</td>
<td>1092</td>
</tr>
<tr>
<td>Major bleeding — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Initial treatment</td>
<td>14 (1.3)</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td>— Entire study</td>
<td>22 (2.0)</td>
<td>26 (2.4)</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— no. (%)</td>
<td>35 (3.2)</td>
<td>57 (5.2)</td>
</tr>
<tr>
<td>— Entire study</td>
<td>62 (5.7)</td>
<td>92 (8.4)</td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Initial treatment</td>
<td>9 (0.8)</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td>— Entire study</td>
<td>57 (5.2)</td>
<td>48 (4.4)</td>
</tr>
</tbody>
</table>
ated heparin is the parenteral anticoagulant most widely used for initial therapy for pulmonary embolism, direct evidence that low-molecular-weight heparins are as effective as unfractionated heparin remains limited, and many clinicians prefer unfractionated heparin for this indication.3

Care was taken to apply the highest treatment standards to the use of unfractionated heparin and vitamin K antagonists. Among the necessary standards were those pertaining to the starting dose and dose adjustments, the minimal duration of treatment, and the target INR to be reached before heparin or fondaparinux could be stopped. Our results indicate that these standards were achieved in almost all the patients.

The objective of the study was to determine whether fondaparinux is noninferior to unfractionated heparin in preventing a recurrence of venous thromboembolism. The predefined margin for the comparison was consistent with those used in previous trials. Whereas an upper 95 percent confidence interval of up to 3.5 percent in favor of unfractionated heparin was allowed, the upper limit of 0.5 percent found in the study firmly establishes the noninferiority of fondaparinux.

Even though patients in the fondaparinux group were not prospectively assigned to early discharge, early discharge was permitted and occurred in 14.5 percent of them, who continued to receive fondaparinux on an outpatient basis. In this subgroup of 158 patients, the rate of recurrence was low (3.2 percent), and no major bleeding occurred.

In the past, bleeding complications were classified as major or minor. Whereas the definition of major bleeding in the setting of treatment for venous thromboembolism is generally well accepted and has been shown to be reliable,20 “minor” bleeding may range from bleeding that is clinically significant but does not quite meet the criteria for major bleeding to much less severe episodes such as gingival bleeding. To overcome this limitation, we introduced and defined a category of “clinically relevant nonmajor bleeding” to identify and assess the relevant hemorrhagic complications associated with antithrombotic therapy more accurately.

In conclusion, once-daily, unmonitored, subcutaneous administration of fondaparinux was not inferior to the use of unfractionated heparin for the initial treatment of hemodynamically stable pulmonary embolism, and rates of adverse events were similar with the two therapies. In our opinion, because of its simplicity, once-daily subcutaneous administration of fondaparinux without anticoagulation monitoring could replace intravenous administration of unfractionated heparin in most patients with this disorder.

Supported by an unrestricted grant from NV Organon (Oss, the Netherlands) and Sanofi-Synthélabo (Paris). Drs. Büller and Prins report having served as paid consultants and members of speakers bureaus for the sponsors.

APPENDIX


Table 4. Rates of Recurrent Venous Thromboembolism and Major Bleeding, According to Body Weight.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Recurrent Venous Thromboembolism during the 3-Month Study Period</th>
<th>Major Bleeding during the Initial Treatment Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;50 kg</td>
<td>50–100 kg</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>5/22 (22.7)</td>
<td>32/945 (3.4)</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>4/25 (16)</td>
<td>41/948 (4.3)</td>
</tr>
</tbody>
</table>

REFERENCES


CORRECTION

Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism

Subcutaneous Fondaparinux versus Intravenous Unfractionated Heparin in the Initial Treatment of Pulmonary Embolism. On page 1702, in the Appendix, the list of participating investigators should have included A. Palla in Pisa, Italy.