Thrombolysis vs Heparin in the Treatment of Pulmonary Embolism

A Clinical Outcome–Based Meta-analysis

Giancarlo Agnelli, MD; Cecilia Becattini, MD; Timo Kirschstein, MD

Background: In patients with acute pulmonary embolism, thrombolysis results in a more rapid resolution of pulmonary emboli than heparin treatment. Whether this advantage results in an improved clinical outcome is unclear. We sought to perform a clinical outcome–based meta-analysis of studies comparing thrombolytic and heparin treatment in patients with pulmonary embolism.

Methods: Data concerning adverse outcome events (death, recurrent pulmonary embolism, and major bleeding events) were extracted from the identified randomized studies.

Results: A total of 56 (23.2%) of 241 patients treated with thrombolytic agents in 9 randomized trials experienced an adverse outcome event compared with 57 (25.9%) of 220 patients treated with heparin (relative risk [RR], 0.9; 95% confidence interval [CI], 0.57-1.32). In the thrombolysis group, 11 patients (4.6%) died compared with 17 (7.7%) in the heparin group (RR, 0.59; 95% CI, 0.27-1.25). Thirty-one patients (12.9%) undergoing thrombolysis had a major bleeding episode compared with 19 patients (8.6%) treated with heparin (RR, 1.49; 95% CI, 0.85-2.81). Five fatal bleeding episodes (2.1%) occurred in the thrombolysis group and none in the heparin group. Six studies provided data on recurrent pulmonary embolism. A recurrence occurred in 14 (6.6%) of 214 patients treated with thrombolytic agents and in 22 (10.9%) of 201 patients treated with heparin (RR, 0.60; 95% CI, 0.29-1.15). Recurrence and/or death occurred in 25 (10.4%) of 241 and in 38 (17.3%) of 220 patients treated with thrombolytic agents and heparin, respectively (RR, 0.55; 95% CI, 0.33-0.96; P=.03).

Conclusions: In patients with pulmonary embolism, thrombolysis had a lower composite end point of death/recurrence than heparin treatment. Excessive bleeding is the trade-off for improved efficacy. A comparative clinical outcome trial of thrombolysis and heparin treatment is warranted in patients with pulmonary embolism and selected for high risk of death and/or recurrence and low risk of bleeding.

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PULMONARY EMBOLISM is a common and life-threatening disease. The incidence of a first episode of pulmonary embolism in acute care hospitals in the United States has been found to be 0.23 per 1000.1 In the 1960s, the introduction of heparin for treatment of pulmonary embolism cut down in-hospital mortality,2 but since then no further reduction has been achieved.3

Thrombolytic agents provide a more rapid lysis of pulmonary emboli and reduction of pulmonary hypertension than heparin.4 Whether these advantages result in an improved clinical outcome and outweigh the increased risk of bleeding complications is unknown. No conclusive clinical outcome studies aimed at comparing thrombolysis and heparin treatment in patients with pulmonary embolism are available. We performed a meta-analysis of studies comparing thrombolysis and heparin treatment in patients with pulmonary embolism with respect to the occurrence of death, recurrence of pulmonary embolism, and bleeding events.

METHODS

STUDY SELECTION

Randomized clinical trials comparing thrombolysis and heparin for treatment of pulmonary embolism were identified by computer-aided search (MEDLINE), scan of meeting abstracts, and scrutiny of the reference lists of original research and review articles. Trials were included in this meta-analysis if data concerning death and major bleeding events were avail-
OUTCOMES

The primary outcome of this meta-analysis was the incidence of adverse clinical outcome events (death, recurrence of pulmonary embolism, and major bleeding events). Recurrence of pulmonary embolism was considered among the adverse clinical outcome events, when reported, because it has been recently shown to be a predictor of in-hospital mortality.5

An analysis of the overall bleeding events (major and minor) was performed. For the purpose of this analysis, bleeding was considered major when it was fatal, intracranial, associated with a decrease in hemoglobin level of at least 2 g/dL, or if it required the transfusion of 2 or more units of red blood cells. Data on patients with intracranial and fatal bleeding were extrapolated from the more general population data of patients with major bleeding. Bleeding events were also considered separately as associated or not with invasive procedures.

STATISTICAL ANALYSIS

No assumption regarding the comparability of patients between the different studies was used because all the statistical calculations are based on the comparison within each single trial. Nevertheless, the homogeneity of the studies was tested with an approximate $\chi^2$ statistic.

The analysis was performed cumulatively for the overall adverse outcome events, separately for each adverse outcome event (death, major bleeding event, and recurrence of pulmonary embolism), and for death and recurrence together. To avoid the overestimation of adverse events, patients with multiple events were counted only once.

The relative risk (RR), the approximate odds ratio with its corresponding 95% confidence interval (CI), and a 2-tailed $P$ value were calculated for each trial and for the overall results. The number needed to treat and the number needed to harm were also indicated when appropriate. The results of each trial were analyzed on an intention-to-treat basis.

RESULTS

Eleven clinical trials comparing thrombolysis and heparin use for the treatment of pulmonary embolism were identified. Two trials were excluded from this analysis because they were nonrandomized.6,7 Therefore, 9 randomized trials,4,8-15 2 of which were double-blind,8,14,15 were included in this analysis (Table 1). Patients included

<table>
<thead>
<tr>
<th>Source</th>
<th>Double-blind</th>
<th>N</th>
<th>Treatment</th>
<th>PE Assessment</th>
<th>Primary Outcome</th>
<th>Observation Period</th>
<th>Criteria for Patient Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPET4</td>
<td>No</td>
<td>82</td>
<td>UK: 2000 U/lb bolus, 2000 U/lb for 12 h Heparin</td>
<td>AGF, LS</td>
<td>AGF hemodynamic improvement</td>
<td>14 d</td>
<td>Confirmed PE</td>
</tr>
<tr>
<td>Tibbutt et al6</td>
<td>No</td>
<td>13</td>
<td>Intrapulmonary SK: 600 000 U bolus, 100 000 U/h for 72 h Intrapulmonary heparin</td>
<td>AGF</td>
<td>AGF reperfusion</td>
<td>72 h</td>
<td>Life-threatening PE</td>
</tr>
<tr>
<td>Ly et al9</td>
<td>No</td>
<td>14</td>
<td>SK: 250 000 U bolus, 100 000 U/h for 72 h Heparin</td>
<td>AGF</td>
<td>AGF reperfusion</td>
<td>72 h</td>
<td>PE involving &gt;1 lobar artery</td>
</tr>
<tr>
<td>Marini et al10</td>
<td>No</td>
<td>11</td>
<td>UK: 600 000 U/12 h for 3 d Heparin</td>
<td>AGF, LS</td>
<td>LS reperfusion</td>
<td>12 mo</td>
<td>Perfusion defect &gt;9 segments at LS</td>
</tr>
<tr>
<td>PAIMS 211</td>
<td>No</td>
<td>20</td>
<td>rt-PA: 100 mg/2 h Heparin</td>
<td>AGF</td>
<td>AGF reperfusion and hemodynamic improvement</td>
<td>20 d</td>
<td>Miller index &gt;11</td>
</tr>
<tr>
<td>Goldhaber et al12</td>
<td>No</td>
<td>16</td>
<td>rt-PA: 100 mg/2 h Heparin</td>
<td>AGF, LS</td>
<td>RVD regression</td>
<td>14 d</td>
<td>PE associated with RVD</td>
</tr>
<tr>
<td>Jerjes-Sanchez et al13</td>
<td>No</td>
<td>4</td>
<td>SK: 1 500 000 U/1 h Heparin</td>
<td>AGF</td>
<td>LS reperfusion</td>
<td>Hospital stay</td>
<td>Perfusion defect &gt;9 segments at LS or perfusion defect &lt;9 segments at LS + RVD</td>
</tr>
<tr>
<td>PIOPED14</td>
<td>Yes</td>
<td>9</td>
<td>rt-PA: 40-80 mg/40-90 min Heparin</td>
<td>AGF, LS</td>
<td>PAP reduction at AGF</td>
<td>Hospital stay</td>
<td>PE involving &gt;2 segmental arteries</td>
</tr>
<tr>
<td>Levine et al15</td>
<td>Yes</td>
<td>4</td>
<td>rt-PA: 0.6 mg/kg every 2 min Heparin</td>
<td>AGF, LS</td>
<td>LS reperfusion</td>
<td>10 d</td>
<td>Confirmed PE</td>
</tr>
</tbody>
</table>

*PE indicates pulmonary embolism; UPET, Urokinase Pulmonary Embolism Trial; PAIMS 2, Plasminogen Activator Italian Multicenter Study 2; PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis; UK, urokinase; SK, streptokinase; rt-PA, recombinant tissue-type plasminogen activator; AGF, angiography; LS, lung scan; RVD, echocardiographical right ventricular dysfunction; and PAP, pulmonary artery pressure.
Adverse clinical events, death, recurrence of pulmonary embolism, and major bleeding events were first analyzed cumulatively. Across all studies, adverse clinical events occurred in 56 patients (23.2%) treated with thrombolytic agents and in 57 patients (25.9%) treated with heparin, resulting in an RR of 0.9 (95% CI, 0.57-1.32; P = .31) (Table 2 and Figure).

In the thrombolysis group, 11 patients (4.6%) died compared with 17 patients (7.7%) treated with heparin, corresponding to an RR of 0.59 (95% CI, 0.27-1.25; P = .51; number needed to treat, 31.6) (Table 2).

Thirty-one patients undergoing thrombolysis (12.9%) had major bleeding events compared with 19 (8.6%) treated with heparin, corresponding to an RR of 1.49 (95% CI, 0.85-2.81; number needed to harm, 23). Overall, 5 patients, all of them in the thrombolysis group (2.1%), had a fatal bleeding event. Fatal bleeding events were as follows: 3 gastrointestinal, 1 intracranial, and 1 cardiac tamponade. One additional patient undergoing thrombolysis died and had intracranial bleeding, but death was attributed to the recurrence of pulmonary embolism.

In 5 of the 9 studies, invasive procedures were performed, essentially catheter insertion for pulmonary angiography. The incidence of major bleeding was 15.2% (40/264) in studies requiring invasive procedures and 5.1% (10/197) in the remaining studies (RR, 2.98; 95% CI, 1.53-5.82; P < .001). The incidence of major bleeding in patients receiving thrombolytic treatment in studies with and without invasive procedures was 18.1% (25/138) and 5.8% (6/103), respectively (RR, 3.1; 95% CI, 1.32-7.30; P < .005). The incidence of major bleeding in patients receiving heparin in studies with and without invasive procedures was 11.9% (15/126) and 4.3% (4/94), respectively (RR, 2.80; 95% CI, 0.96-8.16; P < .05).

Four trials reported adequate data on overall bleeding events (major and minor), the rate ranging from 5% to 70% in the thrombolysis group and from 0% to 50% in the heparin group (Table 3). The rate of overall bleeding events was 42.6% and 26.0% in patients receiving thrombolysis and heparin, respectively, corresponding to an RR of 1.99 (95% CI, 1.61-4.58; P < .001). A statistically significant increase of overall bleeding in patients undergoing thrombolysis was observed in 1 double-blind trial.

Six studies, including 415 patients, reported the incidence of recurrence of pulmonary embolism (Table 2). This event occurred in 14 (6.6%) of 214 patients treated with thrombolysis and in 22 of the 201 patients treated with heparin, corresponding to an RR of 0.60 (95% CI, 0.29-1.15). When death and recurrence were considered together, an RR of 0.57 (95% CI, 0.31-
This death rate is lower than that observed in 2 recent studies, 11.9% of the patients receiving thrombolytic therapy experienced an adverse event with a RR of 0.91 (95% CI, 0.65-1.26). In the 2 double-blind studies, 11.9% of the patients receiving thrombolytic therapy experienced an adverse event compared with 10.3% in the heparin group,14,15 corresponding to an RR of 1.15 (95% CI, 0.27-4.64).

0.89; P = .03) in favor of thrombolysis was observed. For death and recurrence taken together, the number needed to treat was 14.5.

Streptokinase, urokinase, and recombinant tissue-type plasminogen activator were used in 3, 2, and 4 studies, respectively (Table 1). The overall mortality was 8.3% (21/253) in patients included in the streptokinase and urokinase studies, while it was 3.4% (7/208) in patients included in the recombinant tissue-type plasminogen activator studies (RR, 0.41; 95% CI, 0.18-0.94). The overall incidence of major bleeding events in patients included in the streptokinase and urokinase studies was 14.6% (37/253), while it was 6.3% (13/208 patients) in patients included in the recombinant tissue-type plasminogen activator studies (RR, 0.43; 95% CI, 0.23-0.78). Among patients receiving thrombolysis, the incidence of major bleeding was 18.1% (24/133) in patients receiving streptokinase or urokinase and 6.5% (7/108) in patients receiving recombinant tissue-type plasminogen activator (RR, 0.36; 95% CI, 0.16-0.80). The incidence of major bleeding was similar in patients receiving heparin in the streptokinase or urokinase studies (10.8%) and in the recombinant tissue-type plasminogen activator studies (6.0%) (RR, 0.55; 95% CI, 0.22-1.40).

In the non–double-blind studies, 25.6% of the patients receiving thrombolytic therapy experienced an adverse event compared with 28.3% in the heparin group (RR, 0.91; 95% CI, 0.65-1.26). In the 2 double-blind studies, 11.9% of the patients receiving thrombolytic therapy experienced an adverse event compared with 10.3% in the heparin group,14,15 corresponding to an RR of 1.15 (95% CI, 0.27-4.64).

### Table 3. Total Bleeding Events

<table>
<thead>
<tr>
<th>Source</th>
<th>Thrombolysis</th>
<th>Heparin</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Studies</td>
<td>67/155 (43.2)</td>
<td>28/129</td>
<td>2.75 (1.61-4.58)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Levine et al15</td>
<td>15/53 (45)</td>
<td>1/25 (4)</td>
<td>20.00 (2.30-81.30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Marini et al10</td>
<td>1/20 (5)</td>
<td>0/10</td>
<td>(0.06-43.20)</td>
<td>.47</td>
</tr>
<tr>
<td>PAIMS 22</td>
<td>14/20 (70)</td>
<td>6/16 (38)</td>
<td>3.89 (0.94-13.90)</td>
<td>.051</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>37/82 (45)</td>
<td>21/78 (27)</td>
<td>2.23 (1.14-4.25)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval; UPET, Urokinase Pulmonary Embolism Trial; and PAIMS 2, Plasminogen Activator Italian Multicenter Study 2.

The results of the present meta-analysis could make critical the selection of patients with pulmonary embolism who could benefit from thrombolytic therapy. Indeed, this treatment should be reserved for patients at high risk for death and recurrence and at low risk for bleeding. The identification of a high-risk population could be facilitated by the finding of right ventricular dysfunction at echocardiography, which has been shown to be a predictor of inhospital mortality18,19 and recurrence.20 Careful patient selection and the use of noninvasive diagnostic methods for pulmonary embolism could contribute to the reduction of adverse bleeding events.

The results of the present meta-analysis could have been influenced by the use of suboptimal thrombolytic agents and/or regimens. It should be noted that the thrombolysis treatments used in the analyzed trials differ largely in choice of thrombolytic agent and regimen. Indeed, some of the regimens used in the first studies are not conceivable nowadays. It is of interest that the incidence of death and major bleeding events was significantly higher in patients receiving streptokinase or urokinase than in patients receiving recombinant tissue-type plasminogen activator. This reading of the results leaves open the possibility that more effective and safer thrombolytic agents, administered in a more pharmacologically sound regimen, including shorter infusion
time, could produce a higher clinical benefit in terms of safety and efficacy.

The studies included in our meta-analysis provide information limited to the short-term clinical outcome of patients with pulmonary embolism. Thus, it does not test the hypothesis that thrombolytic therapy could produce long-term clinical advantages such as a lower incidence of late recurrence of pulmonary embolism or chronic thromboembolic pulmonary hypertension.

In conclusion, the present meta-analysis of comparative studies in pulmonary embolism showed that death and recurrences are less frequent with thrombolysis than with heparin treatment. The excessive bleeding mainly associated with invasive procedures is the trade-off for this improved efficacy. A comparative clinical outcome trial of thrombolysis and heparin treatment in patients with pulmonary embolism and with a high risk of death and/or recurrence and a low risk of bleeding is warranted and should not be further delayed.

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REFERENCES