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Outcome of Sub-Massive Pulmonary Thromboemboli in Patients Who Received Thrombolytic and or Non-Thrombolytic Therapy

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Abstract

Background: Thrombolytic therapy in patients with sub-massive pulmonary embolism (SMPTE) needs further assessment.
Objectives: The current study aimed to assess a potential benefit of thrombolytic and non-thrombolytic therapy in patients with SMPTE.
Patients and Methods: One hundred-nineteen patients were enrolled with SMPTE from 2006 to 2010 in the tertiary care center of Rajaie medical and research center. The patients who had pulmonary thromboemboli (PTE) and received thrombolytic plus heparin therapy and or non-thrombolytic (unfractionated heparin alone) were evaluated for hemodynamic changes (blood pressure, pulse rate, pulmonary artery systolic pressure, right ventricular failure and right ventricle enlargement), before and after 48 hours of treatment. The mortality rate was also assessed.
Results: Forty-five percent of the patients with SMPTE received thrombolytic therapy (streptokinase) and 55% of SMPTE patients received non-thrombolytic therapy (unfractionated heparin). Pulse rate, pulmonary arterial pressure and tricuspid regurgitation gradient in patients receiving thrombolytic therapy reduced significantly (P = 0.001, P = 0.01 and P = 0.001, respectively). There was no significant difference before and after treatment regarding systolic blood pressure (P = 0.4), diastolic blood pressure (DBP) (P = 0.5), systolic arterial pressure (SPAP) (P = 0.1), Right ventricular (RV) function (P = 0.1) and RV size (P = 0.1). In patients who received a non-thrombolytic therapy, there were no significant differences between the groups regarding SBP (P = 0. 2), DBP (P= 0. 4) and PR (P = 0. 1), SPAP (P = 0.6), TRG (P = 0.4), RV function (P = 0.4) and RV size (P = 0.2) before and after treatment. There were no significant differences between the groups according to mortality rate.
Conclusions: Thrombolytic therapy lead to earlier relief of hemodynamic condition in comparison to non-thrombolytic therapy but no changes were observed in mortality rate.

Keywords: Thrombolytic Therapy, Heparin Therapy, Massive Pulmonary Thromboembolism, Sub-Massive Pulmonary Emboli

1. Background

Massive pulmonary thromboemboli is categorized by arterial hypotension and cardiogenic shock. Arterial hypotension is considered as a systolic arterial pressure less than 90 mmHg or decrease in systolic arterial pressure about 40 mmHg for at least 15 minutes and cardiogenic shock is characterized by tissue hypo perfusion and hypoxia (1). Pulmonary thromboemboli (PTE) is still considered as a great risk factor of mortality and morbidity in society (2). Pulmonary embolism (PE) is one of the most complicated conditions to be diagnosed perfectly. Computed tomography pulmonary angiography (CTPA) was introduced as a noninvasive test to diagnose PE(2). Untreated PTE has a high mortality rate; therefore, appropriate and correct diagnostic tests are necessary to initiate antithrombotic therapy whereas avoiding its hazards in patients without this diagnosis (3). In patients with sub-massive pulmonary thromboemboli (SMPTE) myocardial dysfunction or injury markers may be valuable for risk stratification of patients who are hemodynamically stable. The echocardiography shows that the right ventricular dysfunction is associated with increased mortality rate among patients with acute PE (4, 5). Echocardiogram is a sensible tool to demonstrate the diagnosis by confirming the right ventricular dysfunction and dilatation. In addition, it can also exclude diagnoses that might imitate PE such as aortic dissection, pericardial tampon-

ade, or acute myocardial infarction. Moreover, the echocardiogram can diagnose PE complications such as right heart thrombus and even show thrombus protruding into the left atrium through a patent foramen oval or atrial septal defect (6). According to recent studies (7-9), an echocardiography in which right ventricular dysfunction is demonstrated, is probably a prognostic factor in patients with stable condition and massive PE, this condition leads authors to suggest thrombolysis in such patients. The only anticoagulant applied in combination with thrombolytic therapy in patients with PE is intravenous unfractionated heparin and low-molecular-weight heparin (LMWH). Consequently, preliminary anticoagulation therapy with intravenous unfractionated heparin is suitable in a condition that thrombolytic therapy is considered (10). In a meta-analysis, the effects of thrombolytic therapy demonstrated that intravenous thrombolysis was associated with a mortality reduction between hemodynamically unstable patients with PE (11).

2. Objectives

The current study aimed to compare hemodynamic indices, echocardiographic findings of right ventricular dysfunction, and outcomes in patients treated either by unfractionated heparin plus thrombolytic (HT group) and, heparin (and or low molecular weight heparin) without thrombolytic (HWT group), in patients with SMPT, before and more than 48 hours after the start of each treatment, and also obtain total hospital death in either groups.

3. Patients and Methods

Based on historical cohort studies among patients admitted in the hospital from 20 March 2008 to 20 March 2012, 524 patients had been admitted with primary diagnosis of pulmonary thrombo emboli (PTE). Diagnosis of PTE was based on clinical symptoms and signs of presentation or by diagnosis of primary or referral physicians with or without deep vein thrombosis. Among them 345 patients had the final diagnosis of pulmonary emboli and were eligible for this study.

3.1. Study Design

In this study, all patients admitted and treated in the hospital with diagnosis of PE, and finally labeled by the same diagnosis at discharge note were included. Baseline assessment including clinical examination, ECG, trans-thoracic echocardiography, perfusion lung scan, and pulmonary CT angiography (PCTA) were applied for every patient, and conventional pulmonary angiography reports were depicted from patient documents. Echocardiographic data were obtained from patients documents. Routine technique of echocardiographic examination in the hospital in all of the subjects was patient at left lateral decubitus positioned by an echocardiography machine (vivid 3 General Electric Medical system Vingmed Ultrasound AS, Horten, Norway) prepared with 3.6 MHz transducer. All dimensions were achieved according to the American society of echocardiography guidelines by echocardiologists. In patients who underwent right heart catheterization, pressures were obtained by Swan Ganz catheter (Edward Life Science Company). Pulmonary thromboemboli was accepted if confirmed by (PCTA), there was high probability of perfusion scan according to PIOPED study criteria, clot was observed directly in echocardiography, and emboli confirmed with pulmonary angiography or magnetic resonance imaging (MRI). Patients were labeled as massive PTE and excluded if they had systolic blood pressure below 90 mmHg after primary liquid resuscitation and were hemodynamically unstable. They were accepted as sub massive Pulmonary Emboli group (SMPTE) if they encountered significant right ventricular enlargement and failure was found in echocardiography, and or systolic pressure increased to more than 90 mmHg with primary fluid resuscitation. Patients with PTE, who died because of the other reasons, had criteria and managed as massive PTE by device thrombo-suction or surgical thrombectomy, cases who left hospital before any more diagnostic methods and the patients who had incomplete recorded documents were excluded. Patient with massive burden of clot on PCTA and without hemodynamic or echocardiographic findings in favor of SMPTE were also accepted as SMPTE.Patients were divided into two groups based on physician's decision. Group one those who received unfractionated heparin plus thrombolytic (HT group), either streptokinase (most often) or other thrombolytic; and group two those who received unfractionated heparin or low molecular weight heparin (most often enoxaparin) without thrombolytic (HWT).

3.2. Statistical Analysis

Numeric data are expressed as mean $\pm$ SD. All variables were tested for normal distribution with One-Sample Kolmogorov-Smirnov test. Quantitative variables in each group were evaluated and compared by Student unpaired t-test and Mann-Whitney U test; moreover, the Fisher's exact test or chi-Square test was used to compare the two qualitative variables. Before-after data was were compared by paired t test. SPSS 15.0 for Windows (SPSS Inc., Chicago,

Illinois, USA) was used for all statistical analyses. $P < 0.05$ was considered as the level of the significance.

4. Results

From 2008 to 2012, among 80134 admissions, 345 patients were hospitalized with diagnosis of pulmonary embolism in Rajaie cardiovascular, medical and research center. One hundred-ninety (34%) of these patients had submassive thromboembolism (SMPTE) and 226 (66%) cases had either non massive thromboembolism, or massive thromboemboli leading to other interventions. Forty-five percent of the patients with SMPTE received thrombolytic therapy (streptokinase) and 55% of SMPTE patients received non-thrombolytic therapy (unfractionated heparin).

4.1. Age and Thromboemboli

There were no statistically significant differences between the two groups according to age (50.90±15.18 in HT group vs. 55.03 ± 18.06 in HWT group) (P = 0.2).

4.2. Gender and Thromboemboli

In the current study, no significant relationship was found between the groups in terms of gender. The group that received thrombolytic therapy (HT) consisted of 29 females and the patients who received non-thrombolytic therapy (HWT) consisted of 30 females (P = 0.9).

4.3. Clinical Symptoms and Thromboemboli

Regarding the clinical symptoms, the most prevalent clinical findings among the two groups were dyspnea in 88.7% of the cases, palpitation in 51.3% of the patients and chest pain (39%) and tachypnea in 30% of the cases in patients with SMPTE; however, there was no significant difference between the two groups regarding the mentioned clinical symptoms (P > 0.05). All the demographic data are shown in Table 1.

4.4. Risk Factors and Thromboemboli

Totally 77% of the patients were recognized with some other risk factors. The most prevalent risk factors were previous thromboembolism, cardiac diseases, fractures and deep vein thrombosis observed in 13%, 9.6%, 8.7%, and 7.8% of the patients, respectively.

4.5. Hemodynamic Status and Thromboemboli

Before initial treatment with HT and or HWT, hemodynamic factors were compared between the two groups. All demographic and clinical data are shown in Table 2. no significant changes were observed between the hemodynamic factors before treatment in both groups considering systolic blood pressure, pulse rate, pulmonary artery blood pressure, tricuspid regurgitation gradient, right ventricular size and right ventricular failure measured by echocardiography (Table 2).

According to Table 3, the comparison of the hemodynamic factors after 48 hours of treatment in patients with SMPTE showed no significant differences between the two groups regarding systolic blood pressure, pulse rate, pulmonary artery blood pressure, tricuspid regurgitation gradient, right ventricular size and right ventricular failure.

Hemodynamic factors were measured before treatment, and then compared with these variables measured after treatment in the two groups. As shown in Table 4, in patients who received thrombolytic therapy, pulse rates before, and at 48 hours of treatments were 93.80 ± 17.12 and 83.73 ± 19.85 respectively (P<0.001), and this trend showed that the pulse rate significantly decreased and finally reached the normal level. Pulmonary artery pressure had altered to a great extend before treatment if compared with 48 hours after treatment; (73.75 ± 22.27 before treatment vs. 48.75 ± 22.50 after treatment) (P = 0.01). Tricuspid gradient (TRG) reduced at 48 hours in comparison with initial TRG (51.40 ± 15.56 before treatment vs. 39.80 ± 24.39 after treatment) (P = 0.001).

There were no significant differences before and after treatment in systolic blood pressure (P =0.4), diastolic blood pressure (DBP) (P = 0.5), systolic arterial pressure (SPAP) (P = 0.1), RV function (P = 0.1) and RV size (P = 0.1). In the patients who received a non-thrombolytic therapy, there were no significant differences between the groups regarding SBP (P = 0.2), DBP (P = 0.4) and PR (P = 0.1), SPAP (P = 0.6), TRG (P = 0.4), RV function (P = 0.4) and RV size (P = 0.2) before and after treatment. All the data are depicted in Table 4.

4.6. Mortality and Thromboemboli

Totally, 28 (23.6%) death was observed that 14 of the cases (25%) received thrombolytic therapy (HT group) and 14 cases (20.6%) were in the HWT group (P = 0.1).

5. Discussion

At present there is less controversy over using thrombolytic in patients with massive pulmonary emboli (MPTE), but benefit of using thrombolytic in patients with

Table 1. Demographic Data and the Clinical Results in Patients with and Without Thrombolytic Therapy[a]

Variable	HWT (n = 65)	HT (n = 54)	P Value
Female	29 (44.4)	30 (55.8)	.9
Male	36 (55.6)	24 (44.2)	
Age	55.03±18.06	50.90 ± 18.15	.2
Symptoms			
Dyspnea	55 (87.3)	47 (90.4)	.6
Chest pain	19 (39.2)	19 (36.5)	.4
Coughing	11 (17.5)	6 (11.5)	.3
Syncope	5 (7.9)	9 (17.3)	.1
Hemoptysis	6 (9.5)	4 (7.7)	.7
Signs			
Tachycardia	28 (44.4)	31 (59.6)	.1
Tachypnea	19 (30.2)	19 (36.5)	.4
Hypotension	9 (14.3)	13 (25)	.1
Hypertension	10 (15.9)	5 (9.6)	.3

[a] Data are presented as No. (%) or mean ± SD.

Table 2. The Comparison of the Hemodynamic and Echocardiographic Factors Between the Two Groups Before Treatments

Evaluated Findings	HWT (n = 65)	HT (n = 54)	P Value
Systolic blood pressure	127.87 ± 25.22	119.27 ± 31.60	.16
Diastolic blood pressure	78.92 ± 13.23	78.59 ± 13.23	.47
Pulse	93.17 ± 22.99	93.80 ± 17.12	.24
SPAP	74.41 ± 29.680	73.75 ± 22.27	.34
TRG	42.00 ± 30.296	51.40 ± 15.56	.72

Abbreviations: SPAP, systolic pulmonary artery pressure; TRG, tricuspid regurgitation gradient.

Table 3. The Comparison of the Hemodynamic and Echocardiographic Factors Between the Two Groups 48 Hours After the Treatments

Evaluated Findings	HWT (n = 65)	HT (n = 54)	P Value
Systolic blood pressure	116.19 ± 20.07	120.45 ± 12.12	.23
Diastolic blood pressure	72.00 ± 16.18	75.17 ± 13.71	.53
Pulse	89.67 ± 16.179	83.73 ± 19.85	.93
SPAP	69.57 ± 22.127	48.75 ± 22.50	.12
TRG	35.71 ± 19.337	39.80 ± 24.39	.64

Abbreviations: SPAP: systolic pulmonary artery pressure; TRG: tricuspid regurgitation gradient.

sub-massive pulmonary thromboemboli (SMPTE) is not known. The current study tried to answer this question and define epidemiological and clinical presentations of the patients with pulmonary emboli in Iran. The study specially focused on treatments of SMPTE to define the effect of thrombolytic therapy and heparin on patients with SMPTE.Among 80134 patients admitted in five years from 2008, 345 patients were found with diagnosis of pulmonary thromboemboli (PTE). The prevalence of PTE in the tertiary center, (Rajaei medical and research center)

Table 4. The Comparison of Echocardiographic and Hemodynamic Parameters 48 Hours Before and After Treatments

Groups	Evaluated Findings	Before Treatment	48 Hours After the Treatment	P Value
HWT				
	SBP	127.87 ± 25.22	116.19 ± 20.07	.2
	DBP	78.92 ± 13.23	72.00 ± 16.18	.4
	PR	93.17 ± 22.99	89.67 ± 16.179	.1
	SPAP	74.41 ± 29.680	69.57 ± 22.127	.6
	TRG	42.00 ± 30.296	35.71 ± 19.337	.4
HT				
	SBP	119.27 ± 31.60	120.45 ± 12.12	.4
	DBP	78.59 ± 13.23	75.17 ± 13.71	.5
	PR	93.80 ± 17.12	83.73 ± 19.85	.001
	SPAP	73.75 ± 22.27	48.75 ± 22.50	.01
	TRG	51.40 ± 15.56	39.80 ± 24.39	.001

Abbreviations: DBP: diastolic blood pressure; PR: pulse rate; SBP: systolic blood pressure; SPAP: systolic pulmonary artery pressure; TRG: tricuspid regurgitation gradient.

was estimated 43 cases out of 10000 hospitalized patients and the rate of SMPTE was 15 cases out of 10000. An ICPER study showed that the rate of massive thromboembolism is 4.5% (12), which demonstrated the incidence of an 80% increase in pulmonary emboli from 1998 to 2006 utilizing pulmonary angiography. In the last guideline it is estimated that the thromboembolism occurs in 300000 to 650000 panties in US each year (13, 14).In the current investigation, the prevalence of MPTE in hospitalized patients was approximately the same as other studies (3.8%). But the prevalence of MPTE would be higher if SMPTE is considered as MPTE. In the present study 45% of the patients with SMPTE received thrombolytic therapy (streptokinase) and 55% of SMPTE patients received non-thrombolytic therapy (unfractionated heparin). There are two reasons to explain this difference: firstly the hospital was a tertiary center and received more severe cases from other hospitals, and secondly, as already mentioned a wider range of patients with PTE and right ventricular dysfunction were included (decreased velocity of the right ventricle or right ventricle failure which their emboli is diagnosed by other diagnostic tests) as SMPTE in the study. In the current study, according to the guideline (15), the incidence of thromboemboli was similar in both genders. Another study showed that the incidence of thromboembolism for the second time is more in males than females (13). Stein showed that the incidence of thromboembolism in females over 50 years old was higher than the females below 50 (13). Although there are studies that show significant relationship between age and the incidence of thrombotic therapy usage, the current study did not demonstrated it. Naess et al. showed that the rate of thrombolytic therapy will rise by age increase(14) . The present study compared the hemodynamic indices at two time intervals (0 and 48 hours later) and it was found that the pulmonary arterial pressure reduced significantly with thrombolytic therapy. Therefore it was hypothesized that thrombolytic therapy will stabilize the hemodynamic status. Richard et al. showed the increase in blood flow and improvements in hemodynamic function 24 hours after the treatment in patients with massive thromboemboli receiving urokinase compared to the patients receiving heparin and urokinase, but no significant difference was found in lung scan on the day seven, fourteen and three or six months after treatments in comparison with the two groups (16). The present study showed that, in patients receiving thrombolytic therapy, pulmonary artery pressure altered to a great extend before treatment if compared with that of 48 hours after treatment (P = 0.01). Tricuspid gradient (TRG) reduced at 48 hours in comparison with initial TRG (P=0.001). No significant differences were observed before and after treatment in systolic blood pressure (P = 0.4), diastolic blood pressure (DBP) (P = 0.5), systolic arterial pressure (SPAP) (P = 0.1), RV function (P = 0.1) and RV size (P = 0.1). Another study showed significant improvement in lung scan flow in only the first 24 hours of the treatment in the first group (receiving heparin and thrombolytic) in comparison to the second group (only heparin); however, after 24 hours of the treatments no significant differences were found between the two groups (17). Levine et al. showed that most of the improvement in lung scan was observed in patients receiving thrombolytic treatment

(37%) in comparison to the group receiving heparin in the first 24 hours of the treatment and no significant differences were observed in the clot resolution and perfusion improvements in seven and thirty days after treatments in the two groups (18). Wiener et al. in 2013 showed a decrease in death rate due to thromboemboli (12.5 to 11.9 in each 100000 cases) (12). These results are most likely due to an increase in thromboembolic diagnostic power and sensitivity of the computed tomography (CT) angiography in recent years and quick treatments and finally less morbidity and mortality. The present study showed 28 deaths out of 119 cases receiving thrombolytic therapy (HT group) and 14 cases were in the HWT group (P = 0.1). A systematic review and meta-analysis of nine randomized controlled trial comparing fibrinolyticagents versus intravenous heparin in a total of 461 patients with acute pulmonary embolism found that fibrinolytic therapy had no significant effect on mortality (19). A clinical trial by Dalla-Volta et al.comparing the alteplase combined with heparin versus heparin, showed that the mortality rate in the two groups of study were nearly the same (20) although in a study by Stein et al. treatments with thrombolytic therapy in patients with massive thromboemboli were accompanied by unstable hemodynamic status even in old cases (60 years or more) who have concomitant disease but have no contradiction in patients receiving thrombolytic therapy and the results showed that LMWH administration in qualified patients with deep vein thrombosis is as effective as intravenous heparin administration. The cases receiving thrombolytic therapy had less hospitalized mortality rate than the group who received non thrombolytic therapy (21). Theoretically, thrombolytic therapy will dissolve dangerous clots in pulmonary blood vessels and reduce the size of occlusion, but the current investigation, similar to the other studies, showed less but non-significant mortality in patients receiving thrombolytic therapy. The present study showed that the most prevalent risk factors were previous thromboembolism, cardiac diseases, fractures and deep vein thrombosis observed in 13%, 9.6%, 8.7%, and 7.8% of the patients, respectively. To date, this is the largest and most comprehensive clinical study that evaluated risk factors for recurrent VTE in patients with unprovoked proximal DVT or PE. According to the emergency condition of the patients with massive pulmonary emboli, management of hemodynamic dilemma, oxygenation and resolution of clot need a multidisciplinary of interventional and pharmacological approaches, and a rapid and correct concern of risk and treatment plan should be recognized. Fibrinolysis, catheter intervention, and ongoing cooperation with cardiac surgeons are providentially tools that will aid specialists exploit the probability of absolute revival for such awfully ill patients (22-24). Improvement in knowledge of managing the pulmonary emboli, especially in more severe cases (MPTE and SMPTE) helps to reduce mortality and morbidity of such patients. But considering the study design and methodology, there would probably be a random error that led to the conclusion that patients in HT group had benefited from treatment. It is because of this reality that putting patients in HWT group by primary physicians might be due to better clinical condition of the patients in comparison to the ones receiving thrombolytic in addition to heparin (HT) and there were no randomization at that time.

5.1. Conclusion

Thrombolytic therapy in patients with sub-massive thromboemboli will lead to improvement in echocardiographic and hemodynamic status in comparison to the patients receiving non thrombolytic therapy; however, no effect on mortality rate was observed. Further prospective studies are needed to define status of thrombolytic therapy on patients with sub massive pulmonary emboli more precisely.

5.2. Limitation

It was a retrospective study and there are some limitations in such studies. Physicians had treated patients based on their own experience, and authors had no role in allocation of patients into two groups.

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Footnotes

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References

1. Kucher N, Goldhaber SZ. Management of massive pulmonary embolism. *Circulation.* 2005;**112**(2):e28–32. doi: 10.1161/CIRCULATIONAHA.105.551374. [PubMed: 16009801].
2. Fedullo PF, Tapson VF. Clinical practice. The evaluation of suspected pulmonary embolism. *N Engl J Med.* 2003;**349**(13):1247–56. doi: 10.1056/NEJMcp035442. [PubMed: 14507950].
3. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;**126**(3 Suppl):401S–28S. doi: 10.1378/chest.126.3_suppl.401S. [PubMed: 15383479].
4. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ. Predictors of Recurrence After Deep Vein Thrombosis and Pulmonary Embolism. *Arch Intern Med.* 2000;**160**(6):761. doi: 10.1001/archinte.160.6.761. [PubMed: 10737275].
5. Elman EE, Kahn SR. The post-thrombotic syndrome after upper extremity deep venous thrombosis in adults: A systematic review. *Thromb Res.* 2006;**117**(6):609–14. doi: 10.1016/j.thromres.2005.05.029. [PubMed: 16002126].
6. Torbicki A, Galie N, Covezzoli A, Rossi E, De Rosa M, Goldhaber SZ. Right heart thrombi in pulmonary embolism. *J Am Coll Cardiol.* 2003;**41**(12):2245–51. doi: 10.1016/s0735-1097(03)00479-0. [PubMed: 12821255].
7. Goldhaber SZ, Come PC, Lee RT, Braunwald E, Parker JA, Haire WD, et al. Alteplase versus heparin in acute pulmonary embolism: Randomised trial assessing right-ventricular function and pulmonary perfusion. *The Lancet.* 1993;**341**(8844):507–11. doi: 10.1016/0140-6736(93)90274-k.
8. Kasper W, Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser KD, et al. Management Strategies and Determinants of Outcome in Acute Major Pulmonary Embolism: Results of a Multicenter Registry. *J Am Coll Cardiol.* 1997;**30**(5):1165–71. doi: 10.1016/s0735-1097(97)00319-7. [PubMed: 9350909].
9. Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser K, Rauber K, et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism : Results of a Multicenter Registry. *Circulation.* 1997;**96**(3):882–8. doi: 10.1161/01.cir.96.3.882. [PubMed: 9264496].
10. van Dongen CJ, van den Belt AG, Prins MH, Lensing AW. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev.* 2004(4):CD001100. doi: 10.1002/14651858.CD001100.pub2. [PubMed: 15495007].
11. Jardin F. Echocardiographic pattern of acute Cor pulmonale. *CHEST Journal.* 1997;**111**(1):209. doi: 10.1378/chest.111.1.209.
12. Wiener RS, Schwartz LM, Woloshin S. When a test is too good: how CT pulmonary angiograms find pulmonary emboli that do not need to be found. *Bmj.* 2013;**347**(jul02 2):f3368. doi: 10.1136/bmj.f3368. [PubMed: 23820021].
13. Stein PD, Matta F. Epidemiology and incidence: the scope of the problem and risk factors for development of venous thromboembolism. *Crit Care Clin.* 2011;**27**(4):907–32. doi: 10.1016/j.ccc.2011.09.006. [PubMed: 22082520].
14. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: A population-based study. *J Thromb Haemost.* 2007;**5**(4):692–9. doi: 10.1111/j.1538-7836.2007.02450.x. [PubMed: 17367492].
15. Hunt JM, Bull TM. Clinical review of pulmonary embolism: Diagnosis, prognosis, and treatment. *Med Clin North Am.* 2011;**95**(6):1203–22. doi: 10.1016/j.mcna.2011.08.003. [PubMed: 22032435].
16. Richard D. Urokinase pulmonary embolism trial. Phase 1 results: a cooperative study. *JAMA.* 1970;**214**(12):2163–72. doi: 10.1001/jama.214.12.2163. [PubMed: 5536580].
17. Urokinase-streptokinase embolism trial. Phase 2 results. A cooperative study. *JAMA.* 1974;**229**(12):1606–13. doi: 10.1001/jama.229.12.1606. [PubMed: 4408392].
18. Levine M. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. *CHEST Journal.* 1990;**98**(6):1473. doi: 10.1378/chest.98.6.1473.
19. Thabut G, Thabut D, Myers RP, Bernard-Chabert B, Marrash-Chahla R, Mal H, et al. Thrombolytic therapy of pulmonary embolism. *J Am Coll Cardiol.* 2002;**40**(9):1660–7. doi: 10.1016/s0735-1097(02)02381-1. [PubMed: 12427420].
20. Dalla-Volta S, Palla A, Santolicandro A, Giuntini C, Pengo V, Visioli O, et al. PAIMS 2: Alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen activator Italian multicenter study 2. *J Am Coll Cardiol.* 1992;**20**(3):520–6. doi: 10.1016/0735-1097(92)90002-5. [PubMed: 1512328].
21. Stein PD, Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. *Am J Med.* 2012;**125**(5):465–70. [PubMed: 22325236].
22. Schulman S, Lindmarker P, Holmstrom M, Larfars G, Carlsson A, Nicol P, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. *J Thromb Haemost.* 2006;**4**(4):734–42. doi: 10.1111/j.1538-7836.2006.01795.x. [PubMed: 16634738].
23. Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. *J Clin Oncol.* 2003;**21**(19):3665–75. doi: 10.1200/JCO.2003.08.008. [PubMed: 14512399].
24. Akl EA, Kamath G, Yosuico V, Kim SY, Barba M, Sperati F, et al. Thromboprophylaxis for patients with cancer and central venous catheters: a systematic review and a meta-analysis. *Cancer.* 2008;**112**(11):2483–92. doi: 10.1002/cncr.23479. [PubMed: 18404702].