Pulmonary embolism: advances in diagnosis and prognosis
Douma, R.A.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 12

Thrombolysis for pulmonary embolism and venous thrombosis: is it worthwhile?

Renée A. Douma and Pieter W. Kamphuisen

Seminars in Thrombosis and Haemostasis 2007;33:821-8
ABSTRACT

Venous thromboembolism is a frequently occurring and potentially fatal disease, characterized by short- and long-term sequelae. Conventional treatment consists of heparin and vitamin K antagonists, but there is an ongoing controversy if more aggressive therapy, such as thrombolytic drugs, should be used in selected patients to achieve faster clot lysis in pursuit of better clinical outcome. A review of the literature shows that thrombolytic therapy is not recommended in the treatment of venous thrombosis. While systemically and catheter-directed administered thrombolysis both offer advantages in improving vein patency and reducing the post-thrombotic syndrome (PTS), prevention of severe PTS remains unproven while the bleeding risk is high. In pulmonary embolism (PE), thrombolytic therapy is generally recommended for patients with massive PE and hemodynamic instability, despite scarce and inconclusive evidence. There is no evidence that thrombolysis has a benefit over standard anticoagulant treatment in normotensive patients with acute PE, but more research is needed to better identify the subgroup of patients with non-massive PE in whom the risk-benefit ratio is most favorable. Until this group is defined and the benefit of thrombolytic therapy is demonstrated, thrombolytic therapy should only be considered in patients with signs of massive PE and hemodynamic shock.
INTRODUCTION

Venous thromboembolism (VTE) includes deep venous thrombosis (DVT) and pulmonary embolism (PE). With an annual incidence of 1 per 1000 persons, VTE is a frequently occurring disease with a potentially fatal outcome (1). Although DVT and PE can be effectively treated with heparin and vitamin K antagonists, there are short-term as well as long-term sequelae that characterize the clinical course of VTE. There is an ongoing debate if more aggressive therapy, such as thrombolytic drugs, should be used to achieve faster clot lysis, in pursuit of reducing mortality and long-term sequelae.

Thrombolytic therapy has been used in a variety of thrombotic disorders, such as myocardial infarction, acute ischemic stroke, but also PE and DVT. The process of thrombolytic therapy involves the activation of plasminogen to form plasmin, and causes accelerated lysis of thrombi. Although some VTE patients may benefit from thrombolytic treatment, the indications for more aggressive therapy in these patients are still controversial. Any clinical advantage of thrombolytic therapy must be weighed against an increased risk of major bleeding. In this chapter, the literature will be reviewed for advantages and disadvantages of thrombolytic therapy for both DVT and PE.

DEEP VENOUS THROMBOSIS

Treatment for DVT is aimed at preventing extension of the thrombus and pulmonary embolism, and recurrence of VTE. Conventional anticoagulant therapy is currently the most accepted treatment of DVT. However, its efficacy to prevent one of the major long term complications, the post-thrombotic syndrome (PTS), is unclear. PTS is a chronic condition, with clinical symptoms such as pain, skin discoloration, swelling and venous ulceration. It affects 20-50% of patients 1-2 years after a treatment episode of symptomatic DVT, of whom 5-10% have severe PTS (2). Obstructed venous blood flow, venous valve damage, regurgitation of blood, venous hypertension, and finally persistent stenosis are believed to be the cause of PTS (3). Thrombolysis could be helpful in achieving early clot lysis, restoring a faster patency and preventing valve damage and could thus, theoretically, reduce the incidence of PTS in the long-term. Recent trials of anticoagulant therapy found a mortality of DVT of less than 3% (4). Therefore, the advantage of thrombolysis on mortality in patients with DVT is offset by the short-term risk of major bleeding.

Systemic thrombolytic therapy for DVT

In a meta-analysis published in 2001 (5), the literature was reviewed for trials comparing fibrinolysis with unfractionated heparin in patients with DVT. In seven studies comparing streptokinase with heparin (total number of patients 229), the odds ratio (OR) for significant clot lysis was 8.4 (95% confidence interval (CI) 4.4-16.3) with fibrinolytic treatment, at the cost of an OR for major bleeding of 3.8 (95% CI 1.5-10.3). Intracranial hemorrhage and PE seldom
occurred in these studies. Five studies reported long term follow-up for PTS, and in all but one a benefit of streptokinase was found (OR 0.3; 95% CI 0.2-0.7) (5). Similar results were found in a more recent review of thrombolysis for acute DVT for the Cochrane Database (6). Twelve trials were included in this analysis, comparing any thrombolytic agent (mostly streptokinase, urokinase and tissue plasminogen activator) with unfractionated heparin. Complete clot lysis occurred significantly more often in the thrombolytic group at early follow-up (relative risk (RR) 0.24; 95% CI 0.07-0.82), and during longer follow up (RR 0.37; 95% CI 0.25-0.54). The incidence of PTS was significantly reduced in those patients receiving thrombolysis, (RR 0.66; 95% CI 0.47-0.94), and likewise leg ulceration (a sign of severe PTS) was reduced – although data was limited due to small numbers. Again, to counterbalance these results, significantly more bleeding complications occurred in the 668 patients with thrombolysis (RR 1.73; 95% CI 1.04-2.88), although the incidence of bleeding appeared to decrease with the introduction of stricter selection criteria. No significant effect on mortality was found in either early or late follow up, and there were inconclusive results for the effects on VTE recurrence.

In summary: although systemic thrombolysis offers advantages in improving vein patency and reducing PTS, the prevention of severe PTS in the long term remains unproven, while the price in terms of bleeding is high. In patients with DVT, the use of systemic thrombolysis is therefore not recommended. However, applying stricter selection criteria may improve safety of thrombolysis and may lead to a better risk/benefit ratio.

Catheter-directed thrombolytic therapy
Catheter-directed thrombolytic therapy involves the administration of a fibrinolytic agent directly at the site of the thrombus. A catheter is passed into the clot under radiographic guidance and the thrombolytic agent is applied locally until dissolution of the clot is seen. The only randomized clinical trial of catheter-directed thrombolytic therapy to date included 35 patients with iliofemoral thrombosis (7). After one week, complete thrombolysis was observed in 11 of 18 (61%) patients treated with local streptokinase combined with systemic heparin versus 0 of 17 (0%) patients treated with systemic heparin alone. Improved vein patency was achieved in 13 of 18 (72%) streptokinase treated versus 2 of 17 (12%) patients in the control group (p<0.001) after 6 months. No bleeding occurred in this study and the incidence of post-thrombotic syndrome was not reported.

The largest study with catheter-directed thrombolysis in DVT is the National Venous Thrombolysis Registry (8) and included 287 patients. Patients with DVT were directly treated with urokinase with a follow-up period of one year. Initially, complete lysis was obtained in 31% of patients, partial lysis (50%-99%) in 52% and <50% lysis in 17% of patients. Primary patency was reached in 65% at 6 months and 60% at 12 months. After thrombolysis, 104 patients additionally received intravascular stents. The patency rates were comparable with
the standard anticoagulant therapy. Major bleeding occurred in 16% of patients, mostly at the puncture site, the mortality rate due to fibrinolytic therapy was 0.4%. All other reports of catheter-directed thrombolytic therapy are case studies of either catheter-directed therapy alone or in combination with invasive techniques, such as balloon angioplasty, stents or thrombectomy. In a recent systematic review of six prospective case series including 10 or more patients (9), pooled data showed complete early lysis in 124 of 161 (77%) patients treated with either rtPA or urokinase often followed by adjunct therapy. The bleeding rate was 30%, and PTS developed in 17 of 62 (27%) patients. Based on the current available data, there seems to be no role for catheter-directed thrombolytic therapy in DVT: the long-term advantages are unclear and a high bleeding risk remains.

PULMONARY EMBOLISM

PE remains a cause of high mortality and morbidity with a mortality rate of 2-8% 3 months after diagnosis (10-12). This mortality rate depends mainly on underlying disease and hemodynamic instability. The established treatment for hemodynamically stable patients is anticoagulant therapy (unfractionated heparin or low molecular weight heparin, followed by at least 3 to 6 months of vitamin K antagonists), and has been so ever since the landmark randomized trial by Barritt and Jordan in 1960 (13). This has considerably improved survival. However, certain patients have a higher risk of adverse outcome than others, and these high-risk patients may benefit from more aggressive therapy, such as thrombolysis or embolectomy. The rationale for administering thrombolytic agents for PE is the expected faster lysis of the thrombus, resulting in faster restoration of lung perfusion, a relief of right ventricular overload and thus reducing acute mortality and preventing long term complications such as chronic pulmonary hypertension, right ventricular dysfunction and recurrence of VTE (14,15). To help identify patients in whom such an approach is advantageous, the current clinical research focus is on risk stratification. The thrombolytic agent (urokinase, streptokinase or tissue-type plasminogen activator) is usually applied systemically; evidence of catheter-directed thrombolytic therapy for acute pulmonary embolism is very scarce (16-18).

Mortality in pulmonary embolism

PE can be classified in two main categories: 1) massive PE, with a systolic blood pressure ≤ 90 mmHg or a pressure drop of ≥ 40 mmHg for at least 15 minutes; and 2) non-massive PE, where blood pressure is preserved, but right ventricular function is impaired (19). Registry data showed that the mortality rate among patients that are hemodynamically unstable at the time of presentation is higher compared to hemodynamically stable patients (12). Fortunately, massive PE is rare, representing less than 5% of patients with PE (12). In the Management Strategy and Prognosis in Pulmonary Embolism Trial (MAPPET) registry, mortality due to PE in
patients with cardiac arrest, cardiogenic shock, and arterial hypotension was 60%, 23%, and 14%, respectively (20). Mortality is considerably lower in the majority of patients presenting with normotensive PE. In these patients, the rate of cardiovascular mortality after standard treatment with coagulants varies from 1.5% to 10% during the first three months of follow up (10,21,22). This difference in mortality rate is not well understood and further risk stratification is desired.

Safety outcomes in thrombolysis

Compared with heparin, thrombolytic therapy was associated with a non-significant increase in major bleeding (9.1% versus 6.1%; OR 1.42, 95% CI 0.81 to 2.46) but a significant increase in non-major bleeding (22.7% versus 10.0%, OR 2.63, 95% CI 1.53 to 4.54) (23). Although in a recent meta-analysis the incidence of intracranial hemorrhage was not increased in the thrombolysis group (OR 1.04, 95% CI 0.36-3.04) (23), this incidence was previously reported to be 2% to 3% in registry and review data (12,24). This incidence is higher than, for instance, in myocardial infarction. Data from a Cochrane collaboration review confirmed the non-significant increase in the risks of major and non-major bleeding (25).

Efficacy of thrombolysis in massive pulmonary embolism

Due to the high mortality rates in patients with massive PE associated with cardiogenic shock, thrombolytic therapy in these patients is widely accepted, despite the lack of definitive evidence (19,26). To date, there is only one randomized controlled trial of thrombolysis in patients with massive PE, in which 8 patients were enrolled. All patients with thrombolysis survived, while all patients allocated to heparin died, and the trial was stopped prematurely by the ethics committee. Several meta-analyses assessing the efficacy and safety of thrombolytic therapy for acute PE have been carried out in the past decade, with opposite conclusions about the benefit (23,27-29). Most studies included in these analyses made no distinction between massive or non-massive PE, which makes extrapolation of the data to the two categories difficult. In a subgroup analysis of 5 trials that included patients with massive PE and shock, thrombolysis was associated with a significant reduction in recurrent PE or death compared to heparin-treated patients (Table 1). There was a trend to a higher bleeding risk in the patients treated with thrombolytic therapy in these studies. The benefit of thrombolysis was lost in the 6 trials that excluded hemodynamically unstable patients (23). Data from patients with massive PE in the International Cooperative Pulmonary Embolism Registry (ICOPER) showed no reduction in mortality (hazard ratio (HR) 0.79, 95% CI 0.44 to 1.43) or recurrence of PE (12% in both groups) at 90 days in patients receiving thrombolytic therapy compared to heparin alone (30).

In summary, the available evidence on the benefit of thrombolytic therapy for patients suffering from massive PE is scarce and inconclusive. The only randomized trial in massive PE patients consisted of only eight patients, and other studies were limited by a retrospective
character or obscured by enrolment of patients with non-massive PE. Considering the often critical clinical condition of patients with massive PE and the data from studies suggestive of better outcome, it is generally recommended that these patients should be treated with thrombolysis (19,26).

**Efficacy of thrombolysis in sub-massive pulmonary embolism**

The current debate on thrombolytic therapy for PE focuses on the controversy regarding whether there is an expansion of the indication of thrombolysis in normotensive PE patients with signs of right ventricular dysfunction (RVD), the so-called sub-massive PE. To settle this debate there are two major hurdles that need to be overcome: 1) appropriate risk-stratification to identify the subgroup of patients with a high mortality risk that could benefit from thrombolysis, using simple, rapid and non-invasive techniques; and 2) to find convincing evidence that thrombolytic therapy is indeed preferential to standard heparin treatment in these patients. First, the available evidence on outcome with thrombolytic therapy in patients with sub-massive PE will be reviewed, followed by an overview of methods in risk-stratification.

**Thrombolysis in normotensive patients**

To date, there is only one randomized controlled trial prospectively evaluating the efficacy of thrombolytic therapy in sub-massive PE (31). 256 patients with PE and pulmonary hypertension or RVD on echocardiography were assigned to alteplase plus heparin or heparin plus placebo. The primary end-point consisted of in-hospital mortality and/or clinical deterioration requiring an escalation of treatment. This endpoint occurred significantly more often in patients receiving heparin plus placebo (24.6%) compared to the patients receiving heparin plus thrombolysis (11%, p=0.006). However, this difference was mainly driven by an ‘escalation of treatment’ that more often occurred in patients with placebo, 23.2% versus 7.6%, respectively (p=0.001). This subjective aspect of the trial is debatable: physicians were permitted to break the randomization code prior to the decision to escalate treatment and it is not unlikely that thrombolysis and heparin patients were then treated differently. This, together with the relatively low prevalence of patients with RVD on echocardiography (30%), may have caused the unexpected low mortality rates found in the study (3.4% and 2.2% for alteplase and placebo patients respectively).

This trial was included in a meta-analysis, together with 5 other studies with normotensive patients alone, involving 494 patients in total (Table 1) (23). Compared with heparin, thrombolytic therapy was not associated with a reduction in death. Similar results were found in the Cochrane collaboration review (25): death rates and recurrence rates of PE were similar for thrombolytics and heparin, OR 0.89 (95% CI 0.45 to 1.78) and OR 0.63 (95% CI 0.33 to 1.20) for death rate and PE recurrence rate, respectively (no distinction massive and non-massive PE patients).
Table 1. Trials that included patients with major (hemodynamically unstable) pulmonary embolism compared with those that excluded these patients.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trials that included Patients With Major PE</th>
<th>Trials That Excluded Patients With Major PE</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thrombolysis, n/N (%)</td>
<td>Heparin, n/N (%)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Recurrent PE or death</td>
<td>12/128 (9.4)</td>
<td>24/126 (19.0)</td>
<td>0.45 (0.22-0.92)</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>5/128 (3.9)</td>
<td>9/126 (7.1)</td>
<td>0.61 (0.23-1.62)</td>
</tr>
<tr>
<td>Death</td>
<td>8/128 (6.2)</td>
<td>16/126 (12.7)</td>
<td>0.47 (0.20-1.10)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>28/128 (21.9)</td>
<td>15/126 (11.9)</td>
<td>1.98 (1.00-3.92)</td>
</tr>
</tbody>
</table>

It is clear that based on the current available data, there is no evidence that thrombolysis has a benefit over standard anticoagulant treatment in patients with sub-massive PE. Next to the limited available data, mortality rates in these patients are probably not high enough to counterbalance the increased bleeding risk. More research is needed to better identify the subgroup of patients with non-massive PE in whom the risk-benefit ratio is most favourable. This issue must be addressed before advocating thrombolytic treatment to patients with sub-massive PE.

**RISK STRATIFICATION**

Several tools have been investigated to identify normotensive patients with acute PE who are at high-risk of adverse outcome. A diagnostic test with a high positive predictive value for adverse outcomes can be useful in the decision to initiate thrombolytic therapy. A limitation to the comparison of these tools is that most studies have been carried out including both hemodynamically stable and unstable patients and do not allow for a separate analysis. A summary of characteristics of several diagnostic methods are listed in Table 2.

**Imaging techniques for risk stratification**

Echocardiography has been the classical way to assess right ventricle dysfunction. Unfortunately, the literature is hampered by the various criteria used to assess RVD using this imaging technique. RVD was found to be an independent predictor of mortality (32).

Based on the available data, there is little doubt that echocardiographically assessed RVD in patients with PE is a predictor of mortality. There are, however, several drawbacks to this method of risk-stratification, such as practical problems in the need for experienced personnel on an around-the-clock-basis.

Alternatively, computed tomography (CT) has been investigated to diagnose RVD. Criteria and consequently prevalence of RVD varies widely, ranging from 22% when high cut-off values were used to 70% in studies using a low cut-off (33). The positive predictive value of mortality is low, while absence of RVD on a CT-scan indicates a benign outcome (34,35). Due to the practical drawbacks of echocardiography and the fact that CT is becoming the preferred diagnostic imaging technique, assessing RVD with multidetector CT would be more suitable for clinical practice. The literature suggests that CT could be a reasonable alternative. However, risk-stratification using CT currently has limitations as well and further research in normotensive patients is desirable. Finally, studies that directly compare clinical outcome in patients with acute PE and RVD on echocardiography and CT are lacking.

**Biomarkers for risk stratification**

Recently, cardiac biomarkers have been evaluated as stratification tools. Brain natriuretic peptide (BNP), proBNP, as well as troponins I and T were all associated with an increased risk of
<table>
<thead>
<tr>
<th>Stratification tool</th>
<th>Predictive values*</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>RVD on echocardiography (15,22,32,33)</td>
<td>- Prevalence 27-40% - PPV4-9% - HR 1.94, 95% CI 1.23-3.06</td>
<td>- Independent predictor of mortality - Large experience in diagnosing RVD</td>
<td>- Lack of standardized criteria - Logistical problems - High costs</td>
</tr>
<tr>
<td>RVD on CT (33,34)</td>
<td>- Prevalence 22-70%† - PPV: ~10%† - NPV: 100%†</td>
<td>- CT preferred diagnostic imaging technique for PE - Available in most hospitals</td>
<td>- Lack of standardized criteria - Lack of data on prevalence and predictive value in normotensive patients</td>
</tr>
<tr>
<td>Troponin (I or T) (36,37)</td>
<td>- Prevalence: 21% - PPV: 1.8% - OR 5.9, 95% CI 2.68-12.95 - NPV: &gt;93%</td>
<td>- Easy to perform - Rapidly available in most hospitals</td>
<td>- Lack of standardized cut-off values - Cardiac marker, not specific for RVD</td>
</tr>
<tr>
<td>BNP or pro-BNP (36,49)</td>
<td>- PPV: 17% - NPV: &gt;93%</td>
<td>- Easy to perform - Rapidly available in most hospitals</td>
<td>- Lack of standardized cut-off values - Not an independent predictor of mortality - Cardiac marker, not specific for RVD</td>
</tr>
<tr>
<td>BNP plus Troponin (40,42)</td>
<td>- Prevalence: 20% - PPV: 30% - NPV: 100%</td>
<td>- Easy to perform - Rapidly available in most hospitals</td>
<td>- Cardiac markers, not specific for RVD - Lack of standardized cut-off values</td>
</tr>
<tr>
<td>BNP plus echocardiography (39)</td>
<td>- Prevalence 24%‡ - PPV: 17%‡ - OR 12.2, 95% CI 2.5-60.3‡</td>
<td>- Possible additive prognostic value of combination</td>
<td>- Practical drawbacks of echo - No exact data on prognostic value in normotensive patients</td>
</tr>
<tr>
<td>Troponin plus echocardiography (39)</td>
<td>- Prevalence: 15%‡ - PPV: ~19%‡ - OR 10.0, 95% CI 2.1-46.8‡ - HR 5.6, 95% CI 1.2-25.9</td>
<td>- Additive prognostic value compared to echo or troponin alone</td>
<td>- Practical drawbacks of echo - No exact data on prognostic value in normotensive patients</td>
</tr>
</tbody>
</table>

RVD, right ventricular dysfunction; PPV, positive predictive value; CT, computed tomography; PE, pulmonary embolism; NPV, negative predictive value; BNP, brain natriuretic peptide; OR, odds ratio; HR, hazard rate. *Data from studies including normotensive patients with PE only or separate analyses possible, unless stated otherwise. †N-terminal proBNP was used, hypotensive and normotensive patients with PE combined, OR for complicated in-hospital course. ‡Hypotensive and normotensive patients with PE combined.
death in patients with PE (36,37). Like imaging techniques, these biomarkers have advantages and drawbacks in risk-stratification. Many different cut-off values are used, which makes it difficult to compare results between studies. According to a recent meta-analysis including normotensive patients, the prevalence of elevated serum troponin levels was 21%, and the OR for mortality of high serum troponin levels was 5.9 (95% CI 2.68 to 12.95) (37). For BNP, no meta-analysis is available. Several trials reported that BNP elevation alone was not an independent predictor of mortality or in-hospital complications, but low plasma BNP levels predict benign clinical course in patients with acute PE (38-41). The combination of troponin and BNP has also been evaluated (40,42). However, without the use of an imaging method such as echocardiography, it is not certain if elevated biomarkers are due to PE or another cause, such as (cardiac) ischemia or dysfunction of the left ventricle. Furthermore, cut-off values in the studies evaluating the use of biomarkers vary and were often determined retrospectively.

If biomarkers and managing techniques alone are insufficient to identify high risk non-massive PE patients, how about the combination of these two? Both elevated N-terminal (NT)-proBNP and elevated troponin combined with RVD on echocardiography were associated with an increased risk of adverse outcome in the acute phase of PE (39,43,44). For the combination of troponin and RVD on echo, very high positive predictive values (75%) have been reported, but these rely heavily on mortality in hypotensive patients included in the studies (43). Nonetheless, troponin and echocardiography are independent prognostic factors with an additive prognostive value (37).

Although more research is needed, combinations of risk-stratification tools look promising. They are able to refine the selection of patients with additive prognostic value in risk stratification. Studies investigating the combination of CT-diagnosed RVD with biomarkers are in progress.

**THROMBOLYSIS IN NORMOTENSIVE PATIENTS WITH PE AFTER RISK-STRATIFICATION**

The risk-stratification tools previously discussed are all predictors of mortality or adverse outcome in patients with acute PE. However, the prevalence of identified patients with these diagnostic tools is relatively high, while the positive predictive value for adverse outcome is relatively low. For example, in a theoretical pool of 1000 normotensive patients with PE, biomarkers or assessment of RVD will identify 400 patients with a potentially adverse outcome (prevalence 40%), but only 20 patients will eventually develop an adverse event (positive predictive value 5%). These last patients could benefit from thrombolytic treatment. However, 380 patients in this hypothetical situation have been falsely identified as high-risk patients and would unnecessarily be exposed to a higher risk of bleeding. By introducing biomarkers, such as troponin, to the diagnostic algorithm with echocardiography or CT, the number of patients
falsely identified as having a high-risk of adverse outcome is likely to decrease due to a lower prevalence and higher positive predictive value. The question remains whether this refining is sensitive enough for a favorable risk/benefit ratio.

At this moment, few studies have focused on risk-stratification in normotensive patients with PE alone and the efficacy of thrombolysis in these patients is uncertain. While advocates of more aggressive treatment point towards RVD as a predictor of death and adverse outcome, and emphasize the ability of thrombolytic treatment to improve the function of the right ventricle (45,46), the more skeptical contributors to the debate stress the lack of evidence of a benefit of thrombolytic treatment and the low predictive value of present methods of risk-stratification (47,48).

Once a high-risk patient group is defined and the benefit of thrombolytic therapy is demonstrated in this group in a large-scale adequately designed trial, thrombolytic therapy will be preferential to heparin alone in these patients. At the moment, and even before risk-stratification is optimized, this long desired trial is ready to start. Hopefully, with the results of this trial, we will be one step closer to settling the debate. Until this time, however, thrombolytic therapy should only be considered in patients with signs of massive PE with hemodynamic shock.

**REFERENCE LIST**