Incidence of Major Bleeding in Patients with Pulmonary Thromboembolism Treated with Fixed Dose Alteplase 100 mg

Dae-Hwan Bae 1, Won Jae Lee 1, and Yoon Mi Shin 2

1Department of Internal Medicine, Chungbuk National University Hospital, Cheongju, Korea
2Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea

ABSTRACT

Background: Acute pulmonary thromboembolism (PTE) is a critical cardiopulmonary condition associated with high mortality and morbidity. In massive PTE, recently referred to as high risk PTE, the routine protocol for thrombolysis with recombinant tissue plasminogen activator (alteplase) is 100 mg over 2 hours. However, there are concerns about bleeding in patients with low body weight (< 50 kg), elderly patients, and Asians.

Method: We performed a retrospective study in patients who were diagnosed with intermediate or high risk PTE, and who were treated with a fixed dose of alteplase (100 mg) in a single center at Chungbuk National University Hospital between July 2008 and April 2018.

Results: A total of 42 patients were reviewed, 4 patients dropped out, and 38 patients were included in the analysis. There were 18 males (47.4%), and the average age of the patients was 70.68 years (± standard deviation 13.15). Major bleeding was seen in 10/38 patients (26.3%), and 30/38 patients (78.9%) were successfully discharged.

Conclusion: The major bleeding risk was higher in our study (26.3%) than in a previously published meta-analysis (9.24%). Therefore, we suggest reducing the dose of alteplase in patients who are elderly, Asian, or have cardiovascular disease. Further prospective studies of efficacy and bleeding rate after low dose alteplase should be considered.

Keywords: Pulmonary Thromboembolism; Bleeding; Thrombolysis; Dose

INTRODUCTION

In Europe, 1–2 per 1,000 individuals have venous thromboembolism, which results in a mortality rate of 17%.1,2 In the United States, the prevalence rate of pulmonary thromboembolism (PTE) was 0.4%, and the annual incidence was estimated at 600,000 cases.3 In Korea, the incidence of PTE was 229.36 per 100,000 and the age-sex adjusted standardized incidence rate was 151.28 per 100,000 in a tertiary hospital during the 10-year period from 2006 to 2015.4 Also, a previous study from Korean Health Insurance Review and Assessment service database showed the increasing incidence of PTE in Korea.5 In this study, the annual age- and sex-adjusted incidence (ASR) of venous thromboembolism (VTE) from...
2009 to 2013 in Korea increased yearly. In 2009, ASRs of VTE, deep vein thrombosis, and PTE were 21.3, 8.1, and 13.2 cases per 100,000 individuals and these increased to 29.2, 12.7, and 16.6 cases per 100,000, respectively, in 2013.

Among patients with PTE, thrombolytic therapy is indicated for those with high risk PTE (shock or hypotension). This therapy includes streptokinase, urokinase, or recombinant tissue-type plasminogen activator (rt-PA). The rt-PA drugs include alteplase, reteplase, tenecteplase, and desmoteplase, and there is no particular difference in their therapeutic effects. Alteplase is the only drug currently approved by the Food and Drug Administration for patients with high risk PTE. Alteplase has high specificity and acts rapidly to reduce the resistance of pulmonary blood vessels, with a short half-life, and produces no allergic reactions or hypotensive effects.

The general regimen of alteplase for patients with high risk PTE is 100 mg over 2 hours, or a 10-mg bolus followed by 90 mg over 2 hours. Alteplase initiates local fibrinolysis by binding to fibrin in a thrombus, and converts entrapped plasminogen to plasmin. The details of alteplase metabolism have not yet been revealed, and adjusting the dose according to liver and renal function is not recommended.

Nowadays, the incidence of PTE is increasing, especially in elderly patients due to their comorbidities (cancer, immobilization, fracture, and surgery). There is no routine protocol for dose reduction of alteplase in patients with low body weight, decreased renal function, age over 65, and those with a high risk of bleeding. We have concerns about the bleeding risk when using fixed dose alteplase in these vulnerable patients.

In acute myocardial infarction and stroke, there is evidence about dose reduction of alteplase. In the STREAM trial, in which fibrinolysis was performed in myocardial infarction patients, the incidence of intracranial hemorrhage increased in patients older than 75 years. Therefore, when using rt-PA in patients aged > 75 years, a 50% dose reduction is warranted. The alteplase dose used for patients with stroke is 0.9 mg/kg in most countries, and this dose is particularly low (0.6 mg/kg) in Japan. In the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) trial, compared with standard dose alteplase (0.9 mg/kg), the low dose alteplase (0.6 mg/kg) did not meet any non-inferiority criteria for the outcome of death or disability at 90 days.

Interestingly, in the MOPETT trial of thrombolysis in intermediate-risk PTE, alteplase was used at ≤ 50% of the standard dose. The success rate of thrombolysis was 100%, and the percentage of pulmonary hypertension after thrombolysis was significantly lower than that of the conventional anticoagulation group (16% vs. 63%, \( P < 0.001 \)).

Recent studies halved the dose of alteplase to 50 mg, and have shown no significant difference in efficacy, while there was a decrease in major bleeding. This dose reduction protocol has not been established for patients with high risk PTE. In a Korean retrospective study, a low-dose thrombolytic regimen was as efficient as the standard dose with a lower bleeding risk.

The frequency of bleeding caused by thrombolysis in previous studies reported to be 0%–23%, and a meta-analysis showed a mortality rate of 2.17%, and an incidence of major bleeding events of 9.24%.
The purpose of our study was to evaluate the major bleeding incidence in intermediate to high-risk PTE patients to whom fixed dose alteplase 100mg was administered.

**METHODS**

**Subjects**
We reviewed 42 patients with high risk PTE who had been treated with alteplase 100 mg in Chungbuk National University Hospital, Korea from July 1, 2008 to April 30, 2018. However, one patient voluntarily discharged without performing thrombolysis and we were unable to search the details of medical records of three patients who received alteplase. Thus, the medical records of 38 patients were included in the retrospective analysis. The final diagnosis of PTE was confirmed by chest computed tomography (CT) and echocardiography. Thrombolytic therapy was used in cases when: 1) systolic blood pressure was less than 90 mmHg, or mean arterial pressure was less than 65 mmHg; 2) circulatory shock requiring cardiopulmonary resuscitation occurred; 3) right ventricular (RV) failure occurred with hypoxia, or hypoxemia; or 4) RV dysfunction was ongoing.

**Methods**
We reviewed the medical records and extracted the following data: clinical symptoms; vital signs; laboratory findings (including arterial blood gas analysis, N-terminal pro-brain natriuretic peptide [NT-proBNP], troponin T, D-dimer, hemoglobin); imaging findings (such as chest X-ray, chest contrast CT, including of the pulmonary artery with deep veins, and echocardiography).

Severity of illness was assessed by the duration of intensive care unit hospitalization, and the sequential organ failure assessment (SOFA) score on the day of thrombolysis.

The data was analyzed for overall treatment success rate, incidence of bleeding, and hospital mortality. Criteria of successful thrombolysis were as follows: hemodynamic stability (i.e., the systolic blood pressure was maintained above 90 mmHg, even after stopping inotropes or vasopressors); improved oxygen saturation; and echocardiographic RV dysfunction improved or was absent during hospitalization and follow-up. The consequences of major bleeding were defined as: 1) fatal bleeding; 2) intracranial hemorrhage; 3) bleeding sufficient to require surgery; 4) reduction in hemoglobin by 2 g/dL or more, or the need for transfusion of two or more units of packed red blood cells. Any bleeding that did not match the above criteria was classified as minor bleeding. Thus, patients were categorized into three groups: 1) non-bleeding; 2) minor bleeding; and 3) major bleeding.

**Statistical analysis**
Statistical analysis was performed using SPSS for Windows (version 25.0, SPSS Inc., Chicago, IL, USA). General descriptive statistics were used to determine the mean, standard deviation, and frequency. For categorical data, the nominal variables were analyzed with the $\chi^2$ test or Fisher’s exact test. Student’s $t$-test was used for continuous variables, and the Mann-Whitney U test was also performed when normal distribution could not be assumed, because there were few observations or variances. For the multivariate analysis, logistic regression was used. The two-sided test and analysis of variance were used, and statistical significance was defined as $P < 0.05$. 
**Ethics statement**

The Institutional Review Board of Chungbuk National University Hospital approved the study protocol and waived the need for informed consent because the study was retrospective, and no patients were at risk (approval No. 2018-05-020). The study was performed in accordance with the Declaration of Helsinki.

**RESULTS**

**Patient characteristics**

A total of 38 patients were reviewed for this study. A fixed dose of alteplase (100 mg) was used, as per the guidelines; it was administered over 2 hours, or as a 10-mg bolus followed by the remaining 90 mg over 2 hours. There were 22 patients without bleeding, 6 patients with minor bleeding, and 10 patients with major bleeding. The mean age of these three groups was similar (71, 67, and 73 years, respectively; \( P = 0.659 \) (Table 1)). The SOFA score was significantly higher in the non-bleeding group (8.2 points), and the incidence of cardiovascular disease (70%) was higher in patients with major bleeding than in the other groups. Of the 38 patients, aspirin was used by 10 patients, 5 of whom had major bleeding. Other characteristics did not differ between the three groups.

**Diagnostic tests and laboratory findings**

There were no differences in average systolic blood pressure among the three groups. One of the arterial blood gas parameters, partial pressure of carbon dioxide, was lower in the

| Table 1. Baseline characteristics of patients with PTE who received alteplase 100 mg |
|---------------------------------------------------------------|
| Characteristics | Total (n = 38) | Non-bleeding (n = 22) | Minor bleeding (n = 6) | Major bleeding (n = 10) | \( P \) value |
|-----------------|---------------|----------------------|-----------------------|------------------------|--------------|
| Men             | 18 (47.4)     | 13 (59.1)            | 2 (33.3)              | 3 (30)                 | 0.321        |
| Age, yr         | 70.68 ± 13.15 | 70.86 ± 15.78        | 66.50 ± 7.26          | 72.80 ± 9.15           | 0.659        |
| \(< 65\)        | 8 (21.0)      | 6 (27.3)             | 1 (16.7)              | 1 (10.0)               |              |
| \(65-75\)       | 14 (36.8)     | 6 (27.3)             | 4 (67.7)              | 4 (40.0)               |              |
| \(\geq 75\)     | 16 (42.1)     | 10 (45.5)            | 1 (16.7)              | 1 (10.0)               |              |
| Body weight, kg | 63.55 ± 12.09 | 62.24 ± 14.62        | 63.97 ± 12.10         | 66.17 ± 5.38           | 0.819        |
| \(< 50\)        | 3             | 3                    | 0                     | 0                      |              |
| \(\geq 50\)     | 19            | 10                   | 3                     | 6                      |              |
| BMI, kg/m²      | 23.83 ± 4.04  | 23.00 ± 4.87         | 23.90 ± 1.86          | 23.83 ± 4.04           | 0.448        |
| \(< 18.5\)      | 2             | 2                    | 0                     | 0                      |              |
| \(18.5-25\)     | 10            | 6                    | 2                     | 2                      |              |
| \(\geq 25\)     | 10            | 5                    | 1                     | 4                      |              |
| SOFA score      | 6.24 ± 4.39   | 8.27 ± 4.53          | 2.00 ± 0.00           | 3.71 ± 1.60            | 0.009        |
| Risk of PTE     |               |                       |                       |                        |              |
| High            | 34 (89.5)     | 20 (91.0)            | 4 (66.7)              | 10 (100.0)             |              |
| Intermediate    | 4 (10.5)      | 2 (9.0)              | 2 (33.3)              | 0 (0)                  |              |
| Previous disease |               |                       |                       |                        |              |
| Hypertension    | 20 (52.6)     | 13 (59.1)            | 1 (16.7)              | 6 (60.0)               | 0.189        |
| Diabetes        | 7 (18.4)      | 3 (13.6)             | 0 (0)                 | 4 (40.0)               | 0.139        |
| Cardiovascular disease | 15 (39.5) | 7 (31.8)            | 1 (16.7)              | 7 (70.0)               | 0.081        |
| Pulmonary disease | 4 (10.5)     | 2 (9.1)              | 1 (16.7)              | 1 (10.0)               | 0.791        |
| Renal disease   | 5 (13.2)      | 2 (9.1)              | 0 (0)                 | 3 (30.0)               | 0.251        |
| Malignancy      | 6 (15.8)      | 4 (18.2)             | 0 (0)                 | 2 (20.0)               | 0.690        |
| Use of anticoagulation & antiplatelet agent | | | | | |
| Aspirin         | 10 (26.3)     | 5 (22.7)             | 0 (0)                 | 5 (50.0)               | 0.119        |
| P2Y12 Inhibitor | 2 (5.3)       | 2 (9.1)              | 0 (0)                 | 0 (0)                  | 0.687        |
| Anticoagulant   | 3 (7.9)       | 3 (13.6)             | 0 (0)                 | 0 (0)                  | 0.726        |

Data are presented as mean ± standard deviation or number (%).

PTE = pulmonary thromboembolism, BMI = body mass index, SOFA score = sequential organ failure assessment score.
group with major bleeding, but all groups showed respiratory alkalosis, with no statistically significant differences. Other blood tests such as NT-proBNP, troponin T, D-dimer, platelets, total bilirubin, creatinine, and other results of arterial blood gas analysis revealed no differences, and the PaO2/FiO2 ratio (PF ratio) was similar (Table 2).

On echocardiography, left ventricular ejection fraction was normal, and RV systolic pressure indicated mild pulmonary hypertension, with no differences among the three groups.

## Bleeding complication associated with thrombolytic therapy

The overall frequency of major bleeding was 26.3% (10/38 patients). Only one patient with major bleeding had intracranial hemorrhage, and in the other 9 patients there was a reduction of hemoglobin by 2 g/dL or more, or transfusion of two or more units of packed red blood cells (RBCs).

Six patients (15.8%) had minor bleeding. Bleeding sites varied, and included an intravenous or arterial-line site, gastrointestinal tract, epistaxis, and other sites (Table 3). No deaths were caused by bleeding.

### Table 2. Clinical and laboratory findings

| Variables                  | Total (n = 38) | Non-bleeding (n = 22) | Minor bleeding (n = 6) | Major bleeding (n = 10) | P value |
|----------------------------|----------------|-----------------------|------------------------|------------------------|---------|
| Systolic BP, mmHg          | 70.41 ± 19.63  | 68.44 ± 24.35         | 82.00 ± 11.36          | 70.00 ± 7.56           | 0.169   |
| Diastolic BP, mmHg         | 47.60 ± 14.19  | 47.31 ± 16.74         | 47.67 ± 16.44          | 48.33 ± 4.08           | 0.565   |
| Mean BP, mmHg              | 55.48 ± 15.61  | 54.35 ± 18.76         | 59.11 ± 14.74          | 56.67 ± 3.65           | 0.355   |

| Laboratory findings        |                |                       |                        |                        |         |
|----------------------------|----------------|-----------------------|------------------------|------------------------|---------|
| NT-proBNP, pg/mL           | 5.650 ± 8.457  | 6.256 ± 10.423        | 7.131 ± 6.564          | 3.845 ± 3.626          | 0.724   |
| Troponin T, ng/mL          | 0.12 ± 0.20    | 0.11 ± 0.21           | 0.05 ± 0.07            | 0.19 ± 0.22            | 0.427   |
| D-dimer, µg/mL             | 19.0 ± 29.6    | 26.2 ± 37.6           | 5.3 ± 3.1              | 12.0 ± 7.7             | 0.217   |
| Platelets, /µL             | 218,500 ± 110,386 | 232,730 ± 133,683    | 241,170 ± 71,323       | 173,600 ± 49,916       | 0.330   |
| Total bilirubin, mg/dL     | 0.74 ± 0.43    | 0.78 ± 0.45           | 0.52 ± 0.27            | 0.78 ± 0.46            | 0.387   |
| Creatinine, mg/dL          | 1.15 ± 0.48    | 1.27 ± 0.49           | 0.84 ± 0.38            | 1.06 ± 0.44            | 0.107   |
| pH                         | 7.36 ± 0.12    | 7.32 ± 0.14           | 7.41 ± 0.06            | 7.42 ± 0.09            | 0.063   |
| pCO2, mmHg                 | 31.2 ± 11.5    | 33.4 ± 13.7           | 31.5 ± 8.4             | 26.2 ± 4.5             | 0.272   |
| PaO2, mmHg                 | 81.9 ± 30.7    | 83.3 ± 34.8           | 68.9 ± 22.3            | 85.5 ± 25.1            | 0.598   |
| PF ratio                   | 249.9 ± 168.5  | 223.2 ± 188.9         | 261.1 ± 52.2           | 302.9 ± 155.3          | 0.470   |

| Echocardiographic finding  |                |                       |                        |                        |         |
|----------------------------|----------------|-----------------------|------------------------|------------------------|---------|
| Left ventricular ejection fraction, % | 65.0 ± 9.2 | 63.5 ± 7.2         | 68.8 ± 7.3             | 65.3 ± 12.7            | 0.493   |
| Right ventricular systolic pressure, mmHg | 47.0 ± 17.6 | 45.4 ± 17.9 | 54.7 ± 17.9 | 44.1 ± 17.4 | 0.496 |

Data are presented as mean ± standard deviation. BP = blood pressure, NT-proBNP = N-terminal pro-brain natriuretic peptide, pCO2 = partial pressure of carbon dioxide, PaO2 = partial pressure of oxygen, PF ratio = PaO2/FiO2 ratio.

### Table 3. Number of patients with bleeding complications

| Complications                          | Minor bleeding (n = 6) | Major bleeding (n = 10) |
|----------------------------------------|------------------------|------------------------|
| Major bleeding                          | 0                      | 10                     |
| Intracranial hemorrhage                 | 0                      | 1                      |
| Necessity of surgery                    | 0                      | 0                      |
| Hb reduction ≥ 2 or transfusion ≥ 2 pRBC| 0                      | 9                      |

| Bleeding site                          | Minor bleeding (n = 6) | Major bleeding (n = 10) |
|----------------------------------------|------------------------|------------------------|
| IV or A-line site                      | 2                      | 3                      |
| Gi bleeding                            | 1                      | 2                      |
| Gum bleeding                           | 0                      | 0                      |
| Hematuria                              | 0                      | 0                      |
| Epistaxis                              | 1                      | 0                      |
| Intracranial hemorrhage                | 0                      | 1                      |
| Others                                 | 2                      | 5                      |

HB = hemoglobin, pRBC = packed red blood cell, IV = intravenous, A-line = arterial-line, Gi = gastrointestinal.
Treatment success

The average length of stay in the intensive care unit was 3.25 (± 3.52) days (Table 4). Treatment success was achieved in 31/38 patients (81.6%), and 30/38 patients (78.9%) were successfully discharged from the hospital. The mean duration of intensive care unit admission was 3.14 (± 2.77) days in patients with no bleeding, 0.40 (± 0.90) days in patients with minor bleeding, and 5.11 (± 5.00) days in patients with major bleeding, with no statistically significant difference, but the group with major bleeding showed a tendency to stay in the intensive care unit \( (P = 0.050) \). Treatment success rates were 72.7% (16/22 patients) in the groups with non-bleeding, 100% (6/6 patients) in the groups with minor bleeding, and 90% (9/10 patients) in the major bleeding group, with no significant difference between the three groups \( (P = 0.298) \) (Table 4).

DISCUSSION

This retrospective study aimed to investigate major bleeding risk of thrombolysis with fixed dose of alteplase (100 mg) in patients with PTE according to current guidelines. The incidence of major bleeding was higher in our study (26.3%) than in a previously published meta-analysis (9.24%). In aspect of efficacy, the overall success rate of thrombolysis was 81.6% and mortality rate was 21% and these were similar in the three groups, but generally showed good results in the minor bleeding group.

Compared with previous studies, the most distinctive features of the patients in our study was that the average age was almost 70 years, with 78.9% (30/38 patients) older than 65 years, and only Asian population being considered. We hypothesized that age influenced the higher bleeding incidence rate observed in the present study. As Korea has an aging society, PTE prevalence is on the rise due to increasing co-morbidities, especially cancer and major fracture.

All-cause mortality was not increased in patients 65 years and older. However, the incidence of major bleeding was about 13% in elderly patients and only 3% in younger patients. The major bleeding event rate was increased more than four times, according to a previous meta-analysis. In previous studies that used alteplase 100 mg, the mean age of enrolled patients was less (range, 55.98–64.68 years) than that of our present study and those enrolled in Western countries. Moreover, those data showed low incidences of major bleeding (events range, 0%–15%).

In our retrospective study, there were only 8 patients < 65 years and we could not reach a significant statistical difference in the incidence of major bleeding due to this small number.

In the MOPETT trial, the total alteplase dose of 50 mg was administered in patients with moderate PTE weighing more than 50 kg. Of this dose, 10 mg was administered as a

---

**Table 4. Clinical outcomes of patients treated with alteplase 100 mg**

| Outcomes             | Total (n = 38) | Non-bleeding (n = 22) | Minor bleeding (n = 6) | Major bleeding (n = 10) | \( P \) value |
|----------------------|---------------|-----------------------|------------------------|-------------------------|--------------|
| ICU stay, day        | 3.25 ± 3.52   | 3.14 ± 2.77           | 0.40 ± 0.90            | 5.11 ± 5.00             | 0.050        |
| Treatment success    | 31 (81.6)     | 16 (72.7)             | 6 (100.0)              | 9 (90.0)                | 0.298        |
| Hospital discharge   | 30 (78.9)     | 15 (68.2)             | 6 (100.0)              | 9 (90.0)                | 0.244        |
| Mortality            | 8 (21.0)      | 7 (31.8)              | 0 (0)                  | 1 (10.0)                | 0.212        |

Data are presented as mean ± standard deviation or number (%). ICU = intensive care unit.
bolus, and the remaining 40 mg over 2 hours. In patients weighing less than 50 kg, the total alteplase dose was 0.5 mg/kg, and in another study that compared the use of alteplase and urokinase in terms of bleeding complications, alteplase dose of 50–100 mg was administered in patients with high risk PTE. In trials, 8.3% of the patients had major bleeding.13,16

There is no established guideline for dose reduction of thrombolytics according to body mass index (BMI). However, one study has shown that using thrombolytic agents in patients with a BMI of less than 18.5 kg/m² tends to increase the bleeding risk.26 In addition, Asians have a lower BMI than Westerners, and tend to have higher bleeding risk in cardiovascular and cerebrovascular disease, while Westerners have a higher tendency of thromboembolic risk.27,28

In our 10-year data, there were missing data of weight in 16 patients, therefore it was not suitable to analyze the differences in the incidence of major bleeding events according to the weight or BMI of patients.

Another notable point in our data is that major bleeding events were more common in patients with cardiovascular disease (Supplementary Tables 1 and 2) indicating the tendency of major bleeding in patients who used antiplatelet agents (such as aspirin) before thrombolysis. The current anticoagulant use (for example, warfarin or novel oral anticoagulant) is suggested as a relative contraindication in the current guideline, however, there are no precautions for taking aspirin. Based on our data, dose reduction should be considered in those patients on aspirin and with cardiovascular disease.

Our study has several limitations as it was retrospective, single center, and had a relatively small number of patients.

In conclusion, we suggest reducing the dose of alteplase in patients who are elderly, Asian or have cardiovascular disease. Further prospective studies evaluating the efficacy of low dose alteplase are recommended.

ACKNOWLEDGMENTS

The authors thank the personnel of the medical intensive care unit for their continuous support during treatment of patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Differences in major bleeding incidence according to variables

Click here to view

Supplementary Table 2
Logistic regression analysis of major bleeding risk

Click here to view
REFERENCES

1. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Gallé N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35(43):3033-69, 3069a-3069k.
pubmed | crossref

2. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;353(9162):1386-9.
pubmed | crossref

3. Stein PD, Beemath A, Olson RE. Trends in the incidence of pulmonary embolism and deep venous thrombosis in hospitalized patients. *Am J Cardiol* 2005;95(12):1525-6.
pubmed | crossref

4. Park TY, Jung JW, Choi JC, Shin JW, Kim FY, Choi BW, et al. Epidemiological trend of pulmonary thromboembolism at a tertiary hospital in Korea. *Korean J Intern Med* 2017;32(6):1037-44.
pubmed | crossref

5. Hong J, Lee JH, Yhim HY, Choi WI, Bang SM, Lee H, et al. Incidence of venous thromboembolism in Korea from 2009 to 2013. *PLoS One* 2018;13(1):e0191897.
pubmed | crossref

6. Capstick T, Henry MT. Efficacy of thrombolytic agents in the treatment of pulmonary embolism. *Eur Respir J* 2005;26(5):864-74.
pubmed | crossref

7. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014;370(15):1402-11.
pubmed | crossref

8. Rieves D, Wright G, Gupta G, Shaeter E. Clinical trial (GUSTO-1 and INJECT) evidence of earlier death for men than women after acute myocardial infarction. *Am J Cardiol* 2000;85(2):147-53.
pubmed | crossref

9. Collen D. Molecular mechanism of action of newer thrombolytic agents. *J Am Coll Cardiol* 1987;10(5 Suppl B):11B-15B.
pubmed | crossref

10. Hao Z, Yang C, Liu M, Wu B. Renal dysfunction and thrombolytic therapy in patients with acute ischemic stroke: a systematic review and meta-analysis. *Medicine (Baltimore)* 2014;93(28):e286.
pubmed | crossref

11. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013;368(15):1379-87.
pubmed | crossref

12. Anderson CS, Robinson T, Lindley RJ, Arima H, Lavados PM, Lee TH, et al. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. *N Engl J Med* 2016;374(24):2313-23.
pubmed | crossref

13. Sharifi M, Bay C, Skrocki L, Rahimi F, Mehdipour M; “MOPETT” Investigators. Moderate pulmonary embolism treated with thrombolysis (from the “MOPETT” Trial). *Am J Cardiol* 2013;111(2):273-7.
pubmed | crossref

14. Zhang Z, Zhai ZG, Liang LR, Liu FF, Yang YH, Wang C. Lower dosage of recombinant tissue-type plasminogen activator (rt-PA) in the treatment of acute pulmonary embolism: a systematic review and meta-analysis. *Thromb Res* 2014;133(3):357-63.
pubmed | crossref

15. Yilmazel Ucar E, Araz O, Kerget B, Yilmez N, Akgun M, Saglam L. Comparison of long-term outcomes of 50 and 100 mg rt-PA in the management of acute pulmonary thromboembolism. *Clin Respir J* 2018;12(4):3628-34.
pubmed | crossref

16. Yoo JW, Kim W, Choi CM, Hong SB, Oh YM, Shim TS, et al. The therapeutic efficacy and the bleeding complications of urokinase and alteplase in patients with massive pulmonary thromboembolism. *Tuberculosis* 2009;66(1):6.
crossref

17. Meyer G, Gisselbrecht M, Diehl JL, Journois D, Sors H. Incidence and predictors of major hemorrhagic complications from thrombolytic therapy in patients with massive pulmonary embolism. *Am J Med* 1998;105(6):472-7.
pubmed | crossref

18. Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA* 2014;311(23):2414-21.
pubmed | crossref

https://doi.org/10.3346/jkms.2020.35.e267

8/9
19. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3(4):692-4. [PUBMED] [CROSSREF]

20. Martin C, Sobolewski K, Bridgeman P, Boutsikaris D. Systemic thrombolysis for pulmonary embolism: a review. *P T* 2016;41(12):770-5. [PUBMED]

21. Kwak SH, Jeong CW, Lee SH, Lee HI, Koh Y. Current status of intensive care units registered as critical care subspeciality training hospitals in Korea. *J Korean Med Sci* 2014;29(3):431-7. [PUBMED] [CROSSREF]

22. 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. [PUBMED] [CROSSREF]

23. Goldhaber SZ, Haire WD, Feldstein ML, Miller M, Toltzis R, Smith JL, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet* 1993;341(8844):507-11. [PUBMED] [CROSSREF]

24. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W; Management Strategies and Prognosis of Pulmonary Embolism-3 Trial Investigators. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002;347(15):1143-50. [PUBMED] [CROSSREF]

25. Fasullo S, Scala S, Maringhini G, Ganci F, Cannizzaro S, Basile I, et al. Six-month echocardiographic study in patients with submassive pulmonary embolism and right ventricle dysfunction: comparison of thrombolysis with heparin. *Am J Med Sci* 2011;341(1):33-9. [PUBMED] [CROSSREF]

26. Chatzikonstantinou A, Ebert AD, Wolf ME. The impact of body mass index on the thrombolytic treatment of acute ischemic stroke. *Cerebrovasc Dis* 2016;42(3-4):240-6. [PUBMED] [CROSSREF]

27. Misumida N, Ogunbayo GO, Kim SM, Olorunfemi O, Elbadawi A, Charnigo RJ, et al. Higher risk of bleeding in Asians presenting with ST-segment elevation myocardial infarction: analysis of the national inpatient sample database. *Angiology* 2018;69(6):548-54. [PUBMED] [CROSSREF]

28. Kim YD, Jung YH, Saposnik G. Traditional risk factors for stroke in East Asia. *J Stroke* 2016;18(3):273-85. [PUBMED] [CROSSREF]