Clinical Significance and Prognosis of Right Heart Thrombi Associated With Acute Pulmonary Thromboembolism — Results of a Multicenter Registry of Thrombolysis in Japan —

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**Background:** Thrombolytic therapy is standard treatment in acute pulmonary thromboembolism (PTE) with hemodynamic instability. Although right heart thrombi (RHT) appear to increase mortality in acute PTE, large-scale studies of acute PTE with RHT are scarce.

**Methods and Results:** Patient data (from August 2005 to May 2014) obtained from post-marketing surveillance of thrombolytic therapy using a tissue-type plasminogen activator were analyzed retrospectively. Of the 2,698 confirmed cases of acute PTE who underwent echocardiographic assessment, 166 (6.2%) were diagnosed with RHT. PTE patients with RHT, compared with those without RHT, had higher rates of mortality (20.2% vs. 10.4%, \(P<0.001\)), hemodynamic instability (53.0% vs. 37.7%, \(P<0.001\)), and PTE recurrence (6.6% vs. 2.3%, \(P=0.003\)). When considering PTE-related hemodynamic severity (cardiopulmonary arrest/collapse, massive, submassive, and non-massive), mortality was significantly higher in patients with RHT in the massive (19.8% vs. 7.7%, \(P=0.002\)) and submassive (8.0% vs. 2.8%, \(P=0.018\)) groups, whereas no significant differences was found between those with and without RHT in the cardiopulmonary arrest/collapse (51.7% vs. 52.1%, \(P=0.960\)) and non-massive (1.6% vs. 0%, \(P=0.596\)) groups.

**Conclusions:** PTE patients with RHT had higher mortality, severity, and PTE recurrence rates. RHT was particularly associated with worse outcomes in patients with massive or submassive PTE.

**Key Words:** Acute pulmonary thromboembolism; Right heart thrombi; Thrombolysis

Acute pulmonary thromboembolism (PTE) is a critical condition associated with high morbidity and mortality. Moreover, the presence of right heart thrombi (RHT) with acute PTE appears to increase the risk of death.1,2 Previous reports involving small case series demonstrated a mortality rate of 25–50%.1–9 The most frequently proposed treatments are heparin, surgical embolectomy, and thrombolytic therapy, but the optimal management for RHT associated with PTE remains controversial because relevant prospective randomized trials are limited. Some studies have reported that the efficacy of all 3 treatments were similar,1,3 while other studies documented lower mortality rates in patients administered thrombolytic therapy compared with surgical embolectomy and heparin alone.4,5 The mortality rates in these studies seem to depend on the severity of cases and on the chosen treatments. In the current clinical guidelines, thrombolytic therapy is recommended for acute PTE with unstable hemodynamics.10–12 However, the previously reported series included a heterogeneous group of patients with RHT; the outcomes of patients with various hemodynamic conditions and the effect of thrombolytic agents according to severity are uncertain. Thus, we analyzed the data of a post-marketing surveillance of monteplase (Cleactor®, Eisai Co. Ltd., Tokyo, Japan), a tissue-type plasminogen activator (t-PA), for use in acute PTE. The aims of this study were (1) to evaluate the clinical features of acute PTE with RHT and (2) to assess the outcomes of patients with and without RHT according to severity.

**Study Population**
Monteplase was approved in Japan in 2005 as the first thrombolytic agent for acute PTE with unstable hemodynamics and is the only drug approved by the Ministry of Health, Labour and Welfare (MHLW) as the thrombolytic agent for use in acute PTE in Japan. The Ministry required...
a post-marketing surveillance of all cases with the aim of analyzing the efficacy and safety of monteplase for acute PTE. The efficacy and safety of the drug was reported prior to this study. This study was also based on the results of the post-marketing surveillance of monteplase but focused on RHT. The data were collected from 791 facilities in Japan (mean 4.23 cases per facility, minimum 1 and maximum 71 cases from a facility). We analyzed the data stored by Eisai using the surveillance database. A total of 3,342 patients who received treatment with monteplase between August 2005 and May 2014 were enrolled. The inclusion criteria were acute PTE suspected by clinical presentation and confirmed by ≥1 of the following examinations: enhanced computed tomography (CT), pulmonary angiography (PAG), or echocardiography. In patients who were diagnosed by echocardiography only, right ventricular (RV) dysfunction on echocardiography was needed to confirm the diagnosis of PTE. We excluded patients with unknown severity and lack of clinical data. For the analysis focusing on RHT, 115 patients who did not undergo echocardiographic assessment were also excluded. Overall, 2,698 confirmed cases of acute PTE patients who underwent echocardiographic assessment were analyzed (Figure 1). The study was conducted according to the ethical principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Hiratsuka Kyosai Hospital. Because the study was observational, written informed consent was not obtained from patients in accordance with the ethical guidelines for clinical research issued by the MHLW.

**RHT**

RHT were diagnosed if thrombi were observed in the right atrium or right ventricle by echocardiography or CT within the period of 30 days. Morphological characteristics (e.g., mobility and size) were not available in the post-marketing surveillance data.

**Severity of PTE**

Acute PTE severity was classified into 4 categories based on the initial clinical presentation, hemodynamics, and RV dysfunction: (1) cardiopulmonary arrest (CPA)/col-lapse group (presenting with CPA or circulatory collapse at the onset of PTE), (2) massive (unstable hemodynamics defined as systolic blood pressure <90 mmHg or a pressure drop of at least 40 mmHg for a time period >15 min, not due to a cause other than PTE, such as arrhythmia, hypovolemia, or sepsis), (3) submassive (stable hemodynamics with RV dysfunction), and (4) non-massive (stable hemodynamics without RV dysfunction). The presence of RV dysfunction was defined as RV dilation or RV hypokinesis on echocardiography.

**Outcomes**

The overall 30-day mortality rate after monteplase administration was noted. The efficacy of t-PA was evaluated as improvement of pulmonary circulation by observing improvement of the pulmonary artery obstruction on CT or PAG, or of lung perfusion defects on perfusion lung scan. The diagnosis of PTE recurrence was determined by the worsening of symptoms or hemodynamics, or both. Bleeding complications included any bleeding event after thrombolytic therapy such as intracranial hemorrhage, gastrointestinal hemorrhage, retroperitoneal hematoma, or hematoma at the puncture site. The severity of bleeding complications included any bleeding event after thrombolytic therapy such as intracranial hemorrhage, gastrointestinal hemorrhage, retroperitoneal hematoma, or hematoma at the puncture site.

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**Figure 1.** Flowchart of the study population. CT, computed tomography; PAG, pulmonary angiography; PTE, pulmonary thromboembolism; RHT, right heart thrombi; RVD, right ventricular dysfunction.
could not be evaluated in this study because it was not clearly defined in the surveillance data. Intracranial hemorrhage included brain parenchymal bleeding, subarachnoid hemorrhage, and subdural hematoma.

We compared the clinical characteristics and outcomes between those with and without RHT. In addition, we divided patients into 4 groups according to the severity of PTE (CPA/collapse, massive, submassive, and non-massive) and compared the 30-day mortality rate between those with and without RHT.

### Statistical Analysis
Continuous variables are expressed as mean values and standard deviations. Categorical variables are expressed as frequencies (percentages). Continuous variables were compared between groups using a 2-sample t-test, and categorical variables were compared using the chi-square test or Fisher’s exact test as appropriate. Survival rates were estimated using the Kaplan-Meier method, and score testing was used to analyze relationships for each group. A test for interaction was performed for subgroup analysis. P<0.05 was considered statistically significant. All analyses were performed with SAS® 9.4 (SAS institute, Cary, NC, USA). Statistical analyses were performed by the persons in charge at Eisai on request from the authors.

### Results
Of the 2,698 patients evaluated, 166 (6.2%) had RHT and 2,532 did not (Figure 1). RHT were found before administration of monteplase, and intracranial hemorrhage could not be evaluated in this study because it was not clearly defined in the surveillance data. Intracranial hemorrhage included brain parenchymal bleeding, subarachnoid hemorrhage, and subdural hematoma.

### Risk factors of VTE
Deep vein thrombosis
Prolonged immobilization
Malignant tumor
Cerebrovascular disorder
Surgery (within the past 6 months)
Fracture (within the past 6 months)
Inherited thrombophilia
Recent long-distance travel

### Treatments
Dose of monteplase, IU/kg
Time from onset of symptoms to monteplase administration

### Combined therapy
Heparin
Urokinase
IVC filter
Transcatheter treatment
Surgical embolectomy
ECMO

### Severity of PTE
CPA/collapse
Massive
Submassive
Non-massive

### Table 1. Characteristics of Patients With and Without Right Heart Thrombi

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>RHT(+), n=166</th>
<th>RHT(−), n=2,532</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>64.7±16.6</td>
<td>63.3±15.5</td>
<td>0.263</td>
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<td>Sex, female</td>
<td>85 (51.2)</td>
<td>1,509 (59.6)</td>
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<td>Body weight, kg</td>
<td>62.9±15.7</td>
<td>63.3±15.1</td>
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<tr>
<td>BMI</td>
<td>24.6±5.0</td>
<td>24.8±4.5</td>
<td>0.697</td>
</tr>
<tr>
<td>Hypertension</td>
<td>54 (32.5)</td>
<td>1,015 (40.1)</td>
<td>0.059</td>
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<tr>
<td>Diabetes mellitus</td>
<td>23 (13.9)</td>
<td>321 (12.7)</td>
<td>0.632</td>
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<td>Dyslipidemia</td>
<td>32 (19.3)</td>
<td>477 (18.8)</td>
<td>0.918</td>
</tr>
<tr>
<td>Heart disease</td>
<td>41 (24.7)</td>
<td>315 (12.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Tables and Figures
- Table 1: Characteristics of Patients With and Without Right Heart Thrombi
- Figure 1: Distribution of patients with and without RHT.
tration of monteplase by echocardiography in 156 patients and CT in 3 patients. In 7 patients, RHT were not found before administration of monteplase and were found afterwards in the follow-up echocardiographic study. The characteristics of patients with and without RHT are shown in Table 1. The proportion of females was lower among the RHT(+) patients. Heart disease was more frequent in RHT(+) patients. With respect to risk factors of PTE, RHT(+) patients more often had prolonged immobilization and cerebrovascular disorder than RHT(−) patients. No significant differences were found in other risk factors including deep vein thrombosis, malignant tumor, surgery, fracture, recent long-distance travel, and inherited thrombophilia such as protein C or S deficiency, antiphospholipid syndrome, and antithrombin III deficiency between those with and without RHT.

There were no significant differences in the mean dose of monteplase or the frequencies of combined therapies, namely, heparin, urokinase, and transcatheter treatment between the 2 groups. Nearly 70% of patients in both groups received monteplase within 24 h. The frequencies of early administration of monteplase within 3 and 6 h were higher in RHT(+) patients. Surgical embolectomy and extracorporeal membrane oxygenation were more frequent in RHT(+) patients. Inferior vena cava filter placement was less frequent in RHT(+) patients. RHT(+) patients had a higher severity of PTE graded by hemodynamics in comparison with RHT(−) patients. RHT(+) patients were classified as CPA/collapse in 34 cases (20.5%), massive in 54 cases (32.5%), submassive in 61 cases (36.7%), and non-massive in 17 cases (10.2%), while RHT(−) patients were CPA/collapse in 324 cases (12.8%), massive in 630 cases (24.9%), submassive in 1,151 cases (45.5%), and non-massive in 427 cases (16.9%). RHT(+) patients had a higher rate of hemodynamic instability (CPA/collapse and massive groups) compared with RHT(−) patients (53.0% vs. 37.7%, P<0.001). The prevalence of RHT was increased according to severity (3.8% in the non-massive group, 5.0% in the submassive group, 7.9% in the massive group, and 9.5% in the CPA/collapse group).

The outcomes of patients with and without RHT are shown in Table 2. There was no significant difference in the improvement of pulmonary circulation (54.8% vs. 65.5%, P=0.210). Compared with RHT(−) patients, RHT(+) patients had an increased risk of PTE recurrence (6.6% vs. 2.3%, P=0.003). The Kaplan-Meier plot of overall survival in patients with and without RHT is shown in Figure 2. RHT(+) patients had a significantly higher mortality rate.
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Figure 3. Kaplan-Meier plot of survival in patients with and without RHT in the CPA/ collapse (A), massive (B), submassive (C), and non-massive (D) groups. CPA, cardio-pulmonary arrest; RHT, right heart thrombi.
at 30 days (20.2% vs. 10.4%, P<0.001); 14 of 166 RHT(+) patients died from circulatory failure or multiple organ failure due to the first attack of acute PTE. Other causes of death were recurrence of PTE in 4, bleeding complications in 5, and unspecified in 9 of those with RHT (Table 2). Compared with RHT(−) patients, RHT(+) patients had a higher mortality rate due to the first attack of PTE (8.4% vs. 4.1%, P=0.017) and bleeding (3.0% vs. 1.0%, P=0.038), whereas no significant difference was found in death due to the PTE recurrence between groups.

Bleeding complications often occurred in both the RHT(+) and RHT(−) groups (22.9% vs. 18.9%, P=0.221). Intracranial hemorrhage occurred in 4 patients (2.4%) in the RHT(+) group and in 36 (1.4%) in the RHT(−) group. No significant difference was found in the incidence of intracranial hemorrhage between groups.

A comparison among the 4 groups graded by severity of PTE showed that the overall mortality rate at 30 days increased according to severity in both those with and without RHT (Figure 3). A significant interaction was noted between the presence of RHT and the severity of PTE for death (P<0.001). The mortality rate was significantly higher in RHT(+) patients than in RHT(−) patients in the massive (19.8% vs. 7.7%, P=0.002, Figure 3B) and submassive groups (8.0% vs. 2.8%, P=0.0018, Figure 3C), whereas no significant difference was found in mortality rates between RHT(+) and RHT(−) patients in the CPA/collapse (51.7% vs. 52.1%, P=0.960, Figure 3A) and non-massive (1.6% vs. 0%, P=0.596, Figure 3D) groups.

**Discussion**

In this study, RHT were found in 6.2% of patients treated with t-PA. The International Cooperative Pulmonary Embolism Registry (ICOPER), which included 2,454 patients with PTE, reported that RHT was found in 3.8% of patients and was associated with a higher mortality rate. The prevalence of RHT in our study was higher than in the ICOPER study and the study by Pierre-Justin et al (4.0%). Variation in the prevalence of RHT can be due to the differences in patient characteristics. In our study, all patients were treated with thrombolytic therapy, therefore we likely included more severe patients than previous reports because t-PA is generally used in acute PTE with unstable hemodynamics. Patients with shock or hypotension accounted for 53% of the patients with RHT in the present study, but only for 14% of the same group in the ICOPER study.

The studies by Chartier et al and Casazza et al, which demonstrated shock or hypotension (systolic blood pressure <90 mmHg) in 53% of 38 cases and 65% of 23 cases, respectively, were relatively similar to our study with respect to the severity of cases. The prevalence of RHT in those 2 studies was 8% and 18%, respectively, while the mortality rate was 45% and 30%, respectively.

The mortality rate in the present study (20%) was lower than that noted in the aforementioned reports by Chartier et al and Casazza et al. Thrombolysis was performed in 24% and 61% of cases, respectively, in those 2 reports. Rose et al and Akilli et al reported that thrombolytic therapy was associated with improved survival rates compared with anticoagulation therapy or surgery in patients with RHT, whereas the ICOPER study and another meta-analysis found no significant differences in survival among heparin, thrombolytic therapy, and surgery. Most of the studies have been retrospective and could have been affected by treatment selection bias. Although the mortality rate in the present study was lower than in previous reports, we cannot assess whether thrombolytic therapy is better or not than other treatments.

Acute PTE with RHT is an extreme therapeutic emergency. The mortality rate reported within the first day after admission is 21–22%. However, Ferrari et al reported that all RHT in 16 patients disappeared within 24 h after thrombolytic therapy, and all patients were alive on day 30. Pierre-Justin et al reported that the thrombus dissolved and pulmonary perfusion was rapidly improved within 12 h after infusion of thrombolytic agent in most patients with RHT. In a previous report on the large-scale surveillance of monteplase in Japan, symptoms such as dyspnea and shock improved within 1 h after the administration of monteplase in most cases. Thrombolytic therapy can be performed more rapidly and easily than surgical intervention or catheter intervention, and thrombolytic agents achieve adequate thrombolytic activity rapidly even when injected from the peripheral veins. Conversely, in the recent large-scale study of PTE patients with RHT using the data from the Registro Informatizado Enfermedad Tromboembólica (RIETE), reperfusion therapy including thrombolysis was not associated with reduced mortality rates.

That study had the limitation of reperfusion therapy including multiple strategies (thrombolysis in 74 of 102 RHT cases, percutaneous or surgical thrombectomy in 28 cases). However, the findings indicate that thrombolytic therapy is not appropriate for routine treatment of PTE with RHT. Our data demonstrated that the mortality rate increased according to severity in those with and without RHT. Appropriate therapeutic management should be based on severity in those with RHT, as in those without RHT. Hemodynamically unstable patients should be treated with thrombolytic therapy according to standard guideline recommendations. In our study, patients with RHT had a worse outcome than those without RHT in the massive and submassive groups. The mortality rate for RHT(+) patients in the submassive group and for RHT(−) patients in the massive group was 8.0% and 7.7%, respectively, which indicated that submassive patients with RHT also have a high risk of death. Such patients may need similar therapeutic management as those with hemodynamic instability.

It is unclear whether RHT are simply a marker of hemodynamic compromise or contribute to the worse outcome itself. In our study, the mortality rate was compared between those with and without RHT in 4 categories graded by severity of PTE to avoid bias caused by the hemodynamic variety of PTE. Our data demonstrated that those with RHT had a worse outcome than those without RHT in the massive and submassive groups. The poor prognosis of those with RHT can be due to several reasons. Mobile clots in the right heart can serve as sources of recurrent embolism to the pulmonary artery. Circulatory stasis may accelerate thrombogenesis in the peripheral veins and cause a recurrent embolic event due to peripheral venous thrombosis. Patient characteristics other than hemodynamic severity may also affect outcome.

Acute PTE with hemodynamic instability is related to a worse prognosis, especially in those suffering from CPA. In the German-based Management Strategy and Prognosis of Pulmonary Embolism Registry, the in-hospital mortal-
ity rate due to acute PTE ranged from 8.1% in hemodynamically stable patients to 25% and 65% in those presenting with cardiogenic shock and in those requiring cardiopulmonary resuscitation, respectively. In our study, the CPA/collapse group had a much worse outcome compared with other groups in both patients with and without RHT. These findings indicated that acute PTE patients with CPA or circulatory collapse may need more aggressive therapy such as cardiopulmonary support and surgical embolectomy.

The major complication of thrombolytic therapy is significant bleeding, including intracranial hemorrhage. The prevalence of intracranial hemorrhage in this study was not higher than that noted in previous studies of thrombolysis for acute PTE. A large study of full-dose systemic thrombolytic therapy using tenecteplase in 1,006 submassive PTE patients demonstrated that thrombolysis reduced the risk of death or hemodynamic decompensation, but this benefit was offset by an increased risk of major bleeding and hemorrhagic stroke. In the setting of acute PTE with RHT, the optimal dose of monteplase that provides maximum thrombolytic effect while avoiding bleeding complications remains uncertain. A previous report found no association between the dose of monteplase and clinical efficacy or incidence of severe hemorrhage in Japanese patients with acute PTE. Another study demonstrated that a low-dose t-PA regimen (50mg) for acute PTE with an unstable hemodynamic state reduced the risk of bleeding while maintaining similar efficacy. Critically ill patients may have a disturbance of coagulation and the fibrinolytic system. Both acute PTE itself and bleeding complications were related to higher mortality rates in patients with RHT than those without RHT in the present study. Further research is needed to assess the optimal indication and dose for treatment with t-PA in acute PTE patients with RHT.

**Study Limitations**

There are several to note. First, this was a retrospective observational research of clinical cases, and the investigation was based on clinical efficacy and the assessment of safety by physicians. No specific uniform criteria were set to assess the severity of bleeding and there was no standard for assessing the severity of bleeding such as the International Society on Thrombosis and Haemostasis bleeding scale when the surveillance was planned. Second, there were no specific data on the morphology or mobility of thrombi, and this could affect mortality or recurrence rates of PTE. Third, the details of the timing of echocardiography for detection or follow-up of RHT were unclear. Careful echocardiographic assessment sometimes cannot be performed in the emergency setting. RHT were found by echocardiography after thrombolysis in 7 patients in this study. Thrombus formation might be due to migration to the chambers of the right heart from the peripheral veins after thrombolysis in such cases. We could not investigate whether the thrombus disappeared or diminished after thrombolysis because of the lack of follow-up data. Fourth, we determined the classification of the severity of PTE without cardiac laboratory biomarkers. Current guidelines recommend assessment of PTE severity and the risk of early death with a combination of RV dysfunction on imaging studies and elevated cardiac biomarker levels in patients with stable hemodynamics. However, the surveillance database did not include the levels of cardiac laboratory biomarkers. We defined RV dysfunction as RV dilatation or RV hypokinesis on echocardiography to simplify the classification. Not a few patients who were clinically diagnosed as submassive PTE by a physician were classified as non-massive PTE in this study. Finally, all patients were treated by t-PA and thus could not be compared with untreated cases or other treatments.

**Conclusions**

Acute PTE patients with RHT had higher mortality, severity, and PTE recurrence rates than those without RHT even when treated with t-PA. The prevalence and mortality rate of RHT in patients with acute PTE increased according to the severity of PTE. Particularly, RHT was associated with worse outcomes in patients with massive and submassive PTE.

**Acknowledgments**

This study was conducted by Eisai Co. Ltd., based on instructions from the Ministry of Health, Labor and Welfare of Japan at the time of approval of monteplase for acute PTE. We appreciate the efforts of all the investigators from 791 facilities nationwide. We also thank Mr. Hiroshi Nishioka and Mrs. Kasumi Daidoji (Eisai Co. Ltd.) for their help and useful suggestions in the statistical analysis.

**Data Availability**

The individual deidentified participant data will not be shared.

The study protocol of the post-marketing surveillance will be shared on a request basis. Please directly contact the corresponding author to data sharing.

**Disclosure**

T.M. and N.H. are employees of Eisai Co. Ltd. and were in charge of data collection and analysis of the surveillance. The other authors declare no conflicts of interest.

**IRB Information**

The study was approved by the Institutional Ethics Committee of Hiratsuka Kyosai Hospital, number 2019 (Reiwa 1)-1.

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