THROMBOLYTIC AND ANTICOAGULANT THERAPY FOR PULMONARY EMBOLISM WITH HIGH AND INTERMENDIATE RISK OF EARLY DEATH. PART 1. MORTALITY AND COMPLICATIONS

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BACKGROUND The advantages of thrombolytic therapy over anticoagulant therapy in the treatment of acute pulmonary embolism are uncertain.

AIM OF STUDY To compare primary outcomes and incidence of complications in patients with PE of high and intermediate risk in the course of TLT or ACT and to assess efficacy and safety of TLT and ACT.

STUDY DESIGN Prospective non-randomized study. Intervention was administration of a thrombolytic, the control group consisted of patients who had an anticoagulant introduced.

CHARACTERISTICS OF A SAMPLE 503 patients with a high and intermediate risk of early death at the age of 16 to 93 years (mean age 61±16, Me 63 (51; 74) admitted to the resuscitation department in 2011–2016. Thrombolytics were administered to 222 patients, heparin — 281.

RESULTS The mortality rate was 10.8% (24/222) when treated with thrombolytic vs. 17.8% (50/281) with anticoagulant treatment; odds ratio was 0.56, 95% confidence interval 0.32; 0.97; p=0.031; P=0.60. The mortality rate in the subgroup with unstable hemodynamics was 30.2% (19/63) with thrombolytics vs. 47.1% (32/68) with anticoagulant treatment; OR 0.49 (0.22; 1.06); p=0.051; P=0.51. The mortality rate in the subgroup of intermediate risk was 3.2% (5/158) vs. 8.4% (18/214); OR 0.36 (0.11; 1.05); p=0.049; P=0.54. The use of thrombolytic was associated with a decrease in mortality: in the age group <75 (mortality rate 5.5% (10/181) vs. 16.2% (33/204), OR 0.30 (0.14; 0.67); p=0.001, P=0.92); in the subgroup with acute cardiac arrhythmias (mortality rate 4.5% (1/122) vs. 44.0% (11/25); OR 0.061 (0.003; 0.557); p=0.002; P=0.91); in the subgroup with no hospital recurrence of embolism (mortality rate 1.6% (3/188) vs. 12.9% (32/248); OR 0.14 (0.03; 0.46), p<0.001; P=1.0). With thrombolysis, infarction pneumonia developed less often: in 19.8% (44/222) vs. 28.8% (81/281); OR 0.61 (0.39; 0.95); p=0.022; P=0.64. There were no differences in the incidence of hemorrhagic complications in the treatment of thrombolytics in comparison with anticoagulant therapy: 7.7% (17/222) vs. 10.3% (29/281); OR 0.72 (0.37; 1.40); p=0.35; P=0.17. Severe hemorrhages (including intracranial): 2.7% (6/22) vs. 3.2% (9/281); OR 0.84 (0.26; 2.62); p=0.80; P=0.06. Minor hemorrhages: 5.0% (11/222) vs. 7.1% (20/281); OR 0.72 (0.31; 1.63); p=0.36; P=0.16. Intracranial hemorrhages: 0.90% (2/222) vs. 0.71% (2/281); OR 1.27 (0.13; 12.67); p=0.81; P=0.13). There was no difference in the re-occurrence of embolisms: 15.3% (34/222) and 11.7% (33/281); OR 1.36 (0.79; 2.35); p=0.29; P=0.22.

CONCLUSION Thrombolytic therapy appeared to be more effective for survival compared to anticoagulant therapy with no differences in the incidence of complications.

Keywords: pulmonary embolism, thrombolytic therapy, anticoagulant therapy, intermediate risk of adverse outcome, mortality rate, intracranial hemorrhages, cardiac arrhythmias

For citation Nikitina O.V., Mikhailov I.P., Kosolapov D.A., et al. Thrombolytic and anticoagulant therapy for pulmonary embolism with high and intermendiate risk of early death. Part 1. Mortality and complications. *Russian Sklifosovsky Journal of Emergency Medical Care*. 2018; 7(1): 20–29. DOI: 10.23934/2223-9022-2018-7-1-20-29 (In Russian)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments The study had no sponsorship

ACT — anticoagulant therapy
CI — confidence interval
ICH — intracranial hemorrhage
Me — median with a quartile scale
OR — odds ratio
PE — pulmonary embolism
RR — relative risk
TLT — thrombolytic therapy

ВВЕДЕНИЕ

The main approaches to the treatment of pulmonary embolism (PE) in general, including the use of thrombolytic drugs, are regulated in a number of authoritative conciliation documents:

- in the Russian clinical guidelines for the diagnosis, treatment and prevention of venous thromboembolic complications (2010) [1];
- in the recommendations of the European Society of Cardiology (ESC) for the diagnosis and management of patients with acute embolism of the pulmonary artery system (2014) [2];
- in practical recommendations for clinical practice "Antithrombotic therapy for venous thromboembolic disease" of the American College of Chest Physicians (2008) [3];
- in the scientific statement of the American Heart Association "Treatment of massive and submissive pulmonary embolism" (2011) [4];
- in the recommendations of the British Thoracic Society for the treatment of patients with suspected acute PE (2003) and other documents [5].

Currently, the following provisions are generally accepted:

- Thrombolytic (TLT) and anticoagulant (ACT) therapy are the main methods of treatment for any variant of PE;
- in patients with PE of high risk, thrombolysis reduces mortality;
- for patients with high risk of death, the use of TLT is considered mandatory: evidence level A, recommendation class 1;

- in patients with intermediate risk of death, the advantages of TLT appointment are uncertain; there is evidence that TLT can improve prognosis and accelerate rehabilitation [1-5].

Stratification of the risk of early death in hemodynamically stable patients with PE is hitherto difficult. A search is in progress, but no parameters have been found that predict the outcome with sufficient certainty. In 2008, the European Society of Cardiologists assigns a wide range of patients with confirmed signs of dysfunction and/or damage to the right ventricle to a group of intermediate risks [6]. In the version of the recommendations of 2014, it is recommended to refine the range by means of an additional evaluation based on the original or simplified PESI scale (Pulmonary Embolist Severity Index). The latter estimates the contribution of several anthropometric, anamnestic and clinical parameters [2].

A series of authoritative meta-analyzes conducted by a group of experts from the Cochrane Community (in 2002, 2006, 2009 and 2015) showed that all the identified trends indicating the efficacy of TLT compared to ACT are unstable. According to experts, interpretation of results is complicated by the small size of samples and heterogeneity of studies. Thus, the advantages of TLT in terms of reducing mortality remain unclear. Doubts concern, first of all, the group of intermediate risk [7-9, 10].

In order to improve the quality of further analysis and determine the benefits (or lack thereof) of TLT before ACT in the treatment of pulmonary embolism, the experts of the Cochrane Collaboration formulated recommendations for further research. Among them: to focus on assessing the overall outcomes — mortality, hemorrhagic complications, re-ocurrence of PE; to assess the differences between different age groups; it is very important to differentiate hemodynamically stable and unstable patients [10].

Aim of study: to make a comparative analysis of primary outcomes (lethality and incidence the most significant complications) in patients with high and intermediate risk PE in TLT or ACT and assess the efficacy and safety of TLT and ACT.

Study design: a prospective non-randomized study. Intervention was introduction of thrombolytics. The comparison group consisted of patients who took anticoagulants.

Randomisation was not intended initially, since its use provides for ignoring contraindications thrombolytics, indicated in all clinical recommendations. That is, in favor of increasing objectification, the risk of an unfavorable outcome should be increased. Another way is to exclude patients with an increased and/or unobvious risk of bleeding from the study, which also limits objectification and reduces the number of observations. The choice was made in favor of minimizing the risk to the patient by reducing the objectivity of the study.

Inclusion criteria: age over 15 years; verified diagnosis of PE; verification was performed using scintigraphy or computer angiopulmonography or by a combination of clinical, laboratory and other instrumental data.

Exclusion criteria: doubtful result of pulmonary scanning, absence of deep vein thrombosis of the lower leg with uncertain results of echocardiography.

Statistical processing of data was carried out using the STATISTICA software package (StatSoft Inc., USA). The normality of the distributions was estimated by the Shapiro-Wilk criterion. Since some of distributions did not meet the criterion of normality, assessment of central trends and variations are represented by mean values with standard deviations of M±SD and medians with a quartile-scale Me (1^{st} quartile, 3^{rd} quartile).

For quantitative comparisons of independent groups, the Mann-Whitney test was used. The evaluation of the shares was carried out using the 2-sided Fisher test, in some cases the Mantel-Haensel criterion was additionally used. A 95% confidence interval (95% CI) was calculated for the share estimates. Relative Risk (RR), Odds Ratio (OR), and their 95% confidence intervals were calculated to compare proportions. Exact values of the significance level of the revealed differences of *p* for each pair of comparisons are presented in the text and tables. The threshold value was considered to be $p \leq 0.05$ (type I error control). To control type II errors, the power of the study *P* was calculated; the threshold value $P \geq 0.8$ for $\alpha = 0.05$. To evaluate the strength of differences, a standardized effect (Es) was calculated. To estimate the survival with time function, the Kaplan-Mayer method was used, to estimate the proportional contribution of each of the factors at the time of the onset of an unfavorable outcome, the Cox proportional-intensity model was used. The letter *n* in tables and diagrams indicates the number of observations. A * symbol indicates those correct values for the level of significance of the differences p, which corresponded to the power of the study, equal to or exceeding 0.80.

CHARACTERISTICS OF THE SAMPLE

The study included 503 patients aged 16 to 93 years who were treated in the intensive care unit for surgical patients at the N.V. Sklifosovsky Institute for Emergency Medicine in 2011-2016. There were statistically significantly more women than men: 290 (58%) and 213 (42%); $p<0.001$ (Fisher's test). The mean age was 61±16, Me 63 (51; 74) years. Men and women statistically significantly (Es 0.32) differed in age: 59±15 years, Me 60 (50; 69) and 63±16, Me 65 (53; 76); p=0.005 (Mann-Whitney test).

The average duration of treatment in the intensive care unit was 4±5 days, Me 3 (2; 5), and the average length of hospital treatment was 14±13 days, Me 12 (8; 17).

Out of 503 people 74 died; the overall mortality was 14.7% (95% CI 11.7; 18.1). The mortality rate for men and women did not differ: 13.1% (95% CI 8.9; 18.4) (28/213) and 15.9% (95% CI 11.9; 20.6) (46/290); p=0.45 (Fisher's

test). Survivors and deceased statistically significant and strongly (Es 0.91) differed in age: 60±16 years, Me 61 (49; 72) and 69±13, Me 71 (59; 79); p=0.000009 (Mann-Whitney test).

The majority of deaths occurred in early terms: 76% within 10 days, including 34% on the first day of treatment (Fig. 1).

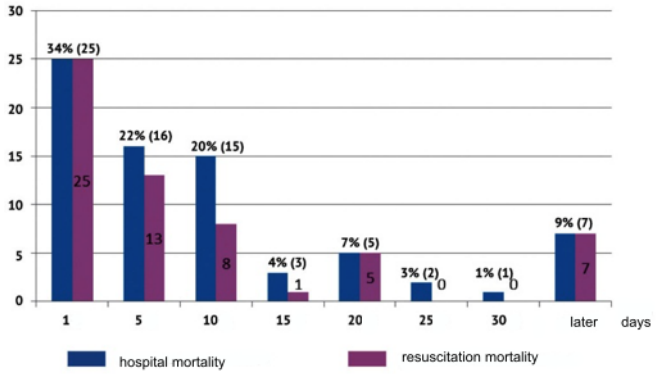


Fig. 1. Timing of deaths

The natural effect of age on survival is illustrated in Table 1.

Table 1

Mortality rates in different age groups

Age groups according to WHO		Number of patients, *n*	Deceased	Mortality (95% CI)
Young	18–44	81	3	3.7% (0.8; 10.4)
Middle	45–59	131	16	12.2% (7.2; 19.1)
Elderly	60–74	173	24	13.9% (9.1; 19.9)
Senile	75–89	113	30	26.5% (18.7; 35.7)
Long-living	90 and more	5	1	20.0% (0.5; 71.6)
Total:		503	74	14.7% (11.7; 18.1)

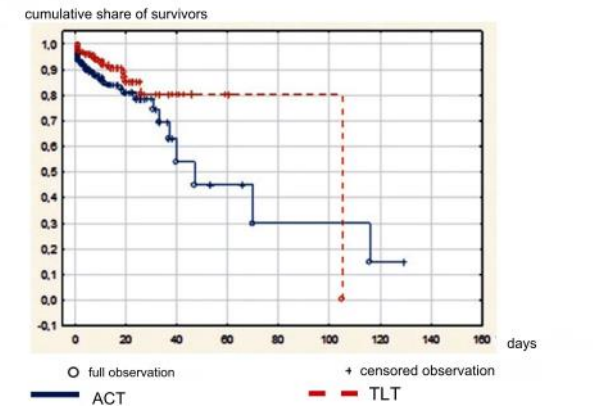
Notes: CI — confidence interval; WHO — World Health Organization

Anticoagulants of direct action were prescribed already at the stage of examination or by verification of PE in all patients. In the vast majority of cases, unfractionated heparin was first applied at a dose of 1.0 to 1.7 thousand units per hour intravenously through the infusor followed by anticoagulants of indirect action on day 3-5. The thrombolytic was administered through the infusor into the peripheral vein: alteplase in 169 cases, urokinase in 30 cases, and streptokinase in 23 cases. TLT was performed in 222 patients out of 503 (44%), isolated ACT was performed in 281 (56%). The mean age in the groups was not statistically significantly different: in the TLT group it was 60±16 years, Me 61 (49; 72), and in the ACT group it was 63±15 years, Me 63 (54; 75); p=0.07 (Mann-Whitney test).

RESULTS

Of the 222 patients who underwent TLT, 24 people died. Of the 281 with ACT, 50 patients died. The lethality during TLT was 10.8% (95% CI 7.1; 15.7) and was lower than in the ACT group 17.8% (95% CI 13.5; 22 ,8); p=0.031 (Fisher's test). The choice of treatment method in favor of TLT reduced the probability of fatal outcome by 1.65 times compared with ACT: RR 0.61 (95% CI 0.37; 0.98). The study power P=0.60 for α= 0.05 does not allow us to conclude that the advantage of TLT before ACT for survival is strictly correct. For an acceptable control of type II error, an increase in the sample size is approximately two-fold.

However, a comparative analysis of the time until the outcome by the Kaplan-Mayer method showed a convincing power level (P=0.96 for α= 0.05) for the survival curves of TLT compared to ACT at a sufficient level of significance (p=0.027*, Gehan-Wilcoxon test), Fig. 2. The median survival time was 56 and 43 days, respectively. The 15-day survival rate, calculated taking into account that the average length of hospital stay was 14 (13) days, 0.901 (95% CI 0.864; 0.922) for the TLT group and 0.840 (95% CI 0.801; 0.864) for the group with ACT. High study power P=0.96 for α=0.05 makes it possible to associate the result with the population.



Group with TLT	Group with ACT
n=222	*n*=281
Me 56 (31; 80)	Me 43 (30; 85)
Share of 15-day survival 0.901 (95% CI 0.864; 0.922)	Share of 15-day survival 0.840 (95% CI 0.801; 0.864)
p=0,027, Gehan-Wilcoxon criterion	
Power *P*=0.96 for α=0.05	

Fig. 2. Survival curves (Kaplan–Meier method) for thrombolytic therapy (TLT) or anticoagulant therapy (ACT)

When stratificating by age, the results were similar to those in other studies [11]: the obvious advantage of TLT in patients under 75 and the lack of this advantage in patients over 75 (Table 2). If at the age of 75 years, TLT was 3 times lower than in the case of ACT: 5.5% versus 16.2%; p=0.001*; RR 0.34 (95% CI 0.16; 0.70), in the age group of patients 75 years of age and older, no differences were found: 34.1% and 22.1%; p=0.20; RR 1.55 (95% CI 0.79; 2.94). The study power for patients under 75 was high: P=0.92, and the result can be trusted. In the subgroup of patients over 75 years, P was 0.30, therefore, as the number of observations increases, the result may change. That is, the issue of TLT advantages over ACT in elderly patients remains open.

Table 2

The influence of TLT and ACT on the lethality in different age groups

Groups	Number of patients, *n*	Deceased	Mortality (95% CI)	Fisher's test, *p*	Мощность исследования для α=0.05
Age<75	385	43	11.2% (8.2; 14.8)	<0.001*	0.96
Age ⩾75	118	31	26.3% (16.4; 32.4)		
TLT – age <75	181	10	5.5% (2.7; 9.9)	0.001*	0.92
ACT – age <75	204	33	16.2% (11.4; 22.0)		
TLT – возраст ⩾75 лет	41	14	34.1% (20.1; 50.6)	0.20	0.30
ACT – age ⩾75	77	17	22.1%(13.4; 33.0)		

Notes: ACT – anticoagulant therapy; TLT – thrombolytic therapy

Totally, 131 patients from 503 entered the resuscitation department with signs of hemodynamic shock of varying severity. This factor, accepted as unconditional in conferring high risk of early death, had the strongest impact on the unfavorable outcome: mortality in unstable hemodynamics was 38.9% vs. 6.2 % for intermediate risk patients (p <0.001*, P=1.0). Systemic hemodynamics disorders increased the probability of a fatal outcomes by 6.3 times; RR 6.30 (95% CI 3.96; 10.20).

In the presence of shock/hypotension, TLT had advantages for survival before ACT: lethality 30.2% vs. 47.1%; p=0.051 (Fisher's test), p=0.048 (Mantel-Haensel test). For the intermediate risk, the results were similar in orientation: the mortality rate in TLT was lower compared to that for ACT: 3.1% and 8.5%; p=0.048 (Fisher's test),

p=0.036 (Mantel-Haensel test). Insufficient power level, P=0.51 and P=0.58, accordingly does not allow to interpret the revealed differences as a reliable result; the latter can be improved with a 2.5 increase in the number of observations (Table 3).

Table 3

The influence of TLT and ACT on the lethality in the development of hemodynamic shock

Groups	Number of patients, *n*	Deceased	Mortality (95% CI)	Fisher's test, *p*	Power for α=0.05
Shock/hypotension	131	51	38.9% (30.5; 47.8)	<0.001*	1.0
No shock/hypotension	372	23	6.2% (4.0; 9.1)		
TLT — shock/hypotension	63	19	30.2% (19.2; 43.0)	0.051	0.51
ACT — shock/hypotwnsion	68	32	47.1% (34.8; 59.6)		
TLT — no shock/hypotension	159	5	3.1% (1.0; 7.2)	0.048	0.58
ACT — no shock/hypotension	213	18	8.5% (5.1; 13.0)		

Notes: ACT — anticoagulant therapy; TLT — thrombolytic therapy

Upon primary examination, in 42.5% of cases (95% CI 38.2; 47.0), the presence of a floating unstable fragment of the thrombus in the venous system of the lower limbs was revealed. The presence of flotation had no effect on the outcome: lethality in the presence of flotation was 16.4%, and 13.5% without it; p=0.38 (Table 4). The choice of treatment method (TLT or ACT) in the presence of flotation also did not influence the outcome: the lethality with TLT was 14.6% and 18.0% with ACT; p=0.58.

Table 4

The influence of TLT and ACT on the lethality in the presence of a floating thrombus in the venous system of the lower extremities

Groups	Number of patients, *n*	Deceased	Mortality (95% CI)	Fisher's test, *p*	Power for α=0.05
Revealed flotation	214	35	16.4% (11.7; 22.0)	0.38	0.15
No flotation	289	39	13.5% (9.8; 18.0)		
TLT — flotation	103	15	14.6% (8.4; 22.9)	0.58	0.10
ACT — flotation	111	20	18.0% (11.4; 26.5)		
TLT — no flotation	119	9	7.6% (3.5; 13.9)	0.014	0.70
ACT — no flotation	170	30	17.6% (12.2; 24.2)		

Notes: ACT — anticoagulant therapy; TLT — thrombolytic therapy

However, in the absence of flotation, thrombolysis was associated with a lower mortality compared with anticoagulant use: 7.6% versus 17.6%; p=0.014; P=0.70. That is, the use of TLT in the absence of flotation reduced the probability of an unfavorable outcome compared to ACT by 2.3 times; RR 0.43 (95% CI 0.19; 0.90).

Data on the most common and significant complications of PE and its treatment are presented in Table 5 and 6. As can be seen in Table 5, all the complications mentioned in it increased the probability of death.

Table 5

The incidence of certain PE complications and its impact on adverse outcome

Complications	Number of patients, *n*	Incidence (95% CI)	Presence	Mortality (95% ДИ)	Fisher's test, *p*	Relative risk (*RR*) (95% CI)
Hospital re-occurrence of PE	67	13.3% (10.5; 16.6)	+	41.8% (29.9; 54.5)	<0.001*	3.96 (2.58; 5.87)
			-	10.6% (7.8; 13.8)		
Bleeding	46	9.1% (6.8; 12.0)	+	30.4% (17.7; 45.8)	0.004*	2.32 (1.31; 3.79)
			-	13.1% (10.2; 16.6)		
Pulmonary infarction	125	24.9% (21.1; 28.9)	+	21.6% (14.7; 29.9)	0.019	1.74 (1.09; 2.71)
			-	12.4% (9.3; 16.2)		
Arrythmias	47	9.3% (7.0; 12.2)	+	25.5% (13.9; 40.4)	0.048	1.88 (1.01; 3.21)
			-	13.6% (10.6; 17.1)		

Notes: PE — pulmonary embolism

Table 6

The influence of TLT and ACT on the outcome in the development of complications

Complications	Therapy	Number of patients, *n*	Incidence (95% CI)	Fisher's test, *p*	Mortality in complications (95% CI)	Fisher's test, *p*
Hospital re-occurrence of PE	TLT	34	15.3% (10.9; 20.7)	0.29	61.8% (43.6; 77.8)	0.62
	ACT	33	11.7% (8.2; 16.1)		54.5% (36.4; 71.9)	
Bleeding	TLT	17	7.7% (4.5; 12.0)	0.35	41.2% (18.4; 67.1)	0.32
	ACT	29	10.3% (7.0; 14.5)		24.1% (10.3; 43.5)	
Pulmonary infarction	TLT	44	19.8% (14.8; 25.7)	0.022	25.0% (13.2; 40.3)	0.50
	ACT	81	28.8% (23.6; 34.5)		19.8% (11.7; 30.1)	
Arrythmias	TLT	22	9.9% (6.3; 14.6)	0.76	4.5% (0.1; 22.8)	0.002*
	ACT	25	8.9% (5.8; 12.9)		44.0% (24.4; 65.1)	

Notes: ACT — anticoagulant therapy; PE — pulmonary embolism; TLT — thrombolytic therapy

Hospital re-ocurrence of PE was diagnosed in 13.3% of cases (67/503). Re-occurrence of the embolism increased the probability of an unfavorable outcome by 4 times, RR 3.96 (95% CI 2.58; 5.87); P=1.0. As can be seen in Table 6, repeated embolisms developed at the same frequency with TLT and ACT: in 15.3% and 11.7%, respectively; p=0.29. With repeated embolism, the predominant effect of the treatment method for survival, TLT or ACT, was not found: mortality was 61.8% (21/34) and 54.5% (18/33), respectively; p=0.62.

If hospital re-occurence did not occur, then thrombolysis was much more effective, and significantly (8 times), reducing the probability of death in comparison with ACT data: lethality was 1.6% (3/188) vs. 12.9% (32/248), respectively; p<0.001*; P=1.0; RR 0.12 (95% CI 0.03; 0.41).

Hypothetically, the presence of a floating thrombus fragment is associated with an increased threat of the next episode of pulmonary embolism. However, in reality, the frequency of repeated embolism in patients with instrumentally confirmed flotation and in patients without flotation did not differ: 15.9% (34/214) and 11.4% (33/289); p=0.147; P=0.32.

Bleeding occurred in 46 observations out of 503 (9.1%), 14 patients died. Mortality in the development of bleeding was statistically significantly higher than that in patients without this complication: 30.4% versus 13.1%; p=0.004*; P=0.83. Hemorrhagic complications apparently had a negative effect on survival, increasing the probability of a fatal outcome by 2.3 times, RR 2.32 (95% CI 1.31; 3.79) (Table 5).

With TLT and ACT, the incidence of bleeding did not differ: 7.7% and 10.3%, respectively; p=0.35, P=0.17. Out of 222 patients undergoing TLT, hemorrhages developed in 17; 7 of them died. Of the 281 patients who received an

anticoagulant, bleeding was noted in 29 cases; 7 patients died. The difference in lethality with different treatment methods was not revealed in patients with bleeding: 41.2% and 24.1%; p=0.32; P=0.23 (Table 6).

In 4 cases, intracranial hemorrhages were diagnosed: in two cases — acute intracerebral hematomas after ALT with alteplase (0.9% (95% CI 0.1; 3.2)); one hematoma and one hemorrhagic stroke after ACT (0.7% (95% CI 0.1; 2.6)). Two patients (67 years and 81 years) died (one in each group) on the 105th and 8th day of treatment; one 49-old-patient survived and was discharged with almost complete regression of neurologic symptoms; a 63-year-old patient with a hemorrhagic stroke was transferred to another medical institution and dropped out of observation on the 6th day of treatment.

In the scientific literature it is common to consider separately "large" and "small" hemorrhagic complications, a clear boundary between which is not defined. The "large" bleedings include those that cause acute anemia, requiring correction, and cases associated with cavity and organ bleedings [7, 10-13]. Extracranial "large" hemorrhages with significant blood loss were observed in 11 cases: 4 with TLT (1.8%) and 7 with ACT (2.5%). These included: extensive hematomas of the soft tissues of the anterior abdominal wall (2), lumbar region (1), neck (1), hip (2); one-sided hemothorax with mediastinal hematoma (1), pancreatic pseudocyst hemorrhage into the cavity (1), intensive pulmonary hemorrhage with massive blood aspiration (1), and intensive gastrointestinal bleeding (2).

In the remaining 31 observations, 46 episodes of low-intensity bleeding were noted: nasal, gastrointestinal, pulmonary, single uterine, short-term macrohematuria, and limited hematomas of soft tissues.

In total, the frequency of "dangerous" hemorrhagic episodes in TLT was 2.7% (95% CI 1.0; 5.8) (6/222), and 3.2% (95% CI 1.5; 6.0) (9/281) with ACT; there was no statistically significant difference (p=0.80, Fisher's test, P=0.06). The frequency of low-intensity bleeding was 5.0% (95% CI 2.5; 8.7) (11/222) with TLT and 7.1% (95% CI 4.4; 10.8) (20/281) with ACT. No statistically significant difference was found in this case (p=0.36, Fisher's test, P=0.16).

Instrumental signs of infarct pneumonia were revealed in 125 patients out of 503 (24.9%). The development of pulmonary infarction increased the probability of an unfavorable outcome by 1.7 times, RR 1.74 (95% CI 1.09; 2.71), p=0.019, P=0.62 (Table 5). It developed 1.5 times more often with ACT than with TLT, RR 0.69 (95% CI 0.49; 0.96), p=0.022, P=0.64. With the development of pulmonary infarction, the treatment method had no statistically significant effect on survival: mortality was 25.0% (11/44) and 19.8% (16/81); p=0.50, P=0.11 (Table 6).

Arrythmias (predominantly atrial fibrillation/atrial flutter) that occurred in the intensive care unit and were caused by acute congestion of the right heart were noted in 9.3% of cases and increased the probability of an unfavorable outcome by 1.9 times, RR 1.88 (95% CI 1.01; 3.21), p=0.048, P=0.58 (Table 5). Arrythmias developed at the same frequency in both TLT and ACT: 9.9% and 8.9%; p=0.76, P=0.07. In those cases when TLT was performed in patients with rhythm disturbances, the lethality was statistically significant and significantly lower in comparison with ACT results: 4.5% (1/22) vs. 44.0% (11/25); p=0.002*, Fisher's test; P=0.91. That is, for acute heart rhythm abnormalities, TLT reduced the probaility of a fatal outcome by 9.7 times compared to ACT, RR 0.103 (95% CI 0.005; 0.645) (Table 6).

The characteristics of the proportional contribution of each of the factors which affected the unfavorable outcome are presented in Table 7. In the Cox proportional intensity model of the 6 factors considered, only 3 were significant predictors of instantaneous risk (p for "beta"<0.05), with unstable hemodynamics and hospital re-occurrence of PE were more important than age: the coefficient "beta" at the parameter "Age" was 62 times less than with "hemodynamic disorder" and 31 times less than with "re-occurrence of PE." The remaining coefficients can be considered equal to 0, since the corresponding values of p were much greater than 0.05. Thus, hemodynamic instability factor had the maximum influence on the time of onset of an unfavorable outcome in acute PE. The second was the hospital re-occurrence of the embolism. The age had a weak influence. The proportional influence of the other factors relative to the listed three can be neglected.

Table 7

Parameters of the Cox proportional hazards model, evaluation of the proportional contribution of each of the predictors of the lifetime in acute PE

Characteristics of the model: χ^2=112.9; df=6; *p*<0.00001			
Factors for time of unfavorable outcome occurrence	Coefficient *«beta»* (95% ДИ)	*SD* for *«beta»*	*p* for *«beta»*
Age	0.033 (0.015; 0.050)	0.009	0.0003
Hemodynamics disturbance	2.012 (1.481; 2.542)	0.271	<0.00001
Re-occurrence of PE	1.009 (0.522; 1.495)	0.248	0.00005
Bleeding	0.497 (-0.276; 1.270)	0.394	0.21
Pulmonary infarction	0.030 (-0.470; 0.531)	0.255	0.91
Arrythmias	0.191 (-0.143; 0.526)	0.171	0.26

Notes: PE — pulmonary embolism

DISCUSSION

As a result of the study, it was found that in acute pulmonary embolism, hemodynamic decompensation, significant bleeding, hospital re-occurrence of the embolism, age, arrythmias and pulmonary infarction had a negative effect on outcome in decreasing order of importance. In turn, TLT showed better efficacy in comparison with ACT and with hemodynamic decompensation, and with rhythm disturbances. In the age group over 75, TLT had no advantages over ACT, manifesting them in younger age groups. Hemorrhagic complications in TLT did not develop more often than with ACT.

The factor of a strong effect on the outcome was a hospital relapse of PE, which incidence did not depend neither on the presence of a floating thrombus, nor on the choice of the treatment method (TLT or ACT). Outside the re-occurence (87% of the total sample (436/503)), the advantage of TLT for survival was unconditional. The death rate was 8 times less: 1.6% compared to 12.9%, $p<0.001^*$, P=1.0.

In general, TLT compared with ACT showed a more powerful effect on mortality reduction: OR 0.56 (95% CI 0.32; 0.97). At the same time, there was no difference in the incidence of complications that increased the risk of death, such as hospital re-occurrence of PE, life-threatening hemorrhages and acute cardiac arrhythmias. At the same time, the pulmonary infarction with TLT developed less often: OR 0.61 (95% CI 0.39; 0.95).

It is worth comparing results with the already accumulated experience of other researchers. Cochrane Collaboration regularly generalizes the results of drug tests. It has been analyzing the advantages of TLT since 2002. The meta-analysis was reproduced in 2006, 2009, 2015, supplemented by new data [7-10]. The last one of 2015 was based on data from 17 samples from 20 countries with a total number of participants 2,167 [10]. The meta-analysis of the American Medical Association (2014) includes 16 samples with a total of 2,115 observations [12]. The data of PEITHO (Pulmonary Embolism Thrombolysis), the largest randomized trial of TLT in PE, conducted in 76 centers in 13 countries with a total of 1,005 participants [11] are highly representative. The most grandiose resource studied is the national data of all US hospitals over 10 years: 72,230 high-risk patients out of 2,110,320 observations with pulmonary embolism [13]. The summarized results of our study, meta-analyzes, PEITHO and Nationwide Inpatient Sample USA, expressed by OR with 95% CI for the two treatment methods (TLT and ACT) are presented in Table 8 and Fig. 3. In the figure, the results of our study are indicated in blue, the results of other authors are lilac [10-13]. Table 8 is the legend for Fig. 3. Visually all the segments that are to the left of the vertical axis and do not intersect it are evidence in favor of TLT, while those on the right are in favor of ACT. The shorter the segment is (the narrower confidence interval is), the more precise the study is, and the higher is its power and the more convincing argument in favor of one or another method of treatment is. On the contrary, the wider it is, the lower the representativeness is, the more uncertain the result is.

The main result, indicating the advantage of TLT for survival, coincided with the results of meta-analyzes (position 1 in Figure 3 and in Table 8). As you can see, all the indicators are correct, since confidence intervals do not include 1.

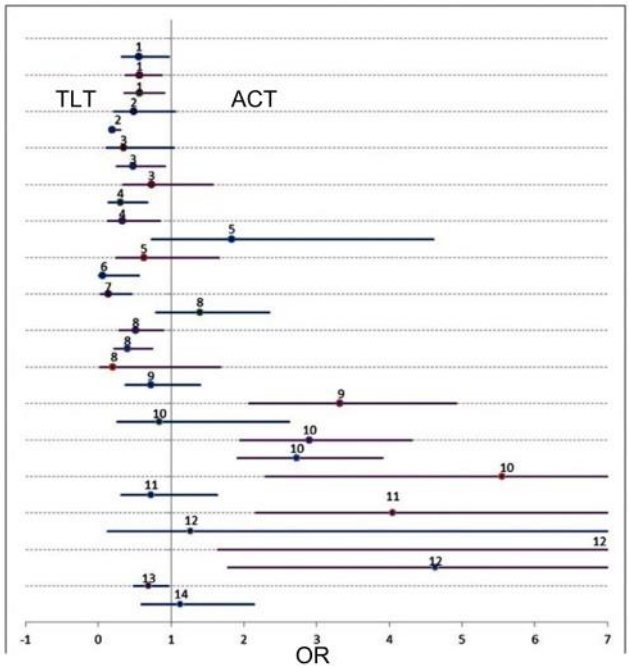


Fig. 3. The comparison of the results with findings of other studies, expressed by OR with 95% CI for both treatment methods (TLT and ACT)
Notes: ACT — anticoagulant therapy; CI — confidence interval; OR — odds ratio; TLT — thrombolytic therapy. The blue color indicates interval estimations, the lilac color indicates results of other authors. The number above the segment is each of the parameters contained in Column 2 of Table 8. Visually, all segments on the left of the vertical axis and not crossing it, evidence in favor of TLT. On the right — in favor of ACT. The shorter the segment is (the narrower confidence interval is), the more precise the study is, and the higher is its power and the more convincing argument in favor of one or another method of treatment is. On the contrary, the wider it is, the lower the representativeness is, the more uncertain the result is

Table 8

The comparison of the results with findings of other researchers

№	TLT / ACT subgroups	OR (95% CI) Our study	OR (95% CI) Other researches
1	Total mortality	0.56 (0.32; 0.97)	0.57 (0.37: 0.87) [10] 0.57 (0.36; 0.91) [12]
2	High risk of death	0.49 (0.22; 1.06)	0,193 (0,185; 0,301) [13]
3	Intermediate risk of death	0.35 (0.11; 1.04)	0.48 (0.25; 0.92) [12] 0.73 (0.34; 1.57) [11]
4	Mortality: age under 75 лет	0.30 (0.14; 0.67)	0.33 (0.13; 0.85) [11]
5	Mortality: age 75 and over	1.83 (0.73; 4.61)	0.63 (0.24; 1.66) [11]
6	Mortality: arrythmias	0.061 (0.003; 0.557)	–
7	Mortality: no repeated PE	0.137 (0.034; 0.455)	
8	Incidence: repeated PE	1.40 (0.79; 2.35)	0.51 (0.29; 0.89) [10] 0.40 (0.22; 0.74) [12] 0.20 (0.02; 1.68) [11]
9	Incidence: all hemorrhagic cimplications	0.72 (0.37; 1.40)	3.19 (2.07; 4.92) [12]
10	Incidence: severe hemorrhagic cimplications	0.84 (0.26; 2.62)	2.90 (1.95; 4.31) [10] 2.73 (1.91; 3.91) [12] 5.55 (2.30; 13.39) [11]
11	Incidence: minor hemorrhagic cimplications	0.72 (0.31; 1.63)	4.05 (2.17; 7.54) [10]
12	Incidence: intracranial bleeding	1.27 (0.13; 12.67)	12.10 (1.64; 250.14) [11] 4.63 (1.78; 12.04) [12]
13	Incidence: pulmonary infarction	0.69 (0.49; 0.96)	–
14	Incidence: arrythmias	1.13 (0.59; 2.14)	–

Notes: ACT — anticoagulant therapy; CI — confidence interval; OR — odds ratio; TLT — thrombolytic therapy.
Column 1 contains the number indicating interval estimation of the corresponding parameter. Column 2 contains the name of the parameter. Column 3 shows the result which is the numerical value of the odds ratio and its 95% confidence interval. Column 4 contains similar results from other researchers; references to particular publications are given in square brackets

The result of the high-risk subgroup also matched, which is now recognized as unconditional: in hemodynamic decompensation TLT is more effective for survival (position 2 in Figure 3). In comparison with the representativeness of the giant sample of P.D. Stein with a very convincing narrow confidence interval (P=1.0, OR 0.193 (95% CI 0.185; 0.301)) our data have lack of accuracy: P=0.51; OR 0.49 (95% CI 0.22; 1.06) [13].

The main question to which the meta-analyzes and the PEITHO program are devoted: is there an advantage of TLT over ACT in the subgroup of intermediate risk? Our incompletely correct data OR 0.35 (95% CI 0.11; 1.04) and the correct data of S. Chatterjee OR 0.48 (95% CI 0.25; 0.92) coincided: thrombolysis was associated with a decrease in mortality at an intermediate risk (position 3 in Figure 3). Moreover, S. Chatterjee noted that such an association was obtained mainly due to the use of thrombolytics in patients with intermediate risk. The results of PEITHO do not confirm this conclusion: OR 0.73 (95% CI 0.34, 1.57) [11]. However, S. Chatterjee notes that the benefits of thrombolytic agents at intermediate risk can be difficult to detect in exactly randomized trials [12].

Our data indicating the loss of the benefits of TLT before ACT in patients of senile age (⩾75 years) coincided with the data of G. Meyer: TLT contributed to survival in patients under 75 (OR 0.30 (95% CI 0.14; 0, 67) and 0.33 (95% CI 0.13; 0.85)) and lost the advantage for the elderly (OR 1.83 (95% CI 0.73; 4.61) and 0.63 (95% CI 0.24; 1.66)) (position 4 and 5 in Figure 3) [11].

In addition, in our study, at a high significance level (p=0.006*, P = 0.91), it was found that in the occurrence of acute cardiac arrhythmias, the lethality among patients receiving thrombolytics was 9.7 times lower compared to the results of anticoagulant treatment: OR 0.006 (95% CI 0.003; 0.557) (position 6 in Figure 3).

There was no evidence of worse survival in a subgroup of patients with a floating thrombus in TLT (OR 0.78 (95% CI 0.35; 1.71)), although hypothetically fragmentation of thrombus due to thrombolytic administration creates conditions for an increased risk of recurrent episodes of embolism. The relation between the presence of flotation and the frequency of hospital re-occurrence was also not established. But the repeated embolism itself influenced on lethality very strongly, regardless of the applied method of treatment (Table 6). In the absence of recurrence (and this is 87% of all observations), the advantage of TLT over ACT was undeniable: at a significance level of $p<0.001$ and P=1.0 the probability of fatal outcomes was lower by 8 times with thrombolysis compared to anticoagulant therapy: OR 0.12 (95% CI 0.03; 0.41); OR 0.14 (95% CI 0.03; 0.46) (position 7 in Figure 3).

The results cocerning incidence of repeated embolism and bleeding differed. In our study, there was no decrease in the risk of recurrence of PE in the use of TLT (OR 1.40 (95% CI 0.79, 2.35)), in contrast to the data of Q. Hao: OR 0.51 (95% CI 0.29; 0.89) and S. Chatterjee: OR 0.40 (95% CI 0.22; 0.74) [10, 12]. However, G. Meyer also did not confirm a decrease in the risk of recurrence of embolism in TLT: OR 0.20 (95% CI 0.02; 1.68) (position 8 in Figure 3) [11].

In our sample, the risk of bleeding in TLT and ACT did not differ: OR 0.72 (95% CI 0.37; 1.40). This concerns "large" (OR 0.84 (95% CI 0.26; 2.62) and "small" haemorrhagic episodes (OR 0.72 (95% CI 0.31; 1.63)) In meta-analyzes and PEITHO, TLT significantly increased the risk of bleeding (position 9, 10 and 11 in Figure 3).

A special issue is intracranial hemorrhage (ICH), which is not comparable with massive PE in its consequences, except for the category of patients with maximum risk. This complication was rare: 0.9% (2/222) for TLT, and 0.7% (2/281) for ACT. Other researchers: G. Meyer [11] — 2.4% (12/506) for TLT and 0.2% (1/499) for ACT; S. Chatterjee [12] — 1.46% (15/1024) and 0.2% (2/1019). The generalized data of ESC 2014 recommendations give an average level of 1.9-2.2% [2]. In our sample, the ICH for TLT and ACT did not differ: OR 1.27 (95% CI 0.13; 12.67). And according to the aggregate data of other authors, the ICH developed 12 and 7 times more often with TLT than with ACT: OR 1.64; (95% CI 12.10; 250.14) and OR 4.63 (95% CI 1.78; 12.04) [11, 12].

All indicators of comparative risk lacked accuracy, which is reflected in a very wide confidence interval and requires further observations (positions 12 in Figure 3). Predictive parameters for intracranial hemorrhages in TLT are not currently defined [2].

In the meta-analysis of S. Chatterjee, there was a correlation with an increased risk of severe hemorrhagic complications in the age group over 65: 12.9% (87/673) vs. 4.10% (27/658); OS 3.10 (95% CI 2.10; 4.56). With this stratification, the same trend was noted in our sample, but no correct differences were found: 4.5% (10/222) vs. 1.8% (5/281); p=0.11 Fisher's test; OR 2.60 (95% CI 0.80; 8.89).

CONCLUSION

The most correct, statistically confirmed (control of errors of type I and II) results, concerning the advantages of thrombolytic therapy before anticoagulant therapy are:

- a decrease in the general lethality (p=0,031, P=0,60); an increase in the survival time and the proportion of survivors (p=0.027, P=0.96, Kaplan-Mayer method);
- a 8-fold mortality reduction in the subgroup without hospital re-occurrence of the embolism (87% of the sample) ($p<0.001$; P=1.0).
- a decrease in mortality in patients under 75 (p=0.001, P=0.92);
- a decrease in mortality in a subgroup with acute cardiac arrhythmias (p=0.002, P=0.91);
- a decrease in the incidence of pulmonary infarction (p=0.022, P=0.64);
- no difference in the frequency of hemorrhagic complications (p=0.35, P=0.17).

Of the factors studied, the strongest proportional effect at the time of onset of an adverse outcome in descending order had the following: disorders of systemic hemodynamics, hospital recurrence of PE and older age.

In a comparative evaluation of findings with the results of other researchers, the disagreements concern two positions: in our study, there was no evidence of a reduction in the frequency of PE re-occurrence and an increase in the frequency of hemorrhagic complications resulting from the use of thrombolytics. Equivalence of the risk of bleeding in both methods of treatment in our case is most likely associated with the lack of randomization. That is thrombolysis was not prescribed in patients with a high threat of bleeding, so hemorrhagic complications occurred less often. It is likely that compliance with the rules for thrombolytics prescription, indicated in clinical recommendations, is able to equalize the risk of hemorrhagic complications, and thus neutralizing doubts about the better efficacy of TLT over ACT in acute pulmonary embolism, especially in patients with intermediate risk of sudden death.

FINDINGS

1. Mortality in thrombolytic therapy among patients with a high and intermediate risk of early death from acute pulmonary thromboembolism was 10.8% (95% CI 7.1; 15.7) (24/222) and was lower compared to that for the use of anticoagulant therapy 17.8% (95% CI 13.5; 22.8) (50/281) at a significance level of p=0.031 at a study power of P=0.60. The use of thrombolytic therapy reduced the probability of a lethal outcome by 1.65 times: the relative risk was 0.61 (95% CI 0.37-0.98), odds ratio 0.56 (95% CI 0.32; 0.97). The study power P=0.60 for α=0.05 does not allow us to conclude that the advantage of TLT over ACT for survival is strictly correct.

2. In a subgroup of high-risk patients, the lethality with thrombolytics was lower compared to anticoagulant treatment, reaching 30.2% (95% CI 19.2; 43.0) (19/63) versus 47.1% (95% CI 34.8; 59.6) (32/68), p=0.051, P=0.51; as in the subgroup of intermediate risk, where the mortality rates were 3.1% (95% CI 1.0; 7.2) (5/159) and 8.5% (95% CI 5.1; 13.0) (18/213), p=0.048, P=0.58. Insufficient level of research power of 0.51 and 0.58 for α=0.05 does not allow to conclude that the advantage of TLT over ACT for survival in each of the subgroups is strictly correct.

3. The proportion of 15-day survival with thrombolytic therapy was statistically significantly higher than that of anticoagulant therapy, amounting to 0.901 (95% CI 0.864; 0.922), respectively, against 0.840 (95% CI 0.801; 0.864); the significance level of the difference p=0.027 at a convincing power level P=0.96 for α=0.05. The median survival time was 56 and 43 days, respectively.

4. The use of thrombolysis compared to anticoagulant therapy was associated with a statistically significant reduction in mortality in the subgroup of patient under 75: mortality was 5.5% (95% CI 2.7; 9.9) (10/81) and 16.2% (95% CI 11.4; 22.0) (33/204), respectively, p=0.001; P=0.92, relative risk (RR) 0.61 (95% CI 0.37, 0.98), odds ratio 0.56 (95% CI 0.32; 0.97). In the age group of 75 years and older, TLT did not have advantages over ACT.

5. In acute heart rhythm disorders due to PE, TLT statistically significantly decreased the probability of fatal outcome by 9.7 times compared to the results of anticoagulant use: lethality 4.5% (95% CI 0.1, 22.8) (1/22) vs. 44.0% (95% CI 24.4; 65.1) (11/25), p=0.002, P=0.91, RR 0.103 (95% CI 0.005 to 0.645).

6. Hemorrhagic complications in TLT did not develop more often than with ACT. The incidence of all hemorrhagic complications in TLT and ACT was 7.7% (95% CI 4.5; 12.0) (17/222) and 10.3% (95% CI 7.0; 14.5) (29/281), respectively, p=0.351, P=0.17; Severe clinically significant bleeding (including intracranial): 2.7% (95% CI 1.0; 5.8) (6/222) and 3.2% (95% CI 1.5; 6.0) (9/281); p=0.80; P=0.06; minor bleeding: 5.0% (95% CI 2.5; 8.7) (11/222) and 7.1% (95% CI 4.4; 10.8) (20/281); p=0.36; P=0.16; intracranial hemorrhages: 0.90% (95% CI 0.11; 3.22) (2/222) and 0.71% (95% CI 0.09; 2.55) (2/281); p=0.81; P=0.13. No statistically significant differences were found.

7. Repeated embolisms in the hospital period developed at the same frequency with TLT and ACT: in 15.3% (95% CI 10.9; 20.7) (34/222) and 11.7% (95% CI 8.2; 16.1) (33/281), respectively; p=0.29, P=0.15. There were no statistically significant differences in this.

8. In acute pulmonary embolism, hemodynamic decompensation (RR 6.30 (95% CI 3.96; 10.16)), significant bleeding (RR 4.51 (95% CI 2.37; 6.51)), hospital re-occurrence of embolism (RR 3.96 (95% CI 2.58, 5.87)), age 75 years and older (RR 2.35 (95% CI 1.51; 3.62)), acute cardiac arrhythmias RR 1.88 (95% CI, 1.01; 3.21)) and the development of pulmonary infarction (RR 1.74 (95% CI 1.09; 2.71)) had a negative effect on outcome in decreasing order of significance.

9. The following factors had the strongest proportional effect at the time of onset of an adverse outcome in order of decreasing significance: systemic hemodynamics disorders (beta 2.012 (95% CI 1.481; 2.542)), hospital re-occurrence of PE (beta 1.009 (95% CI 0.5228 1.495)) and the senior age (beta 0.033 (95% CI 0.015; 0.050)).

REFERENCES

1. Savel'ev V.S., Chazov E.I., Gusev E.I., Kirienko A.I. Russian clinical recommendations for the diagnosis, treatment and prevention of venous thromboembolic complications. *Flebologiya*. 2010; 4(2-1): 3–37. (In Russian)
2. Konstantinides S.V., Torbicki A., Agnelli G., et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J.* 2014; 35(43): 3033-69, 3069a-3069k. PMID: 25173341. DOI: 10.1093/eurheartj/ehu283.
3. Kearon C., Kahn S.R., Agnelli G., et al. American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008; 133(6 Suppl):454S–545S. PMID: 18574272. DOI: 10.1378/chest.08-0658.
4. Jaff M.R., McMurtry M.S., Archer S.L., et al. Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension A Scientific Statement From the American Heart Association. *Circulation*. 2011; 123(16): 1788–1830. PMID: 21422387. DOI: 10.1161/CIR.0b013e318214914f.
5. British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development Group. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. *Thorax*. 2003; 58(6): 470–484. PMID: 12775856.
6. Torbicki A., Perrier A., Konstantinides S., et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2008; 29(18): 2276–2315. PMID: 18757870. DOI: 10.1093/eurheartj/ehn310.
7. Dong B., Pineo G., Mulrooney T. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev*. 2002; (3). DOI: 10.1002/14651858.CD004437.
8. Dong B.R., Yue J., Liu G.J., et al. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev*. 2006 Apr 19; (2): CD004437. PMID: 16625603. DOI: 10.1002/14651858.CD004437.pub2.
9. Dong B.R., Hao Q., Yue J., et al. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev*. 2009 Jul 8; (3): CD004437. PMID: 19588357. DOI: 10.1002/14651858.CD004437.pub3.
10. Hao Q., Dong B.R., Yue J., et al. Thrombolytic therapy for pulmonary embolism. *Cochrane Database Syst Rev.* 2015 Sep 30; (9): CD004437. PMID: 26419832. DOI: 10.1002/14651858.CD004437.pub4.
11. Meyer G., Vicaut E., Danays T., et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med.* 2014; 370(15): 1402–1411. PMID: 24716681. DOI: 10.1056/NEJMoa1302097.
12. Chatterjee S., Chakraborty A., Weinberg I., et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA*. 2014; 311(23): 2414-2421. PMID: 24938564. DOI: 10.1001/jama.2014.5990.
13. Stein P.D., Matta F. Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused. *Am J Med*. 2012; 125(5): 465–470. PMID: 22325236. DOI: 10.1016/j.amjmed.2011.10.015.

Received on 23.10.2017

Accepted on 30.11.2017