Possible Gender-Related Differences in the Risk-to-Benefit Ratio of Thrombolysis for Acute Submassive Pulmonary Embolism

Annette Geibel, MD a, Manfred Olschewski, PhD b, Manfred Zehender, MD a, Mareile Wilsch, MD a, Katja Odening, MD a, Fritz Heinrich, MD a, Wolfgang Kasper, MD c, and Stavros Konstantinides, MD d,*

The indications for thrombolytic treatment in normotensive patients with pulmonary embolism (PE) are still the subject of debate, and it also remains questionable whether the efficacy and safety of thrombolysis are similar in men and women. To address the latter issue, the present study analyzed a large population of 428 women and 291 men with acute submassive PE derived from a prospective multicenter registry. Initial treatment consisted either of thrombolysis (<24 hours after diagnosis) or heparin alone. Thirty-day overall mortality was almost identical (11%) in heparin-treated men and women. Early thrombolysis was associated with drastically reduced death rates (2.7% vs 11% in the heparin group, p = 0.033) in men, whereas the reduction was nonsignificant (p = 0.181) in women. Multivariate analysis revealed that early thrombolysis was independently associated with reduced mortality rates in men (odds ratio 0.21, 95% confidence interval 0.05 to 0.96). In comparison, its favorable effect in women was marginal (odds ratio 0.77, 95% confidence interval 0.30 to 1.97). Gender-specific differences were also observed with regard to the reduction of symptomatic PE recurrence (in men, from 21.6% to 8.2%, p = 0.009; in women, from 16.9% to 8.3%, p = 0.049). In contrast, thrombolysis resulted in a more than threefold increase in major bleeding in women (from 8.4% to 27.1%, p <0.001), a more pronounced effect than in men (from 6.9% to 15.1%, p = 0.055). In conclusion, the present study generated the hypothesis that women with submassive PE might benefit less from thrombolytic treatment in terms of survival and PE recurrence and that they could be exposed to a higher bleeding risk compared with men. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:103–107)

The present study analyzed the data from a large prospective multicenter registry that included 1,001 patients with acute pulmonary embolism (PE).1 Our analysis focused on the population of 719 men and women with submassive PE, that is, those who were normotensive but had evidence of right ventricular (RV) dysfunction at presentation. On the basis of clinicians’ judgment, these patients either underwent early thrombolysis (<24 hours after presentation) or were treated with heparin alone. In this large population, we assessed the possible differential effects of thrombolysis in the 2 genders with regard to clinically relevant, predefined end points, particularly overall 30-day mortality, symptomatic PE recurrence, and major bleeding.

Methods

Study population: The rationale, study protocol, and inclusion criteria of the Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET) have been described.1,2 Briefly, 204 participating centers in Germany prospectively registered a total of 1,001 consecutive patients in whom the diagnosis of submassive or massive PE was made according to predefined criteria. The inclusion criteria of the registry consisted of the following findings signifying RV dysfunction and/or pulmonary hypertension caused by PE: (1) arterial hypotension (systolic blood pressure <90 mm Hg or a pressure decrease of ≥40 mm Hg for >15 minutes, if not caused by new-onset arrhythmia, hypovolemia, or sepsis); (2) cardiogenic shock (arterial hypotension as defined previously accompanied by clinical signs of organ perfusion and hypoxia); (3) circulatory collapse with a need for cardiopulmonary resuscitation; (4) echocardiography indicating RV dysfunction and/or pulmonary hypertension (RV dilation, paradoxic septal wall motion, loss of inspiratory collapse of the inferior vena cava, or tricuspid regurgitation jet velocity >2.8 or <2.5 m/s in the absence of inspiratory collapse of the inferior vena cava) without evidence of mitral valve disease or left ventricular dysfunction; and (5) diagnosis of precapillary pulmonary hypertension (mean pulmonary artery pressure >20 mm Hg in the presence of normal pulmonary artery occlusion pressures) by right-sided cardiac catheterization.

For inclusion in the registry, patients had to have clinical suspicion of PE and fulfill ≥1 of these criteria at presentation. Patients in whom PE was an accidental finding, not the
primary clinical diagnosis on admission, were excluded. Confirmation of venous thromboembolism by imaging studies was recommended in agreement with guidelines existing at the time the registry was performed.3,4 The steering committee of the registry did not dictate specific management strategies to the participating centers and physicians.

The present analysis included only patients with submassive PE, that is, those who had evidence of pulmonary hypertension and/or RV dysfunction but no arterial hypotension at presentation and patients who initially had arterial hypotension but no clinical signs of cardiogenic shock or need for catecholamine infusion (except \( \geq 5 \mu \text{g kg}^{-1} \text{min}^{-1} \) dopamine). On the basis of the therapeutic strategy after confirmation of PE, we defined 2 treatment groups. The first or thrombolysis group consisted of patients who underwent early thrombolytic treatment (i.e., \(< 24 \) hours after diagnosis) accompanied by heparin anticoagulation. The second group included patients who were treated with (unfractionated) heparin alone and those who initially received heparin but were later (after the first 24 hours) judged by the attending physician to require thrombolytic treatment because of clinical deterioration. Intravenous anticoagulation was continued for 5 to 7 days in the 2 treatment groups, and the dose (infusion rate) of heparin was adjusted to keep the activated partial thromboplastin time at 2.0 to 3.0 times normal. After overlapping administration with warfarin, heparin was discontinued when the international normalized ratio reached the therapeutic range of 2.0 to 3.0.

**Clinical end points:** The predefined primary clinical end point was 30-day overall mortality. Secondary end points were the symptomatic recurrence of PE and major bleeding episodes during the hospital stay. Major bleeding was defined as hemorrhagic stroke confirmed by computed tomography or autopsy or as a bleeding episode that fulfilled \( \geq 1 \) of the following criteria: a decrease in hemoglobin levels of \( \geq 2 \) g/dl, requirement for a blood transfusion of \( \geq 2 \) U, retroperitoneal bleeding, or bleeding that required surgical intervention or the discontinuation of heparin anticoagulation or thrombolytic treatment.

**Statistical analysis:** According to the intent-to-treat principle, patient assignment to the thrombolysis or heparin group was based on the primary treatment (i.e., thrombolysis plus heparin vs heparin alone) given to the patients within the first 24 hours after diagnosis, regardless of changes in treatment undertaken later during the hospital course. Patients belonging to the 2 groups were compared by Fisher’s exact test for dichotomous variables and by Wilcoxon’s rank test for continuous variables. The impact of primary thrombolytic treatment and other clinically important baseline variables on 30-day mortality and on the secondary clinical end points in men and women was analyzed univariately by the chi-square test. To investigate whether the prognostic effect of early thrombolysis in either gender was independent of other clinical variables, a multiple logistic regression model was applied to the end point of overall 30-day mortality. In this model, we took into account all clinical variables that reached a value of \( p < 0.20 \) in the univariate comparison. The results of the logistic regression models are presented as estimated odds ratios with the corresponding 95% confidence intervals. All significance tests were 2 sided, with a \( p \) value \(< 0.05 \) considered to indicate clinical significance. Data processing and analysis were performed with SAS (SAS Institute Inc., Cary, North Carolina).

**Results**

**Patient characteristics at diagnosis:** Table 1 lists the clinical characteristics of the registry patients at presentation. There were no significant differences between men and women with regard to most baseline parameters, including systolic or diastolic blood pressure, heart rate, or the severity of dyspnea or arterial hypoxemia. Moreover, and agreeing with a previous report,5 there were no gender-specific differences with regard to the number or type of diagnostic procedures performed to confirm the presence of PE (not shown).

After the diagnosis of PE, 22% of the women and a similar proportion of men (25%; \( p = 0.42 \)) received early (i.e., within the first 24 hours) thrombolytic treatment. The baseline parameters of thrombolysis-treated compared with heparin-treated patients are listed in Table 2. Of note, there were no significant differences between thrombolysis- and heparin-treated patients of either gender with regard to systolic blood pressure at presentation (111 \( \pm 31 \) vs 112 \( \pm 32 \) mm Hg, \( p = 0.17 \)), breathing rate (26 \( \pm 7 \) vs 25 \( \pm 6 \) breaths/min, \( p = 0.42 \)), or partial arterial pressure of oxygen while breathing room air (56 \( \pm 12 \) vs 58 \( \pm 13 \) mm Hg, \( p = 0.11 \)).

**Differential effects of thrombolysis on clinical outcome:** Overall 30-day mortality was 9.6% in the registry population, and death was directly related to the pulmonary thromboembolic event in almost all patients (65 of 69 deaths, 94%). As listed in Table 3, mortality in the heparin-only group was almost identical (11%) in men and women with acute major PE. In contrast, the effects of early thrombolytic treatment differed between men and women. Women had a lower risk of mortality than men with acute major PE (hazard ratio \( 0.34 \), \( 95\% \) CI \( 0.11 \) to \( 0.98 \), \( p = 0.04 \)).
bolysis on clinical outcome exhibited remarkable differences between the 2 genders. Thus, thrombolytic treatment was associated with a pronounced, significant reduction in mortality from 11% to 2.7% in men (p = 0.033), whereas the reduction was smaller (from 11.1% to 6.3%) and did not reach statistical significance (p = 0.182) in women. Similarly, the symptomatic recurrence of PE was significantly reduced after thrombolytic therapy in men (from 21.5% to 8.2%, p = 0.009), whereas a less pronounced effect was observed in women (from 16.8% to 8.3%, p = 0.05). Univariate analysis revealed that apart from treatment with heparin alone, the following clinical characteristics at presentation were significantly associated with higher 30-day mortality in men: tachycardia (13.1% in patients who died vs 0% in those who survived, p < 0.001), arterial hypotension (13.5% vs 6.1%, p = 0.036), congestive heart failure (27.2% vs 10%, p = 0.01), and chronic pulmonary disease (23.7% vs 13.4%, p = 0.002). In women, age >65 years (13.4% vs 5.5%, p = 0.009), syncope (16.7% vs 7.5%, p = 0.007), congestive heart failure (15.5% vs 7.3%, p = 0.01), and chronic pulmonary disease (28.1% vs 8.6%, p = 0.002) were more frequent in patients who died of PE.

Major bleeding episodes occurred in 80 patients (11.1% of the population). Although bleeding rates were similar between men and women treated with heparin alone, the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women</th>
<th>Men</th>
<th>p Value</th>
<th>Women</th>
<th>Men</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom onset ≤48 h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse rate &gt;100 beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of deep vein thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of pulmonary embolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
occurrence of major bleeding was almost twice as frequent in women treated with thrombolysis compared with men (27.1% vs 15.1%, p = 0.09). Thrombolysis was associated with a more than threefold increase in the rate of major bleeding in women, a highly significant difference (Table 3). In contrast, the effects of thrombolysis on major bleeding were modest in men and did not reach statistical significance. Of note, intracranial bleeding rates increased to 2.1% in the thrombolysis-treated women, whereas no intracranial bleeding episodes were observed in men treated with thrombolysis (Table 3). One man and 1 woman died of bleeding complications after receiving thrombolytic therapy.

Multiple logistic regression analysis confirmed that in men, the reduction in 30-day mortality associated with early thrombolytic treatment remained significant after adjusting for other relevant clinical characteristics at presentation (Table 4). In women, however, the (independent) favorable effect of early thrombolysis on clinical outcome was much less pronounced (odds ratio 0.77) and remained far less than statistical significance. Table 4 further indicates that chronic lung disease, syncope, and (marginally) age >65 years were independent predictors of early death in women, whereas these parameters did not appear to affect the outcomes of men with acute PE.

Discussion

Data from the MAPPET, a large, prospective, multicenter registry, suggested that thrombolytic treatment might improve the in-hospital survival of normotensive patients with PE, if they have evidence of pulmonary hypertension and/or RV dysfunction as an indicator of an elevated death risk.2 Since that time, significant progress has been made in the diagnosis of submassive PE thanks to advances in imaging methods and cardiac biomarkers. These modalities form the basis for contemporary risk stratification algorithms.6,7 However, the appropriate treatment of submassive PE will continue to be the subject of debate until the risks and benefits of thrombolysis are accurately determined by a large randomized trial.8,9 Reservations against the use of thrombolytic agents in this setting are based on their short-lasting hemodynamic benefits compared with heparin anticoagulation,10 the relatively high intracranial bleeding rates,11 and the wide confidence interval in terms of survival benefit, as reported by a recent meta-analysis.12 In contrast, it also remains uncertain whether similar benefits and/or complication rates can be expected in men and women treated with thrombolysis for acute PE. There is an almost complete absence of systematically obtained data on the clinical course, the response to treatment, and the prognosis of PE in the 2 genders. For example, 1 study found that the duration of hospitalization for PE was comparable between men and women,9 but gender-related differences were reported with regard to the recurrence of venous thromboembolism over the long term.13

The present study, which analyzed a large population of 428 women and 291 men with acute submassive PE, found that 30-day overall mortality rate was almost identical (11%) in the 2 genders under treatment with heparin alone. This observation appears to agree with the results of another large multicenter registry.14 However, in contrast to a previous meta-analysis,15 we observed significant differential effects of thrombolysis in the 2 genders, which may be of prognostic relevance. Overall, early thrombolytic treatment was a significant independent predictor of improved survival in men, resulting in a mean risk reduction of almost 80% on multivariate analysis. In comparison, its favorable effect was marginal in women (mean risk reduction approximately 20%), and it remained far less than statistical significance. Gender-specific differences in the response to thrombolysis were also observed with regard to symptomatic PE recurrence. Again, the reduction of recurrence rates in association with early thrombolytic treatment was pronounced and significant in men but much less so in women. Finally, analysis of bleeding episodes revealed a highly significant, more than threefold increase in major bleeding in women as opposed to an only moderate overall increase and the absence of intracranial bleeding episodes in men. Thus, although it is currently assumed that the incidence of venous thromboembolism is approximately equal in men and women,16 our results suggest that gender-related differences could exist with regard to prognosis and the response to therapy. In particular, women with submassive PE not only appear to benefit less from thrombolytic treatment in terms of survival and PE recurrence but may also be exposed to a higher bleeding risk compared with men. A pathophysiologic explanation for our results remains to be found, but the large study population of 719 patients and the confirmation of the differential effects of thrombolysis by multivariate analysis minimizes the possibility that they were due simply to differences between the men and women with regard to age or co-morbidities.

As mentioned earlier, a previous meta-analysis of 5 thrombolysis trials observed similar (favorable) effects of thrombolytic treatment in men and women,15 a finding that is apparently contradicted by the present study. However, that report, and the studies on which it was based, evaluated scintigraphic (degree of reperfusion), angiographic (improvement in the quantitative score), and hemodynamic (decrease in mean pulmonary arterial pressures) parameters to assess treatment efficacy. In contrast, the original design of the MAPPET registry and the present analysis focused on clinical end points, namely, overall mortality and symptomatic PE recurrence. Thus, our study adds further support to the thesis that hemodynamic improvement in response to thrombolytic therapy is not automatically translated into improved survival and thus cannot be used as a surrogate for clinical outcome when designing thrombolysis trials. Of note, because our results were derived from a registry, not from a controlled, randomized trial, they should not be interpreted as proof that women with PE do not benefit from thrombolysis. Moreover, all registry patients received unfractionated heparin as the initial anticoagulant, and thus the present study could not address the efficacy and safety of subcutaneous low-molecular-weight heparin treatment alone or in combination with thrombolytic agents. Keeping these limitations in mind, our findings add to the growing body of evidence suggesting that gender-specific issues need to be seriously considered when designing controlled therapeutic trials and, in this particular case, a large multi-
center trial aimed at resolving the thrombolysis debate in submassive PE.


