The effect of fibrinolytic therapy on 30-day outcome in patients with intermediate risk pulmonary embolism – propensity score-adjusted analysis

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INTRODUCTION

Patients with submassive or intermediate-risk pulmonary embolism (PE) represent a very heterogeneous group, whose therapeutic strategy still questions whether some groups of patients would have net clinical benefit from fibrinolytic therapy (FT).

In the institutional pulmonary embolism registry, 116 patients with submassive PE were identified, and the relation of their outcome to FT was analyzed using the propensity score (PS) adjustment. The primary endpoint was the composite of death, in-hospital cardiopulmonary deterioration, or recurrence of PE. Safety outcomes were updated TIMI non-CABG related major and minor bleeding.

According to Cox regression analysis, the incidence of composite endpoint was significantly lower in patients treated with FT compared to anticoagulant therapy (AT) only (PS adjusted HR 0.22; 95% CI 0.05–0.89; p = 0.039). But, when patients were stratified into four PS quartiles, only patients in the highest PS quartile that received fibrinolysis, had significantly lower composite event rate than patients treated with AT (HR 0.20; 95% CI 0.01–0.56; p = 0.016). The overall mortality of the study group was 5.2% and there was no significant difference between the treatment groups. Total bleeding was significantly more frequent in FT patients (HR 3.07; 95% CI 1.02–13.29; p = 0.047), but not the major one.

Conclusion: The use of FT was associated with a better outcome compared to AT in patients with submassive PE, but the benefit was mainly driven from those with highest values of PS, i.e. with the highest baseline risk. The rate of major bleeding was not significantly increased by FT.

Keywords: pulmonary embolism; intermediate risk; fibrinolytic therapy; propensity score

SUMMARY

Introduction/Objective: Patients with submassive (intermediate risk) pulmonary embolism (PE) represent a very heterogeneous group, whose therapeutic strategy still questions whether some groups of patients would have net clinical benefit from fibrinolytic therapy (FT).

Methods: From the institutional pulmonary embolism registry, 116 patients with submassive PE were identified, and the relation of their outcome to FT was analyzed using the propensity score (PS) adjustment. The primary endpoint was the composite of death, in-hospital cardiopulmonary deterioration, or recurrence of PE. Safety outcomes were updated TIMI non-CABG related major and minor bleeding.

Results: According to Cox regression analysis, the incidence of composite endpoint was significantly lower in patients treated with FT compared to anticoagulant therapy (AT) only (PS adjusted HR 0.22; 95% CI 0.05–0.89; p = 0.039). But, when patients were stratified into four PS quartiles, only patients in the highest PS quartile that received fibrinolysis, had significantly lower composite event rate than patients treated with AT (HR 0.20; 95% CI 0.01–0.56; p = 0.016). The overall mortality of the study group was 5.2% and there was no significant difference between the treatment groups. Total bleeding was significantly more frequent in FT patients (HR 3.07; 95% CI 1.02–13.29; p = 0.047), but not the major one.

Conclusion: The use of FT was associated with a better outcome compared to AT in patients with submassive PE, but the benefit was mainly driven from those with highest values of PS, i.e. with the highest baseline risk. The rate of major bleeding was not significantly increased by FT.

Keywords: pulmonary embolism; intermediate risk; fibrinolytic therapy; propensity score

INTRODUCTION

Patients with submassive or intermediate-risk pulmonary embolism (PE) represent a very heterogeneous group with large variations, both in terms of presentation and prognosis [1, 2]. According to large older registries, Management Strategy and Prognosis of Pulmonary Embolism Registry and International Cooperative Pulmonary Embolism Registry (ICOPER), their mortality ranged 9.6–15.1% [3, 4] and according to recent meta-analysis of randomized trials and newer the Computerized Registry of Patients with Venous Thromboembolism (RIE-TE) registry data 2–5% [5, 6, 7]. Despite the fact that clinical scores do predict adverse outcomes in acute PE [8, 9] and that hybrid studies demonstrate that combinations of right ventricular (RV) dysfunction and elevated biomarkers indicate adverse prognosis [10, 11], still management of submassive PE crosses the zone of equipoise [1]. The latest European guidelines are more precise, in terms of not recommending routine use of primary systemic thrombolysis in patients not suffering from shock or hypotension, but on the other hand, they strongly suggest close monitoring in patients with intermediate-high risk PE to permit early detection of hemodynamic decompensation or circulatory collapse, and timely initiation of rescue reperfusion therapy. In addition, set-up of multidisciplinary teams for management of selected cases of intermediate-risk PE should be considered [2].

Although no study has yet shown clear benefits of fibrinolytic therapy (FT) in terms of overall survival in patients with intermediate-risk PE, there are data indicating beneficial effects on other important short and long-term outcomes [12, 13, 14]. Randomized, prospective studies have found beneficial effect of FT on clinical outcomes, although in the largest one, at the expense of increased risk of major and intracranial bleeding [15, 16, 17]. Therefore, the main unresolved issue remains whether specific group of patients with intermediate risk PE would profit from FT, without increasing the risk of serious adverse events.

The ideal design of the study investigating treatment effects implies random allocation of patients to different types of therapy. However, these studies may have limited applicability, and their conclusions often correspond less to everyday clinical practice than those from
observational, registry studies. On the other hand, registry data usually have significant baseline between-group differences in observed covariates, which need to be adjusted by adequate statistical methods. Therefore, based on clinical and echocardiographic criteria, we designed this observational registry study, in order to investigate the propensity score-adjusted association of FT and 30-days outcome in patients with acute submassive/intermediate risk PE.

METHODS

This is a single center, investigator initiated, observational cohort study, conducted in a tertiary, academic teaching hospital, from January 2011 to May 2014. The diagnosis of acute submassive/intermediate risk PE was made as follows: typical symptoms and signs of PE lasting no more than seven days, without systemic hypotension at the admission (i.e. with systolic blood pressure > 90 mmHg and absence of a drop of systolic blood pressure by ≥ 40 mmHg compared to standard values, lasting > 15 minutes), but with RV dysfunction confirmed by echocardiography. The criteria for RV dysfunction were [18]:
1. RV end-diastolic diameter > 3 cm in parasternal long axis and right/left ventricular end-diastolic diameter ratio > 0.6 (both in the absence of RV hypertrophy);
2. hypokinesia of RV-free wall in any view and/or Mc Connell sign;
3. tricuspid regurgitant jet velocity 2.5–3.5 m/s in the absence of inferior vena cava collapse on inspiration and/or estimated RV systolic pressure 40–60 mmHg. Patients had to fulfill at least one from each of three above-mentioned criteria. The diagnosis of PE was confirmed either by multidetector computed tomography scan, when available (n = 68), or by ventilation/perfusion mismatch on lung scintigraphy scan (n = 48). Contraindications to fibrinolysis were any prior intracranial hemorrhage, known structural or malignant intracranial disease, ischemic stroke within six months, gastrointestinal bleeding within the last month, uncontrolled hypertension (systolic blood pressure > 180 mmHg), any active bleeding, or known bleeding diathesis, recent major trauma/surgery/head injury in the preceding three weeks.

The study protocol was approved by the University of Belgrade, Faculty of Medicine Ethical Committee and done in accordance with the legal standards. Since we used routine data registry, written informed consent was not required, but all patients gave an oral informed consent for the use of their unidentified data and follow-up participation.

Study protocol

All patients included in the study received an intravenous bolus of unfractionated heparin (80 U/kg) and underwent immediate clinical, ECG, echocardiographic, arterial blood gas and D-dimer evaluation, in addition to standard laboratory analysis. Cardiac troponin I (when available) was measured using micro particle enzyme immunoassay – MEIA kit (Abbott Laboratories) and the reference value was < 0.04 ng/mL. Since at the study time, no prognostic score was officially recommended, all further decisions concerning the treatment were made at the discretion of the clinician caring for each patient. If the decision was made for FT, Food and Drug Administration approved protocol for alteplase was applied (10-mg iv bolus, followed by a 90-mg intravenous infusion over a period of two hours), followed by an intravenous infusion of unfractionated heparin after getting an activated partial-thromboplastin time (aPTT) < 70 sec. If the decision was made for anticoagulant therapy only, the infusion of unfractionated heparin was started at a rate of 18 U/kg/h, and the rate was subsequently adjusted to maintain the aPTT at 1.5–2 times the control. Measurements of the aPTT were performed at six-hour intervals on day one and two and at 12-hour intervals thereafter. Overlapping with oral anticoagulant therapy started on hospital day three and was maintained until a therapeutic range of the international normalized ratio (INR 2.5–3) was stable for two days. Patients were examined for symptoms, blood pressure, and heart rate every six hours for the first 48 hours, then every 12 hours until clinical stabilization, and daily up to discharge; Sat O₂ was continuously monitored for the first 48 hours. All patients had complete blood count and fibrinogen concentration measured at enrollment and daily until discharge. On each day, every patient was examined for the occurrence of any bleeding episodes. During hospitalization, color-Doppler scan of the inferior limbs’ deep veins was also performed in all the patients.

Outcomes

Primary outcome of the study was the composite of death, cardiopulmonary deterioration, or recurrence of PE (non-fatal) within 30 days of presentation. Cardiopulmonary deterioration was defined as:
1. the need for cardiopulmonary resuscitation or any spontaneous episode of hypotension (drop of systolic blood pressure below 20 mmHg compared to the admission value) with signs of end-organ hypoperfusion;
2. respiratory failure (worsening dyspnea with drop of arterial oxyhemoglobin saturation level below 90%).

Confirmation of recurrent PE was done by appearance of a new perfusion defect by lung scan or multidetector computed tomography in patients having symptoms and signs of recurrent PE attack. Safety outcomes were updated TIMI non-CABG related major and minor bleeding [19].

Statistical analysis

Continuous variables were expressed as means ± standard deviation or medians with interquartile ranges, depending on their type of distribution, examined by Kolmogorov–Smirnov test. Logistic regression analysis was used for unadjusted (univariate) comparisons of baseline demographic, clinical, electrocardiographic, echocardiographic, and
biochemical characteristics between two groups (patients receiving FT vs. patients with anticoagulant therapy only). To control for baseline differences in observed covariates between groups, a propensity score-based approach was applied [20, 21]. We estimated the odds ratios (ORs) of receiving thrombolysis by fitting separate invariable logistic regression models, with each individual covariate as the independent variable. Variables with p-value ≤ 0.1 were selected, and further tested for mutual correlation (Pearson or Spearman correlation, depending on their type of distribution). For those variables with significant and high (> 0.7) correlation, only one was used for building a multiple logistic regression model, that finally gave predicted probabilities (propensity scores) for each patient to receive FT. In order to evaluate the association of FT and 30-days outcomes, propensity score-adjusted Cox regression analysis was performed. Finally, predefined sub-group analysis of patients stratified into four risk groups, according to their PS values (PS quartiles) was done (highest PS quartile – highest risk). For each group, Cox regression analysis was performed, in order to assess the potential heterogeneity of fibrinolytic treatment impact on primary endpoint. Kaplan–Meier method was used to present difference in event-free survival curves of treatment groups in PS quartiles. For all analyses, p-value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS software Version 15.0 for Windows (SPSS, Inc., Chicago, IL, USA).

RESULTS

Study population

From the institutional PE registry, 314 patients with acute PE were identified. Sixty-two of them (19.7%) had massive/high risk PE; 120 (38.3%) patients had submassive/intermediate risk PE (in 116 of them, being the first episode of PE), and 132 (42%) patients had non-massive/low risk PE. In all 116 patients included in the study, the post-hoc calculation of simplified PESI score was ≥ 1. Baseline characteristics of the study patients, according to treatment groups, are presented in Table 1. At the beginning of the study, troponin was not routinely measured, so values for the first 35 patients were not available. Analysis of the rest 81 patients showed that patients in the highest PS quartile had significantly higher values of cardiac troponin I compared to those in lower quartiles (quartile IV (1.64 ± 1.10 ng/mL) vs. quartiles I (0.15 ± 0.08 ng/mL) and II (0.17 ± 0.10 ng/mL) – p < 0.01; quartile IV vs. quartile III (1.02 ± 0.91 ng/mL), p = 0.08).

Treatment

Fibrinolytic therapy was given to 25/116 (21.5%) patients with intermediate risk PE, and only anticoagulant therapy to 91/116 (78.5%) patients. Patients who received thrombolysis had higher incidence of cyanosis at the admission, as well as higher respiration rate, greater end-diastolic diameter of the right ventricle, higher D-dimer values and lower Sat O₂ level. Propensity score was constructed as previously described, and included following variables in multiple logistic regression model: respiration rate, cyanosis, D-dimer value, and Sat O₂ level. After PS-adjustment, treatment groups did not differ in observed covariates (Table 1).

Outcomes

During the first 30 days after admission, primary composite clinical endpoint occurred in 18/116 (15.5%) patients; in 3/25 patients (12%) treated with thrombolysis, and in 15/91 patients (16.5%) treated with heparin only. According to PS-adjusted Cox regression analysis, the rate of primary composite endpoint was significantly lower in patients treated with FT compared to those treated with heparin only (PS-adjusted HR 0.22; 95% CI, 0.05–0.89; p = 0.039) (Table 2). After risk stratification of patients into quartiles according to their PS values, predefined sub-group Cox analysis showed that only patients in the highest PS quartile that received thrombolysis, had significantly lower primary composite event rate compared to patients treated with heparin only (13.3% vs. 50%; HR 0.20; 95% CI 0.01–0.56; p = 0.016) (Table 3). Figure 1 shows Kaplan–Meier analysis of event free survival between two treatment groups in the highest risk (PS) quartile. The overall mortality was 5.2%. Individual events did not differ significantly between treatment groups (Table 2).

Total bleeding rate was higher in patients who received thrombolysis (12%, vs. 5.5% in the anticoagulant therapy group; PS-adjusted HR 3.07; 95% CI 1.02–13.29; p = 0.047). Major bleeding rate was similar in both groups (4% vs. 2.3%, p = 0.643) (Table 2); one patient (in the fibrinolytic group) had non-fatal intracranial bleeding, and no patient had fatal bleeding.

DISCUSSION

The main findings of our study are:

1. Fibrinolytic therapy was associated with lower 30-days PS-adjusted rate of primary composite endpoint (death, cardiopulmonary deterioration, or PE recurrence) in patients with intermediate-risk PE;
2. The observed reduction in primary composite endpoint rate was largely driven by reduction of events in patients with the highest baseline risk (i.e. in patients within the highest PS quartile);
3. Bleeding was more frequent in patients receiving thrombolysis, but not a major or a fatal one.

Our study population was homogenous in terms of the uniform definition of intermediate-risk PE at admission, which was further confirmed by Simplified Pulmonary Embolism Severity Index score ≥ 1 for all patients. Nevertheless, we observed a large heterogeneity in terms of a wide range of important parameters like respiration rate, incidence of cyanosis, D-dimer values, and Sat O₂ level (Table 1), which eventually influenced therapy decision.
Table 1. Baseline characteristics and their unadjusted and propensity score (PS) adjusted comparison between treatment groups

| Variable                                      | Heparin (n = 91) | Thrombolysis (n = 25) | Unadjusted OR (95% CI) | Unadjusted p | PS-adjusted OR (95% CI) | PS-adjusted p |
|-----------------------------------------------|------------------|-----------------------|------------------------|--------------|------------------------|--------------|
| Demographics                                  |                  |                       |                        |              |                        |              |
| Age (years), X ± SD                          | 61 ± 11          | 59 ± 17               | 1.01 (0.98–1.04)       | 0.576        | 1.01 (0.97–1.05)       | 0.613        |
| Sex (male) %                                  | 41.7             | 39.1                  | 1.07 (0.43–2.70)       | 0.881        | 1.31 (0.43–3.97)       | 0.630        |
| Previous or concomitant disease               |                  |                       |                        |              |                        |              |
| Previous surgery, %                           | 29.7             | 26.1                  | 0.84 (0.29–2.35)       | 0.735        | 0.78 (0.25–2.57)       | 0.704        |
| Previous immobilization, %                    | 10.1             | 17.4                  | 1.71 (0.48–6.03)       | 0.407        | 3.26 (0.76–13.88)      | 0.110        |
| Chronic cardiopulmonary disease, %           | 21.9             | 26.1                  | 1.25 (0.44–3.59)       | 0.675        | 1.82 (0.52–6.36)       | 0.349        |
| History of cancer, %                          | 12.1             | 13                    | 0.90 (0.23–3.46)       | 0.878        | 0.66 (0.11–3.85)       | 0.642        |
| Symptoms                                      |                  |                       |                        |              |                        |              |
| Dyspnea, %                                    | 90.1             | 95.6                  | 2.41 (0.29–20.09)      | 0.415        | 0.70 (0.07–6.55)       | 0.758        |
| Pleural pain, %                               | 29.5             | 27.8                  | 0.94 (0.37–2.34)       | 0.889        | 1.28 (0.43–3.79)       | 0.661        |
| Syncope, %                                    | 17.3             | 19.7                  | 1.53 (0.49–4.79)       | 0.467        | 1.67 (0.45–6.21)       | 0.447        |
| Palpitations, %                               | 21.9             | 26.1                  | 1.25 (0.44–3.59)       | 0.675        | 1.51 (0.44–5.14)       | 0.510        |
| Signs                                         |                  |                       |                        |              |                        |              |
| Cyanosis, %                                   | 7.7              | 30.4                  | 3.62 (1.12–11.02)      | **0.031**    | 0.44 (0.08–2.47)       | 0.349        |
| SAP (mm Hg), X ± SD                           | 126.1 ± 21       | 127.5 ± 23.4          | 0.99 (0.97–1.02)       | 0.847        | 1.01 (0.99–1.04)       | 0.391        |
| DAP (mm Hg), X ± SD                           | 80.4 ± 12.1      | 85.5 ± 19.8           | 1.09 (0.97–1.04)       | 0.865        | 1.02 (0.98–1.06)       | 0.319        |
| Heart rate, X ± SD                            | 103.1 ± 20.5     | 107.1 ± 22.4          | 1.01 (0.98–1.03)       | 0.340        | 0.98 (0.95–1.01)       | 0.184        |
| Respiration rate, med (IQR)                   | 21 (15, 26)      | 30 (24, 32)           | 1.14 (1.04–1.24)       | **0.004**    | 1.03 (0.92–1.14)       | 0.629        |
| Right S3, %                                   | 23.1             | 43.5                  | 2.56 (0.98–6.68)       | 0.054        | 0.64 (0.17–2.43)       | 0.510        |
| Signs of DVT, %                               | 71.6             | 78.2                  | 1.22 (0.45–3.33)       | 0.796        | 1.11 (0.33–3.71)       | 0.869        |
| Electrocardiographic                          |                  |                       |                        |              |                        |              |
| S1Q3T3, %                                     | 58.2             | 52.2                  | 0.78 (0.31–1.96)       | 0.600        | 0.39 (0.12–1.24)       | 0.111        |
| New RBBB, %                                   | 13.1             | 13                    | 0.99 (0.25–3.83)       | 0.986        | 0.84 (0.18–3.96)       | 0.830        |
| Negative T in V1-V3, %                        | 25.2             | 39.1                  | 1.90 (0.73–4.97)       | 0.191        | 2.27 (0.73–7.05)       | 0.155        |
| Echocardiographic                             |                  |                       |                        |              |                        |              |
| EDDRV (cm), X ± SD                            | 3.2 ± 0.45       | 3.5 ± 0.5             | 3.01 (1.09–8.29)       | **0.033**    | 1.69 (0.53–5.38)       | 0.376        |
| EDRV/EDLV, X ± SD                             | 0.8 ± 0.2        | 0.9 ± 0.2             | 0.88 (0.03–28.38)      | 0.578        | 0.18 (0.01–12.08)      | 0.427        |
| RVSP (mmHg), X ± SD                           | 45.4 ± 18.5      | 50.2 ± 15.5           | 1.01 (0.98–1.05)       | 0.488        | 0.99 (0.96–1.04)       | 0.881        |
| Mc Connell sign, %                            | 76.9             | 91.3                  | 1.56 (0.32–7.59)       | 0.581        | 0.90 (0.18–5.01)       | 0.904        |
| Laboratory                                    |                  |                       |                        |              |                        |              |
| D-dimer (ng/mL), X ± SD                       | 1647 ± 1524      | 2690 ± 2152           | 1.69 (1.11–2.57)       | **0.014**    | 1.18 (0.72–1.71)       | 0.514        |
| pO2 (kPa), X ± SD                             | 8.3 ± 1.9        | 8 ± 3.8               | 1.11 (0.82–1.51)       | 0.505        | 1.22 (0.83–1.79)       | 0.311        |
| Sat O2 (%), X ± SD                            | 89.1 ± 5         | 83.1 ± 7              | 0.87 (0.80–0.95)       | **0.002**    | 0.98 (0.88–1.09)       | 0.708        |

SAP – systolic arterial pressure; DAP – diastolic arterial pressure; DVT – deep vein thrombosis; RBBB – right bundle branch block; EDDRV – end-diastolic dimension of the right ventricle; EDDLV – end-diastolic dimension of the left ventricle; RVSP – right ventricular systolic pressure; Sat O2 – arterial oxyhemoglobin saturation level

Table 2. Propensity score-adjusted comparison of 30-days clinical outcomes in the two treatment groups

| Parameters                                      | Heparin (n = 91) | Thrombolysis (n = 25) | PS-adjusted HR (95% CI) for thrombolysis | PS-adjusted p |
|------------------------------------------------|------------------|-----------------------|-----------------------------------------|--------------|
| Primary composite endpoint                      | 15 (16.5%)       | 3 (12%)               | 0.22 (0.05–0.89)                        | 0.039        |
| Death                                           | 5 (5.5%)         | 1 (4%)                | 0.32 (0.03–3.58)                        | 0.352        |
| CP deterioration*†                               | 6 (6.6%)         | 1 (4%)                | 0.25 (0.01–1.66)                        | 0.123        |
| Pulmonary embolism recurrence*                 | 4 (4.4%)         | 1 (4%)                | 0.71 (0.06–9.06)                        | 0.795        |
| Bleeding (total)                                | 5 (5.5%)         | 3 (12%)               | 3.07 (1.02–13.29)                       | 0.047        |
| Major                                           | 2 (2.2%)         | 1 (4%)                | 1.93 (0.46–26.37)                       | 0.643        |
| Minor                                           | 3 (3.3%)         | 2 (8%)                | 3.54 (1.41–16.34)                       | 0.049        |

*Non fatal; †not related to pulmonary embolism recurrence
Obviously, patients who received FT were “sicker,” according to significantly higher values of previously mentioned variables, as well as larger end-diastolic diameter of the right ventricle. Propensity score values were calculated as a chance of receiving thrombolysis for every patient, therefore representing their baseline risk of adverse outcome (highest quartile – highest risk). This was confirmed by the incidence of primary endpoint in different PS quartiles, being 0% in the first, 13.8% in the second, 17.2% in the third, and 31% in the fourth quartile. Similar rate of an adverse 30-days outcome (29.2%) for patients in the highest-risk stratum was found by Bova et al. [22], using a new prognostic model on the basis of four simple variables, in order to ameliorate stratification of patients with intermediate-risk PE.

The benefit of FT in our study was mainly driven by the reduction of events in patients within the highest PS quartile, i.e. with the highest baseline risk, depicted in variables that constituted PS (respiration rate, cyanosis, D-dimer value, and Sat O2 level). In addition, patients in the highest PS quartile had significantly higher values of cardiac troponin I compared to quartiles I and II, which further supports their higher risk. In such subset of patients, waiting for hemodynamic deterioration to occur could be dangerous, since it can abruptly progress to shock or need for cardiopulmonary resuscitation, which puts them in a significantly higher risk of death and probably less effective “rescue thrombolysis” [23, 24, 25]. Therefore, Kearon et al. [26], in the CHEST guidelines, propose that in patients without hypotension, deterioration in markers such as increased heart rate, a decrease in systolic BP (which remains > 90 mmHg), worsening gas exchange, progressive right heart dysfunction on echocardiography, or an increase in cardiac biomarkers, may also prompt the use of FT. In the remaining three PS quartiles of patients in our study, 11.5% of patients received FT, without any clinical benefit. This confirms the statement that FT should not be considered for less severe forms of intermediate-risk PE.

As expected, total bleeding was more frequent in patients who received thrombolysis; but no major bleeding occurred. Several meta-analyses have evaluated the bleeding risk of FT in intermediate risk PE, most of them showing significant association with major or intracranial bleeding [5, 6, 27, 28]. However, the subgroup analysis based on the type of fibrinolytic agent, by Marti et al. [6], suggested a higher risk for both major and fatal or intracranial hemorrhage in patients treated by tenecteplase compared to those treated with alteplase. The absence of significant difference in major bleeding in our study could probably be a result of the following facts:

1. the mean age of the thrombolyzed patients was 59 years (of note, only two patients in that group were over 70 and one of them had non-fatal intracranial bleeding);
2. we used alteplase;
3. heparin was withheld during the alteplase infusion and started after optimal aPTT was obtained;
4. before the initiation of FT meticulous bleeding risk evaluation was done.

Still, the safety issue should be interpreted cautiously, because of the limited sample size, as well as the fact that major bleeding rate in patients with fibrinolysis was almost twice of that with anticoagulant therapy only (though not reaching statistical significance).

Although not designed to evaluate risk stratification, our results support the statement that current risk stratification scheme needs further improvement for intermediate-risk PE.

| PS quartiles | Therapy | Number of patients | Number of events (%) | PS-adjusted HR (95% CI) for thrombolysis | PS-adjusted p |
|--------------|---------|--------------------|----------------------|------------------------------------------|---------------|
| I (≤ 0.030)  | Heparin | 28                 | 0                    | NA                                       | NA            |
|              | Thrombolysis | 1                  | 0                    |                                          |               |
|              | Overall    | 29                 | 0                    |                                          |               |
| II (0.031–0.089) | Heparin | 26                 | 4 (15.4)             | NA                                       | NA            |
|              | Thrombolysis | 3                  | 0                    |                                          |               |
|              | Overall    | 29                 | 4 (13.8)             |                                          |               |
| III (0.090–0.227) | Heparin | 23                 | 4 (17.4)             | 1.03 (0.11–9.22)                         | 0.982         |
|              | Thrombolysis | 6                  | 1 (16.7)             |                                          |               |
|              | Overall    | 29                 | 5 (17.2)             |                                          |               |
| IV (> 0.227) | Heparin | 14                 | 7 (50)               | 0.20 (0.01–0.56)                         | 0.016         |
|              | Thrombolysis | 15                  | 2 (13.3)             |                                          |               |
|              | Overall    | 29                 | 9 (31)               |                                          |               |

Table 3. Distribution of primary composite events in treatment groups across propensity score quartiles

Figure 1. Kaplan–Meier curves of event-free survival in patients in the highest propensity score quartile, according to therapy

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risk group of patients, in order to optimize better identification of candidates for reperfusion treatment [2, 29]. Further potential benefit could eventually be accomplished by development and incorporation of a new major/intracranial bleeding risk score in PE, like the PE-CH score, proposed by Chatterjee et al. [30].

**Study limitations**

First, since our study was performed in a single-center acute cardiac care unit, on a relatively small number of patients, selection bias may exist. Second, due to non-randomized allocation of FT, in spite of using PS-adjustment, we could not control for non-observed covariates. Third, patients in our study (especially those who received FT) were younger than in other cohort/registry studies, which makes the extrapolation of the results uncertain. Therefore, our results should prospectively be validated in a larger, randomized trial.

**CONCLUSION**

We demonstrated that the use of FT was associated with better outcome compared to anticoagulant therapy in patients with the highest baseline risk among submassive/intermediate risk PE patients. Although FT increased the incidence of total bleeding events, the rate of major bleeding in our study was not significantly higher in these patients; still, one patient who received fibrinolysis had non-fatal intracranial bleeding.

**NOTE**

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**Conflict of interest:** None declared.

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Утицај фибрилолитичке терапије на 30-дневни исход болесника са средњеризичном плућном емболијом – анализа прилагођен „пропензити скором”

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САЖЕТАК
Увод/Циљ Болесници са субмасивном (средњеризичном) плућном емболијом (ПЕ) представљају веома хетерогену групу и код њих још увек постоји дилема у вези са укупном терапијском користи од фибринолитичке терапије (ФТ) у односу на лечење хепарином, код одређених болесника.

Методе Из институционалног регистра плућних емболија идентификовано је 116 болесника са субмасивном ПЕ и анализиран је исход тих болесника у односу на примену ФТ коришћењем пропензити скора (ПС), који је представљао шансу сваког болесника да добије ФТ. Примарни циљ је био композитни догађај – смрт, интрахоспитално кардиопулмонално погоштање и рецидив ПЕ. Безбедносни исходи су били ревидирана TIMI non-CABG related велика и мала крварења.

Резултати Коксовом регресном анализом добијена је значајно нижа учесталост композитног циља код болесника лечених ФТ у односу на оне лечени хепарином (ПС прилагођен HR 0,22; 95% CI 0,5–0,89; p = 0,039). Али, када су болесници стратификовани у четири групе, на основу ПС квартила, само болесници из највишег ПС квартила лечени ФТ имали су значајно ређи композитни циљ у односу на оне лечени хепарином (HR 0,20; 95% CI 0,01–0,56; p = 0,016). Укупни морталитет посматране групе је био 5,2% и није било значајне разлике међу групама. Укупна крварења су била чешћа у фибринолитичкој групи (HR 3,07; 95% CI 1,02–13,29; p = 0,047), али не и велика крварења.

Закључак Примена ФТ била је удружене са бољим исходом у односу на лечење хепарином, али је корист доминантно добијена код оних са највишим вредностима ПС, тј. са најтеžом клиничком сликом при пријему. Учесталост великих крварења није била значајно повећана применом ФТ.

Кључне речи: средњеризична плућна емболија; фибрилолитичка терапија; пропензити скор

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