ORIGINAL RESEARCH

Midterm Prognosis of Patients With Pulmonary Embolism Receiving Catheter-Directed Thrombolysis or Systemic Thrombolysis: A Nationwide Population-Based Study

Donna Shu-Han Lin, MD; Yu-Sheng Lin, MD; Cho-Kai Wu, MD, PhD; Heng-Hsu Lin, MD; Jen-Kuang Lee 🕑, MD, PhD

BACKGROUND: This study compared the efficacy and safety between catheter-directed thrombolysis (CDT) and systemic thrombolysis for patients with acute pulmonary embolism (PE) with midterm follow-up.

METHODS AND RESULTS: We conducted a prospective open cohort study by using data from the Taiwan National Health Insurance Research Database for 2001 to 2013. Patients who were first admitted for PE and were treated by either systemic thrombolysis or CDT were included and compared. Inverse probability of treatment weighting, based on the propensity score, was used to mitigate possible selection bias. A total of 145 CDT-treated and 1158 systemic thrombolysis–treated patients with PE were included. The in-hospital mortality rate was significantly lower in the CDT group (12.7% versus 21.4%; odds ratio, 0.49; 95% CI, 0.36–0.67) after inverse probability of treatment weighting. No significant differences between the groups were observed for the safety (bleeding) outcomes. In patients who survived the index PE admission, the 1-year all-cause mortality rate was significantly lower in the CDT group after inverse probability of treatment weighting (12.2% versus 13.2%; hazard ratio [HR], 0.73; 95% CI, 0.56–0.94). Treatment with CDT was also associated with lower risks of recurrent PE (9.3% versus 17.5%; subdistribution HR, 0.52; 95% CI, 0.41–0.66). The difference remained through the last follow-up.

CONCLUSIONS: Among patients with PE requiring reperfusion therapy, those accepting CDT had lower all-cause mortality and recurrent PE over both short-term and midterm follow-up periods than those receiving systemic thrombolysis. The bleeding risk was similar for both groups. These findings should be cautiously validated in future randomized trials.

Key Words: catheter-directed thrombolysis = intravenous infusion = pulmonary embolism = thrombolytic therapy

A cute pulmonary embolism (PE) is one of the leading causes of cardiovascular death worldwide, with 34% of patients dying suddenly or within hours after the symptoms of PE developed.^{1,2} Therefore, timely diagnosis and effective therapies are crucial to saving the lives of patients with acute PE. According to the recent guideline for PE management, published by the European Society of Cardiology, the severity of PE can be stratified into 3 categories: low, intermediate, and high.³ The initiation of anticoagulant therapy without delay is recommended for most patients in all risk groups, whereas reperfusion treatment is reserved only for patients in shock or exhibiting hemodynamic deterioration on anticoagulation treatment.

For patients with PE receiving reperfusion therapy, current guidelines advocate the systemic

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CLINICAL PERSPECTIVE

What Is New?

- This is the first and largest observational study undertaken to compare the safety, short-term efficacy, and midterm outcomes of catheterdirected thrombolysis with those of systemic thrombolysis in patients with acute pulmonary embolism.
- Among patients with pulmonary embolism requiring reperfusion therapy, those accepting catheter-directed thrombolysis had lower all-cause mortality and recurrent pulmonary embolism over both short-term and midterm follow-up periods than those receiving systemic thrombolysis.

What Are the Clinical Implications?

• Catheter-directed thrombolysis should be considered in high-risk patients with pulmonary embolism because of its efficacy and safety.

Nonstandard Abbreviations and Acronyms

CDT CTEPH	catheter-directed thrombolysis chronic thromboembolic pulmonary hypertension
IPTW	inverse probability of treatment weighting
NHI	National Health Insurance
NHIRD	National Health Insurance Research Database
ST USAT	systemic thrombolysis ultrasound-assisted thrombolysis

administration of thrombolytic drugs as the treatment of choice.^{3,4} Systemic thrombolysis (ST) may promptly restore pulmonary circulation and reduce mortality, but it also carries higher bleeding risks, including a 2% risk of intracranial hemorrhage, which is 4- to 5-fold higher than that for anticoagulation treatment.⁵ Moreover, the rates of bleeding complications increase with age, especially for patients aged >65 years.⁵ Hence, ST has a limited role in patients with PE who are thought to be at unusually elevated risk for bleeding or intracranial hemorrhage.

Catheter-directed thrombolysis (CDT) provides an alternative way to deliver thrombolytic agents to patients with PE. Because CDT can achieve a higher local concentration of thrombolytic agents by directly infusing drugs into the pulmonary trunk, it may require a lower dose of thrombolytic agents than ST. This lower-dose regimen is expected to entail a lower risk of bleeding, which is advocated by guidelines for patients with higher bleeding risk.^{3,4} Despite these expected advantages of CDT, however, there has been a lack of randomized trials directly comparing the safety and efficacy of CDT and ST. Observational studies comparing these 2 strategies were also rare, and only provided short- and intermediate-term prognosis.^{6–9} Relatedly, because there is no clear evidence for using CDT instead, the current guidelines still suggest ST as the first-line therapy for patients with PE requiring reperfusion therapy.

The present study aimed to compare the efficacy and safety of CDT with ST in patients with acute PE both in short-term and midterm prognosis. We enrolled patients from the largest cohort in Asia using a nationwide database, including nearly 100% of the adult patients with PE in Taiwan. The patients were subjected to propensity score matching, according to their clinical characteristics.

METHODS

Data Source

Data that support the findings of this study are available from the corresponding author on reasonable request. We conducted a prospective open cohort study by using data collected retrospectively from the Taiwan National Health Insurance Research Database (NHIRD) for 2001 through 2013. Taiwan's National Health Insurance (NHI) program is a single-payer system that was established in March 1995 and currently provides coverage to >99.8% of the population of Taiwan (≈23.7 million people at present). Moreover, the NHIRD contains data on the patients covered by the NHI program from 1995 through 2013. Because enrollment in the NHI program is mandatory and affordable, the vast majority of patients receive appropriate longterm follow-up care and evaluations. To protect privacy, all personal information contained in the NHIRD is deidentified and anonymized, so a full review by the Ethics Institutional Review Board of Taiwan University Hospital was not needed for the present study. Further information on the NHI program and the NHIRD has been provided in previous publications.^{10–12}

Study Patients

Patients who were first admitted for PE (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*], code 415.1) between January 1, 2001, and December 31, 2013, were identified. We then excluded any patients who (1) had missing demographical data (<0.1%), (2) were aged <20 years, or (3) were not treated by thrombolysis during the index PE admission. Those patients who were ultimately

included were separated into 2 groups: the ST group and the CDT group (Figure 1). This definition of PE was frequently reported in previous NHIRD studies.^{13–15}

Study Group and Thrombolytic Exposure

The included patients with PE with thrombolytic agent use were separated into 2 groups, according to their delivery method. The patients who received thrombolytic agents through multi–side-hole catheters were assigned to the CDT group, whereas those who received thrombolytic agents without multi–side-hole catheters were assigned to the systemic thrombolytic group. The thrombolytic agents consisted of tPA (tissue-type plasminogen activator), urokinase, and streptokinase. The information on the above therapies of interest was extracted using the Taiwan reimbursement codes included in the inpatient claims data.

Outcomes

The clinical outcomes in this study included in-hospital and follow-up outcomes. The in-hospital outcomes were in-hospital death, length of stay in intensive care unit, cardiovascular complications (ie, heart failure and new-onset atrial fibrillation), and the safety (bleeding) outcomes (ie, major bleeding, gastrointestinal bleeding, intracranial hemorrhage, and bleeding requiring transfusion). The follow-up outcomes were all-cause mortality, recurrent PE, heart failure, and new-onset pulmonary hypertension. All-cause mortality was defined by a withdrawal from the NHI program.¹⁶ Admission for recurrent PE or heart failure was detected using the principle inpatient diagnosis. New-onset pulmonary hypertension was ascertained by using 2 outpatient diagnoses or any single inpatient diagnosis. Patients were followed up from the discharge date to the date of death, date of event occurrence, or December 31, 2013, whichever came first.

Covariates

The covariates were age, sex, previous venous thromboembolism history, 17 comorbidities, recent traumatic injuries or major surgeries (ie, orthopedic, gastroenterological, and gynecological injuries or surgeries), Charlson Comorbidity Index score, pregnancy in the previous year, 11 kinds of medication after discharge, and in-hospital conditions or treatments (including extracorporeal membrane oxygenation, cardiogenic shock with use of inotropic agents, and intubation). We used the *ICD-9-CM* diagnostic and *ICD-9-CM* procedure codes and the Taiwan NHI reimbursement codes to obtain the baseline characteristics and surgical details of the patients based on the outpatient and inpatient claims data. Details of the *ICD-9-CM* diagnostic codes used in this study are provided in Table S1.

Statistical Analysis

To mitigate against possible confounding and selection bias when comparing outcomes between the CDT and systemic thrombolytic groups, we calculated the inverse probability of treatment



Figure 1. Study patient selection. PE indicates pulmonary embolism.

weighting (IPTW) based on the propensity score. The propensity score was estimated using a multivariable logistic regression model without interaction terms in which the study group (1, CDT; and 0, ST) was regressed on all of the covariates listed in Table 1 with a force entry, except that the follow-up year was replaced with the date of index admission. To prevent the impact of extreme values of the estimated propensity scores, we used a stabilized weight to mitigate the influence of outliers. The quality of weighting was checked using the absolute value of standardized difference between the groups after weighting, where a value of <0.1 was considered a negligible difference and a value of <0.2 was considered a small effect size of group difference.17,18

The in-hospital outcomes during the admission between groups (CDT versus ST) were compared by logistic regression for binary outcomes or by linear regression for continuous outcomes. As to the follow-up outcomes, the mortality rates between the groups were compared by a Cox proportional hazard model. The incidences of other time-to-event outcomes (eq. recurrent PE) between the groups were compared by the Fine and Gray subdistribution hazard model, with death during the follow-up period being considered a competing risk. Because of the absolute values of standardized difference >0.1 after IPTW, the following covariates were additionally adjusted in the regression analyses to account for the possibility of residual confounding: sex, hyperlipidemia, hyperthyroidism, previous stroke, Charlson Comorbidity Index score, statin and anticoagulant use, and intubation during admission. For all the regression models, the interactions between the treatment variable and covariates were not considered.

The assumption of proportional hazard was tested using a time-varying variable by creating an interaction of the study group (CDT versus ST) and the natural logarithm of survival time. Subgroup analysis was further conducted to evaluate the consistency of the observed treatment effect on outcomes across different levels of subgroup variables. The outcomes for the subgroup analysis were in-hospital death, 1year mortality, including in-hospital death, all-cause mortality by the end of follow-up, and recurrent PE. The subgroup variables were age (dichotomized by 65 years), sex, chronic kidney disease, cancer, Charlson Comorbidity Index score (dichotomized by 3 scores), cardiogenic shock, and intubation during the index admission. A 2-sided P value <0.05 was considered to be statistically significant, and no adjustment of multiple testing (multiplicity) was made in this study. All the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

A total of 145 CDT-treated and 1158 ST-treated patients with PE, seen from January 1, 2001, to December 31, 2013, were included. The mean follow-up years were 3.8 and 3.4 years for the CDT and ST groups, respectively. Overall, the patients with PE who received thrombolysis were predominantly women (61.4% in the CDT group and 54.5% in the ST group). The CDT group had a higher incidence of cardiogenic shock (42.8% versus 37.4%) and extracorporeal membrane oxygenation (8.3% versus 3.8%) than the ST group. After propensity score weighting, the 2 study groups were well balanced in terms of most of the characteristics (Table 1).

In-Hospital Outcomes

During the index hospitalization, 22 (15.2%) patients in the CDT group died and 250 (21.6%) patients in the ST group died. The in-hospital mortality rate was significantly lower in the CDT group (12.7% versus 21.4%; odds ratio [OR], 0.49; 95% Cl, 0.36–0.67) after IPTW. The incidence of heart failure events in the CDT cohort was also lower than that in the ST cohort after IPTW (6.9% versus 10.0%; OR, 0.68; 95% Cl, 0.51– 0.90). However, no significant differences between the 2 groups were observed in terms of intensive care unit stay, new-onset atrial fibrillation, or the safety (bleeding) outcomes (Table 2).

Follow-Up Outcomes in Patients Who Survived the Index PE Admission

A total of 1031 patients who survived the index hospitalization, comprising 123 CDT-treated patients and 908 ST-treated patients, were eligible for further analysis. There were 16 (13%) of these patients in the CDT group who died and 122 (13.4%) patients in the ST group who died within 1 year after the index hospitalization. The 1-year all-cause mortality rate was significantly lower in the CDT group after IPTW (12.2% versus 13.2%; hazard ratio [HR], 0.73; 95% CI, 0.56-0.94). Treatment with CDT was also associated with lower risks of recurrent PE (9.3% versus 17.5%; subdistribution HR, 0.52; 95% CI, 0.41–0.66). In addition, the CDT group had a lower incidence of new-onset pulmonary hypertension (0.3% versus 1.6%; subdistribution HR, 0.20; 95% CI, 0.06-0.72) (Table 3).

As of the last follow-up, the all-cause mortality rate and the recurrence rate of PE remained significantly lower in the CDT group than in the ST group after IPTW (Figure 2A and 2B). The incidence of heart failure was also lower in the CDT group, whereas there

Table 1.	Baseline Characteristics of the Patients With PE Treated by CDT or ST Before and After Propensity Score
Weightin	9

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Ápp. y616:16:062:9-17-0.0963:4-16.062:8-170Mala sex66:8:8:075:0-0.0110.010.010.0Vencos thrombosinbolarh history11:0.720:1.7-0.0113.315.0-0.03Depvent trombosis21:0.720:1.0-0.0113.015.0-0.01Cardometabolic disease22:0.0-0.0323.023.023.0-0.05Diabeles mellicas13:0.223:0.0-0.0323.023.0-0.03Diabeles mellicas81:0.523:0.0-0.0323.020.0-0.03Proprinderindina81:0.523:0.0-0.0323.0-0.03-0.03Diabeles mellicas81:0.523:0.0-0.0323.020.0-0.03Cour81:0.523:0.0-0.0324.425.5-0.01Diabeles mellicas81:0.520:0.124.425.5-0.01Cour81:0.520:0.124.025.5-0.01Diabeles mellicas81:0.114:0.8-0.0224.025.0Cour81:0.120:0.124.025.0-0.01Diabeles mellicas81:0.112:0.112:0.124.025.0Cour81:0.121:0.114:0.1-0.0214:0.114:0.1Diabeles mellicas81:0.112:0.112:0.112:0.112:0.1Diabeles mellicas81:0.112:0.112:0.112:0.112:0.1Diabeles mellicas<	Characteristics	CDT (n=145)	ST (n=1158)	STD	CDT	ST	STD
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Previous myocardial infraction 3 (2.1) 4 0 (3.5) -0.08 3.3 3.3 <.011 Arial fbrillation 6 (4.1) 79 (6.8) -0.12 6.4 6.5 <0.01	Ischemic heart disease	37 (25.5)	296 (25.6)	<0.01	24.4	25.5	-0.03
Atrial Ibrillation6 (4.1)79 (6.8)-0.126.4.4(6.5.)-0.07Procous stroke326 (7.2)127 (10)-0.076.4.410.7.9-0.15Chronok kichey disease0.26 (7.2)126 (1.6)14.316.9-0.07Provoking cator of PE	Previous myocardial infarction	3 (2.1)	40 (3.5)	-0.08	3.3	3.3	<0.01
Previous stroke13 (9.0)127 (11.0)-0.076.6.410.7.0-0.7.1Chronic kichey disease263 (7.2)196 (6.8)0.014.310.9.010.7.0Provoking factor dPE75 (6.5)0.226.9.07.2.010.0.0Cancer119 (13.1)154 (13.3)0.206.9.013.3.0-0.01Pregnant in the previous month86 (5.5)61 (6.3)0.015.0.05.3.0-0.01Major surgery in the previous month42 (2.8)61 (6.3)0.015.0.05.3.0-0.01Other corrobidity111 (7.6)161 (1.3.0)10.9.011.0.013.2.0-0.01CoPD111 (7.6)161 (1.3.0)-0.0.111.0.012.0.0-0.0.1-0.0.1Liver disease116 (1.1.0)140 (12.1)-0.0.311.0.012.0.0-0.0.1CoPD111 (7.6)161 (1.3.0)0.0.210.1.012.0.0-0.0.1Liver disease12.0.1.114.0.0.1-0.0.311.0.012.0.0-0.0.1Copesitive heart failure9.0.2.2114 (9.0)0.0.212.1.224.2.6-0.0.1Autoimmandisease32.0.1.2114 (9.0)0.0.212.1.224.2.6-0.0.1Copesitive heart failure32.2.222.2.222.2.222.2.222.2.222.2.220.0.1Charlson Corrobidity Index score32.2.214.1.010.0.214.1.010.0.214.1.010.0.1Autoimman Edisease12.2.2.2 <td>Atrial fibrillation</td> <td>6 (4.1)</td> <td>79 (6.8)</td> <td>-0.12</td> <td>6.4</td> <td>6.5</td> <td><0.01</td>	Atrial fibrillation	6 (4.1)	79 (6.8)	-0.12	6.4	6.5	<0.01
Chronic kidney disease26 (17.2)196 (16.9)0.0114.316.9-0.07Provider Generation of Constraint and the previous distant of Plantant in the previous year19 (13.1)75 (6.3)-0.0112.013.3-0.01Cancer19 (13.1)15 (13.3)-0.0112.013.20.0112.013.3-0.01Pregnant in the previous year10 (0.7)27 (2.3)-0.0112.015.0-0.0110.0 </td <td>Previous stroke</td> <td>13 (9.0)</td> <td>127 (11.0)</td> <td>-0.07</td> <td>6.4</td> <td>10.7</td> <td>-0.15</td>	Previous stroke	13 (9.0)	127 (11.0)	-0.07	6.4	10.7	-0.15
Provoking factor of PEParalysis (immobilization)19 (13.1)76 (5.8)0.226.9.97.2-0.01Cancer19 (13.1)154 (13.3)1-0.0112.013.3-0.04Pregnant in the previous wonth8.6 (5.0)0.015.05.3-0.01Taruma lyiny in the previous month8.6 (5.0)0.015.05.3-0.01Major surgery in the previous month8.4 (2.8)17 (1.5)0.091.7.71.8.6-0.01Other comorbidity1.4 (2.8)17 (1.5)0.091.7.71.8.6-0.01COPD111 (7.6)140 (12.1)-0.0311.01.0.2-0.03Congestive heart failure9.9 (2.2)114 (3.6)-0.031.0.99.4-0.03Congestive heart failure9.9 (2.2)114 (3.6)0.011.1.21.0.9-0.03Autoimmune disease0.7 (1.8)21 (1.8)0.021.2.22.4.2.6-0.01Autoimmune disease17 (1.7)144 (9.0)0.091.4.39.4.3-0.01Autoimmune disease17 (1.7)144 (9.0)0.032.4.20.00-0.01Actiz/AB13 (1.1)12 (2.2)0.032.4.20.01-0.01Actiz/AB13 (2.1)114 (9.0)0.032.4.20.020.03Actiz/AB13 (2.1)13 (2.1)13 (2.1)1.0.1-0.021.0.1-0.02Actiz/AB18 (1.4)192 (16.0)1.0.11.0.11.0.11.0.11.0.1 </td <td>Chronic kidney disease</td> <td>25 (17.2)</td> <td>196 (16.9)</td> <td>0.01</td> <td>14.3</td> <td>16.9</td> <td>-0.07</td>	Chronic kidney disease	25 (17.2)	196 (16.9)	0.01	14.3	16.9	-0.07
Paralysis (immobilization) 19(13.1) 75 (6.5) 0.22 6.9.0 7.2.0 9.0.1 Cancer 19(13.1) 154(13.3) -0.01 12.0 13.3 -0.04 Pregnant in the previous year 10.07 27 (2.3) 0.01 27.0 2.0 0.03 Trauma Injury in the previous month 8 (5.5) 61 (5.3) 0.01 5.0 5.0 0.01 Major surgery in the previous month 4 (2.6) 10.1 0.01 10.0 0.01 <	Provoking factor of PE	• •					
Cancer19(13.1)154(13.3)-0.0112.013.3-0.04Pregnant in the previous point10.0727 (2.3)0.012.72.20.03Tamma injury in the previous month86.5061 (6.3)0.015.72.20.03Major surgery in the previous month4 (2.8)61 (6.3)0.015.71.60.01Other comobilityImage: ComobilityImage: ComobilityImage: Comobility1.01.01.01.01.00.0COPO111 (7.6)161 (1.3)-0.0311.01.2.0-0.031.0-0.031.0-0.030.056.04.0-0.03-0.030.056.04.0-0.030.056.04.0-0.030.056.04.0-0.030.056.04.0-0.030.056.04.0-0.030.056.04.00.091.02.12:52.42:60.010.01.02.12:52.42:60.010.01.02.12:52.42:60.010.01.01.00.01.00.00.01.00.0 <td>Paralysis (immobilization)</td> <td>19 (13.1)</td> <td>75 (6.5)</td> <td>0.22</td> <td>6.9</td> <td>7.2</td> <td>-0.01</td>	Paralysis (immobilization)	19 (13.1)	75 (6.5)	0.22	6.9	7.2	-0.01
Pregnant in the previous year 1 (0.7) 27 (2.3) -0.13 2.7 2.2 0.03 Trauma injury in the previous month 8 (5.5) 61 (5.3) 0.01 5.0 5.3 -0.01 Major surgery in the previous month 4 (2.8) 17 (1.5) 0.09 1.7 1.6 0.01 Other comorbidity - - - - - - -0.03 COPD 111 (7.6) 161 (13.9) -0.21 10.99 13.2 -0.07 Liver disease 16 (1.10) 140 (12.1) -0.03 11.0 12.0 -0.03 Congestive heart failure 9 (6.2) 114 (8) 0.01 7.9 9.4 -0.05 Autoinmune disease 3 (2.1) 21 (1.8) 0.02 1.2 1.8 -0.05 Autoinmune disease 3 (2.1) 21 (1.8) 0.02 1.2 2.4±2.6 -0.11 Medication after discharge 3 (2.1) 21 (1.8) 0.02 1.2 2.4±2.6 -0.01 Action After discharge	Cancer	19 (13.1)	154 (13.3)	-0.01	12.0	13.3	-0.04
Trauma injury in the previous month 8 (6.5) 61 (6.3) 0.01 5.0 5.3 -0.01 Major surgery in the previous month 4 (2.8) 17 (1.5) 0.09 1.7 1.6 0.01 Other comorbidity Image and the previous month 4 (2.8) 17 (1.5) 0.09 1.7 1.6 0.01 Other comorbidity Image and the previous month 11 (7.6) 16 (11.0) 1.00 1.0.0 1.3.2 -0.07 Liver disease 16 (11.0) 140 (12.1) -0.03 11.0 12.0 -0.03 Autoinmune disease 3 (2.1) 21 (1.8) 0.05 6.0 4.1 0.09 Autoinmune disease 3 (2.1) 21 (1.8) 0.02 1.12.2 1.8.8 -0.01 Medication after discharge 2.2±2.4 2.4±2.6 -0.07 2.1±2.5 2.4±2.6 -0.01 Medication after discharge 31 (2.1,4) 2.3±2 (2.0) 0.02 1.4±2.6 -0.02 Actel/ARB 31 (2.1,4) 2.3±2 (2.0) 0.02 1.6.7 -0.02 <td>Pregnant in the previous year</td> <td>1 (0.7)</td> <td>27 (2.3)</td> <td>-0.13</td> <td>2.7</td> <td>2.2</td> <td>0.03</td>	Pregnant in the previous year	1 (0.7)	27 (2.3)	-0.13	2.7	2.2	0.03
Major surgery in the previous month 4 (2.8) 17 (1.5) 0.09 1.7 1.6 0.01 Other comorbidity Image: comorbi	Trauma injury in the previous month	8 (5.5)	61 (5.3)	0.01	5.0	5.3	-0.01
Other comorbidity Image: field state Image: field state COPD 111 (7.6) 161 (13.9) -0.21 10.9 13.2 -0.07 Liver disease 116 (11.0) 140 (12.1) -0.03 11.0 12.0 -0.03 Congestive heart failure 9 (6.2) 114 (9.8) -0.13 7.9 9.4 -0.05 Pulmonary hypertension 7 (4.8) 45 (3.9) 0.05 6.0 4.1 0.02 Autoimmune disease 3 (2.1) 21 4.26 0.02 1.2.2 4.2.42 -0.01 Medication after discharge 2.2.2.4 21 4.26 0.02 1.2.2 2.4.2.2 -0.01 Statin 17 (11.7) 104 (9.0) 0.09 14.3 9.3 0.15 ACE/ARB 31 (21.4) 232 (20.0) 0.03 24.2 20.2 0.09 GCB 26 (17.9) 190 (16.4) 0.09 118.3 9.3 0.15 Diuretics 18 (12.4) 192 (16.6) -0.12 15.4 16.1 -0.02	Major surgery in the previous month	4 (2.8)	17 (1.5)	0.09	1.7	1.6	0.01
COPD 111 (7.6) 161 (13.9) -0.21 10.9 13.2 -0.07 Liver disease 116 (11.0) 140 (12.1) -0.03 11.0 12.0 -0.03 Congestive heart failure 96.2 114 (9.8) -0.13 7.9 9.4 -0.05 Pulmonary hypertension 77.4.8) 45 (3.9) 0.05 6.00 4.1 0.09 Autoimmune disease 3 (2.1) 21 (1.8) 0.02 1.2 1.8 -0.05 Charlson Comorbidity Index score 2.2±2.4 2.4±2.6 -0.07 2.1±2.5 2.4±2.6 -0.17 Medication after discharge 104 (9.0) 0.09 14.3 9.3 0.15 Statin 17 (11.7) 104 (9.0) 0.09 14.3 9.3 0.05 GCB 31 (21.4) 23 (20.0) 0.03 24.2 20.2 0.09 β-Blocker 31 (21.4) 190 (16.4) 0.09 18.6 16.7 0.02 GCB 21 (14.5 190 (16.1) -0.01	Other comorbidity						
Liver disease146 (11.0)140 (12.1)-0.0311.012.0-0.03Congestive heart failure9 (6.2)114 (9.8)-0.137.99.4-0.05Pulmonary hypertension7 (4.8)45 (3.9)0.056.0.04.10.09Autoimmune disease3 (2.1)21 (1.8)0.021.2.21.8.8-0.05Charlson Comorbidity Index score2.2±2.42.4±2.6-0.072.1±2.52.4±2.6-0.11Medication after discharge2.2±2.42.4±2.6-0.072.1±2.52.4±2.6-0.11Statin17 (17.7)104 (9.0)0.0914.39.3.30.15-0.15ACEI/ARB31 (21.4)232 (20.0)0.0324.220.20.09β-Blocker29 (20.0)190 (16.4)0.0918.616.70.05GCB2.2 (19.1)10.0211.616.1-0.02β-Blocker2.2 (19.1)190 (16.4)0.0918.616.1-0.02β-Blocker2.2 (19.1)192 (16.6)-0.1211.610.1-0.02β-Blocker18 (12.4)192 (16.6)-0.1211.610.1-0.02β-Blocker18 (12.4)192 (16.6)-0.1211.211.7-0.02β-Blocker18 (12.4)192 (16.6)-0.0211.211.7-0.01β-Blocker3.2 (11.4)18 (12.7)-0.0211.211.7-0.01β-Blocker3.2 (11.5)18 (11.7)10.211.21	COPD	11 (7.6)	161 (13.9)	-0.21	10.9	13.2	-0.07
Congestive heart failure 9 (6.2) 114 (9.8) -0.13 7.9 9.4 -0.05 Pulmonary hypertension 7 (4.8) 45 (3.9) 0.05 6.0 4.1 0.09 Autoimmune disease 3 (2.1) 21 (1.8) 0.02 1.2 1.8 -0.05 Charlson Comorbidity Index score 2.2±2.4 2.4±2.6 -0.07 2.1±2.5 2.4±2.6 -0.01 Medication after discharge 31 (21.4) 2.32 (20.0) 0.03 2.4±2.8 9.3 0.15 ACEI/ARB 31 (21.4) 232 (20.0) 0.03 24.2 20.2 0.09 β-Blocker 29 (20.0) 190 (16.4) 0.09 18.6 16.7 0.05 CCB 26 (17.9) 221 (19.1) -0.03 22.0 18.9 0.08 Diuretics 18 (12.4) 192 (16.6) -0.12 15.4 16.1 -0.02 Antiplatelet 21 (14.5) 201 (17.4) -0.08 17.7 17.0 0.02 OHA 16 (11.0) 136 (17.7)	Liver disease	16 (11.0)	140 (12.1)	-0.03	11.0	12.0	-0.03
Pulmonary hypertension 7 (4.8) 45 (3.9) 0.05 6.0.0 4.1 0.09 Autoimmune disease 3 (2.1) 21 (1.8) 0.02 1.2 1.8 -0.05 Charlson Comorbidity Index score 2.2±2.4 2.4±2.6 -0.07 2.1±2.5 2.4±2.6 -0.17 Medication after discharge -0.17 104 (9.0) 0.09 14.3 9.3 0.15 ACEI/ARB 31 (21.4) 232 (20.0) 0.03 24.2 20.2 0.09 β-Blocker 29 (20.0) 190 (16.4) 0.09 18.6 16.7 0.05 CCB 26 (17.9) 221 (19.1) -0.03 22.0 18.9 0.08 Diuretics 18 (12.4) 192 (16.6) -0.12 11.6 -0.02 Antiplatelet 21 (14.5) 201 (17.4) -0.08 17.7 17.00 0.02 OHA 16 (11.0) 136 (17.7) -0.04 51.1 3.3 0.09 Antidepressants 8 (5.5) 87.75 -0.08	Congestive heart failure	9 (6.2)	114 (9.8)	-0.13	7.9	9.4	-0.05
Autoimmune disease3 (21)2 1 (1.8)0.021.21.8-0.05Charlson Comorbidity Index score2.2±2.42.4±2.6-0.072.1±2.52.4±2.6-0.11Medication after discharge104 (9.0)0.0914.39.30.15Statin17 (11.7)104 (9.0)0.0914.39.30.15ACEI/ARB31 (21.4)232 (20.0)0.0324.220.20.09β-Blocker29 (20.0)190 (16.4)0.09118.616.70.05CCB26 (17.9)221 (19.1)-0.0322.018.80.08Diuretics18 (12.4)192 (16.6)-0.1215.416.1-0.02Antiplatelet21 (14.5)201 (17.4)-0.0311.211.7-0.01OHA16 (10.0)136 (11.7)-0.0211.211.7-0.01Insulin4 (2.8)39 (3.4)-0.045.13.30.09Antidepressants6 (6.5)87 (7.5)-0.088.47.30.04Hormone therapy3 (2.1)10 (0.9)0.100.71.0-0.03In-hospital condition or treatment50 (10.2)743 (64.2)0.1336.037.9-0.04Lex62 (42.8)433 (37.4)0.193.94.2-0.02Lex12 (8.3)44 (8.8)0.193.94.2-0.02	Pulmonary hypertension	7 (4.8)	45 (3.9)	0.05	6.0	4.1	0.09
Charlson Comorbidity Index score2.2±2.42.4±2.6-0.072.1±2.52.4±2.6-0.011Medication after dischargeStatin17 (11.7)104 (9.0)0.0914.39.30.15ACE/ARB31 (21.4)232 (20.0)0.0324.220.20.09β-Blocker29 (20.0)190 (16.4)0.0918.6116.70.05CCB26 (17.9)221 (19.1)-0.0322.018.90.08Diuretics18 (12.4)192 (16.6)-0.1215.416.1-0.02Artiplatelet21 (14.5)201 (17.4)-0.0811.211.7-0.02OHA16 (11.0)136 (17.7)-0.0211.211.7-0.01Insulin4 (2.8)39 (3.4)-0.045.13.3.30.09Antidepressants8 (5.5)87 (7.5)-0.088.47.30.04Hormone therapy3 (2.1)10 (0.9)0.100.71.0-0.03Anticoagulant102 (70.3)743 (64.2)0.130.11-0.030.11In-hospital condition or treatment12 (8.3)44 (3.8)0.193.94.2-0.04ECMO12 (8.3)44 (3.8)0.193.94.2-0.02	Autoimmune disease	3 (2.1)	21 (1.8)	0.02	1.2	1.8	-0.05
Medication after dischargeStatin17 (17.7)104 (9.0)0.0914.39.30.15ACEI/ARB31 (21.4)232 (20.0)0.0324.220.20.09β-Blocker29 (20.0)190 (6.4)0.0918.616.70.05CCB26 (7.9)221 (19.1)-0.0322.018.90.08Diuretics18 (12.4)192 (16.6)-0.12115.416.1-0.02Antiplatelet21 (14.5)201 (17.4)-0.0817.717.00.02OHA16 (10.0)136 (11.7)-0.0211.211.7-0.01Insulin44 (2.8)39 (3.4)-0.045.13.30.09Antidepressants68 (5.5)87 (7.5)-0.088.4.47.30.04Hormone therapy30 (2.1)10 (0.9)0.130.71.0-0.03In-tospital condition or treatment102 (70.3)743 (64.2)0.1336.037.9-0.04ECMO12 (8.3)44 (3.8)0.193.94.2-0.02	Charlson Comorbidity Index score	2.2±2.4	2.4±2.6	-0.07	2.1±2.5	2.4±2.6	-0.11
Statin17 (11.7)104 (9.0)0.0914.39.30.15ACEI/ARB31 (21.4)232 (20.0)0.0324.220.20.09β-Blocker29 (20.0)190 (16.4)0.0918.6116.70.05CCB26 (17.9)221 (19.1)-0.0322.018.90.08Diuretics18 (12.4)192 (16.6)-0.1215.416.1-0.02Antiplatelet21 (14.5)201 (17.4)-0.0817.717.00.02OHA16 (11.0)136 (11.7)-0.0211.211.7-0.01Insulin4 (2.8)39 (3.4)-0.045.13.30.09Antidepressants68 (5.5)87 (7.5)-0.088.47.30.04Hormone therapy30 (2.1)10 (0.9)0.100.71.0.0-0.03Anticoagulant102 (70.3)743 (64.2)0.1370.264.90.11In-hospital condition or treatment62 (42.8)433 (37.4)0.1136.037.9-0.04ECMO12 (8.3)44 (3.8)0.193.94.2-0.02	Medication after discharge						
ACEI/ARB31 (21.4)232 (20.0)0.0324.220.20.09β-Blocker29 (20.0)190 (16.4)0.0918.616.70.05CCB26 (17.9)221 (19.1)-0.0322.018.90.08Diuretics18 (12.4)192 (16.6)-0.1215.416.1-0.02Antiplatelet21 (14.5)201 (17.4)-0.0817.717.00.02OHA116 (11.0)136 (11.7)-0.0211.211.7-0.01Insulin4 (2.8)39 (3.4)-0.045.13.30.09Antidepressants8 (5.5)87 (7.5)-0.088.47.30.04Hormone therapy3 (2.1)10 (0.9)0.100.71.0-0.03In-hospital condition or treatment102 (70.3)743 (64.2)0.1336.037.9-0.04ECMO12 (8.3)44 (3.8)0.193.94.2-0.02	Statin	17 (11.7)	104 (9.0)	0.09	14.3	9.3	0.15
β-Blocker29 (20.0)190 (16.4)0.0918.616.70.05CCB26 (17.9)221 (19.1)-0.0322.018.90.08Diuretics18 (12.4)192 (16.6)-0.1215.416.1-0.02Antiplatelet21 (14.5)201 (17.4)-0.0817.717.00.02OHA16 (11.0)136 (11.7)-0.0211.211.7-0.01Insulin4 (2.8)39 (3.4)-0.045.13.3.30.09Antidepressants8 (5.5)87 (7.5)-0.088.47.30.04Hormone therapy3 (2.1)10 (0.9)0.100.71.0-0.03Anticoagulant102 (70.3)743 (64.2)0.1370.264.90.11In-hospital condition or treatment62 (42.8)433 (37.4)0.1136.037.9-0.04ECMO12 (8.3)44 (3.8)0.193.94.2-0.02	ACEI/ARB	31 (21.4)	232 (20.0)	0.03	24.2	20.2	0.09
CCB26 (17.9)221 (19.1)-0.0322.018.90.08Diuretics18 (12.4)192 (16.6)-0.1215.416.1-0.02Antiplatelet21 (14.5)201 (17.4)-0.0817.717.00.02OHA16 (11.0)136 (11.7)-0.0211.211.7-0.01Insulin4 (2.8)39 (3.4)-0.045.13.30.09Antidepressants8 (5.5)87 (7.5)-0.088.47.30.04Hormone therapy3 (2.1)10 (0.9)0.100.71.0-0.03Anticoagulant102 (70.3)743 (64.2)0.1370.264.90.11In-hospital condition or treatment62 (42.8)433 (37.4)0.1136.037.9-0.04ECMO12 (8.3)44 (3.8)0.193.94.2-0.02-0.02	β-Blocker	29 (20.0)	190 (16.4)	0.09	18.6	16.7	0.05
Diuretics18 (12.4)192 (16.6)0.1215.416.10.02Antiplatelet21 (14.5)201 (17.4)0.0817.717.00.02OHA16 (11.0)136 (11.7)0.0211.211.70.01Insulin4 (2.8)39 (3.4)0.045.13.30.09Antidepressants8 (5.5)87 (7.5)0.088.47.30.04Hormone therapy3 (2.1)10 (0.9)0.100.71.00.03Anticoagulant102 (70.3)743 (64.2)0.1370.264.90.11In-hospital condition or treatment62 (42.8)433 (37.4)0.1136.037.9-0.04ECMO12 (8.3)44 (3.8)0.193.94.2-0.02	ССВ	26 (17.9)	221 (19.1)	-0.03	22.0	18.9	0.08
Antiplatelet 21 (14.5) 201 (17.4) -0.08 17.7 17.0 0.02 OHA 16 (11.0) 136 (11.7) -0.02 11.2 11.7 -0.01 Insulin 4 (2.8) 39 (3.4) -0.04 5.1 3.3 0.09 Antidepressants 8 (5.5) 87 (7.5) -0.08 8.4 7.3 0.04 Hormone therapy 3 (2.1) 10 (0.9) 0.10 0.7 1.0 -0.03 Anticoagulant 102 (70.3) 743 (64.2) 0.13 70.2 64.9 0.11 In-hospital condition or treatment 62 (42.8) 433 (37.4) 0.11 36.0 37.9 -0.04 ECMO 12 (8.3) 44 (3.8) 0.19 3.9 4.2 -0.02	Diuretics	18 (12.4)	192 (16.6)	-0.12	15.4	16.1	-0.02
OHA 16 (11.0) 136 (11.7) -0.02 11.2 11.7 -0.01 Insulin 4 (2.8) 39 (3.4) -0.04 5.1 3.3 0.09 Antidepressants 8 (5.5) 87 (7.5) -0.08 8.4 7.3 0.04 Hormone therapy 3 (2.1) 10 (0.9) 0.10 0.7 1.0 -0.03 Anticoagulant 102 (70.3) 743 (64.2) 0.13 70.2 64.9 0.11 In-hospital condition or treatment 62 (42.8) 433 (37.4) 0.11 36.0 37.9 -0.04 ECMO 12 (8.3) 44 (3.8) 0.19 3.9 4.2 -0.02	Antiplatelet	21 (14.5)	201 (17.4)	-0.08	17.7	17.0	0.02
Insulin 4 (2.8) 39 (3.4) -0.04 5.1 3.3 0.09 Antidepressants 8 (5.5) 87 (7.5) -0.08 8.4 7.3 0.04 Hormone therapy 3 (2.1) 10 (0.9) 0.10 0.7 1.0 -0.03 Anticoagulant 102 (70.3) 743 (64.2) 0.13 70.2 64.9 0.11 In-hospital condition or treatment 62 (42.8) 433 (37.4) 0.11 36.0 37.9 -0.04 ECMO 12 (8.3) 44 (3.8) 0.19 3.9 4.2 -0.02	ОНА	16 (11.0)	136 (11.7)	-0.02	11.2	11.7	-0.01
Antidepressants 8 (5.5) 87 (7.5) -0.08 8.4 7.3 0.04 Hormone therapy 3 (2.1) 10 (0.9) 0.10 0.7 1.0 -0.03 Anticoagulant 102 (70.3) 743 (64.2) 0.13 70.2 64.9 0.11 In-hospital condition or treatment 433 (37.4) 0.11 36.0 37.9 -0.04 ECMO 12 (8.3) 44 (3.8) 0.19 3.9 4.2 -0.02	Insulin	4 (2.8)	39 (3.4)	-0.04	5.1	3.3	0.09
Hormone therapy 3 (2.1) 10 (0.9) 0.10 0.7 1.0 -0.03 Anticoagulant 102 (70.3) 743 (64.2) 0.13 70.2 64.9 0.11 In-hospital condition or treatment 433 (37.4) 0.11 36.0 37.9 -0.04 ECMO 12 (8.3) 44 (3.8) 0.19 3.9 4.2 -0.02	Antidepressants	8 (5.5)	87 (7.5)	-0.08	8.4	7.3	0.04
Anticoagulant 102 (70.3) 743 (64.2) 0.13 70.2 64.9 0.11 In-hospital condition or treatment	Hormone therapy	3 (2.1)	10 (0.9)	0.10	0.7	1.0	-0.03
In-hospital condition or treatment Cardiogenic shock 62 (42.8) 433 (37.4) 0.11 36.0 37.9 -0.04 ECMO 12 (8.3) 44 (3.8) 0.19 3.9 4.2 -0.02	Anticoagulant	102 (70.3)	743 (64.2)	0.13	70.2	64.9	0.11
Cardiogenic shock 62 (42.8) 433 (37.4) 0.11 36.0 37.9 -0.04 ECMO 12 (8.3) 44 (3.8) 0.19 3.9 4.2 -0.02	In-hospital condition or treatment	·			I	I	
ECMO 12 (8.3) 44 (3.8) 0.19 3.9 4.2 -0.02	Cardiogenic shock	62 (42.8)	433 (37.4)	0.11	36.0	37.9	-0.04
	ECMO	12 (8.3)	44 (3.8)	0.19	3.9	4.2	-0.02

(Continued)

Table 1. Continued

	Before	IPTW*	After IPTW [†]			
Characteristics	CDT (n=145)	ST (n=1158)	STD	CDT	ST	STD
Intubation	38 (26.2)	288 (24.9)	0.03	20.6	24.9	-0.10
Follow-up time, y	3.8±4.0	3.4±3.6	0.10	4.1±3.7	3.4±3.7	0.18
Follow-up time, y	2.1 (0.3–7.2)	2.2 (0.2–5.6)		3.3 (0.7–6.7)	2.2 (0.2–5.6)	

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CDT, catheter-directed thrombolysis; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; IPTW, inverse probability of treatment weighting; OHA, oral hypoglycemic agent; PE, pulmonary embolism; ST, systemic thrombolysis; and STD, standardized difference.

*Data are presented as frequency (percentage), mean±SD, or median (25th-75th percentile).

[†]Data are presented as percentage, mean±SD, or median (25th–75th percentile).

was no statistical significance in the difference in newonset pulmonary hypertension between the 2 groups (Table 3). In addition, the results showed that the assumption of proportional hazard was not violated with the statistical significance for the interaction term (timevarying variable) of 0.750, 0.244, 0.755, and 0.457 for all-cause mortality, recurrent PE, heart failure hospitalization, and new-onset pulmonary hypertension, respectively.

Subgroup Analysis

The subgroup analysis of in-hospital death showed that the beneficial effect of CDT was more apparent in patients with chronic kidney disease and patients with cardiogenic shock or intubation during the PE admission (*P* for interaction <0.05; Figure 3A). The subgroup analysis of 1-year mortality (including in-hospital death)

and all-cause mortality showed that female patients, patients with chronic kidney disease, and patients having cancer tended to benefit more from CDT (*P* for interaction <0.05; Figure 3B and 3C). The subgroup analysis of recurrent PE showed that the beneficial effect of CDT was more obvious in patients with cancer, patients with more comorbidities, and patients with cardiogenic shock during the PE admission (*P* for interaction <0.05; Figure 3D). However, the sample size of patients undergoing CDT was only 145; therefore, the aforementioned subgroup analysis may be underpowered.

DISCUSSION

This is the first and largest observational study undertaken to compare the safety, short-term efficacy, and

 Table 2.
 In-Hospital Complications and Events of the Patients With PE Treated by CDT or ST Before and After Propensity

 Score Weighting

	Data Bet	fore IPTW*	Data After IPTW [†]					
Outcome	CDT (n=145)	ST (n=1158)	CDT	ST	B or OR of CDT (95% Cl) [‡]	P Value		
In-hospital death	22 (15.2)	250 (21.6)	12.7	21.4	0.49 (0.36 to 0.67)	<0.001		
ICU length of stay, d	5.6±6.6	4.8±6.6	4.8±5.8	4.8±6.6	0.29 (-0.32 to 0.91)	0.349		
Cardiovascular complication								
Heart failure	9 (6.2)	117 (10.1)	6.9	10.0	0.68 (0.51 to 0.90)	0.008		
Acute myocardial infarction	2 (1.4)	19 (1.6)	1.1	1.7	0.71 (0.36 to 1.41)	0.326		
New-onset atrial fibrillation	2 (1.4)	22 (1.9)	1.3	1.8	0.73 (0.39 to 1.38)	0.332		
Safety outcome	• •	` 				-		
Major bleeding	13 (9.0)	91 (7.9)	7.6	7.8	1.02 (0.75 to 1.37)	0.913		
Bleeding requiring transfusion	2 (1.4)	20 (1.7)	1.7	1.7	1.21 (0.64 to 2.26)	0.561		
Gastrointestinal bleeding	11 (7.6)	70 (6.0)	5.9	6.0	0.99 (0.71 to 1.38)	0.944		
Intracranial hemorrhage	2 (1.4)	21 (1.8)	1.7	1.8	1.19 (0.64 to 2.23)	0.582		

B indicates regression coefficient; CDT, catheter-directed thrombolysis; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; OR, odds ratio; PE, pulmonary embolism; and ST, systemic thrombolysis.

*Data are presented as frequency (percentage) or mean±SD.

[†]Data are presented as percentage or mean±SD.

[‡]Adjusted for sex, hyperlipidemia, hyperthyroidism, previous stroke, Charlson Comorbidity Index score, statin use, anticoagulant use, and intubation.

	Data Befo	Data After IPTW [†]					
Outcome	CDT (n=123)	ST (n=908)	CDT	ST	HR or SHR of CDT (95% Cl) [‡]	P Value	
1-y Outcome							
All-cause mortality	16 (13.0)	122 (13.4)	12.2	13.2	0.73 (0.56–0.94)	0.015	
Recurrent PE	12 (9.8)	160 (17.6)	9.3	17.5	0.52 (0.41–0.66)	<0.001	
Heart failure	3 (2.4)	31 (3.4)	3.6	3.4	1.17 (0.68–1.99)	0.576	
New-onset pulmonary hypertension	1 (0.8)	15 (1.7)	0.3	1.6	0.20 (0.06–0.72)	0.013	
As of the last follow-up							
All-cause mortality	34 (27.6)	303 (33.4)	29.5	32.8	0.84 (0.72–0.98)	0.031	
Recurrent PE	22 (17.9)	219 (24.1)	22.2	23.9	0.81 (0.68–0.97)	0.021	
Heart failure	4 (3.3)	71 (7.8)	4.2	7.6	0.55 (0.37–0.80)	0.002	
New-onset pulmonary hypertension	5 (4.1)	29 (3.2)	1.8	3.1	0.58 (0.33–1.03)	0.065	

 Table 3.
 Time-to-Event Outcomes of the Patients With PE Who Survived the Index Hospitalization Treated by CDT or ST

 Before and After Propensity Score Weighting
 Patients

CDT indicates catheter-directed thrombolysis; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PE, pulmonary embolism; SHR, subdistribution HR; and ST, systemic thrombolysis.

*Values are given as number (percentage).

[†]Values are given as percentage.

[‡]Adjusted for sex, hyperlipidemia, hyperthyroidism, previous stroke, Charlson Comorbidity Index score, statin use, anticoagulant use, and intubation.

midterm outcomes of CDT with those of ST in patients with acute PE. Previous studies showed that CDT could effectively reduce pulmonary artery pressures and improve right ventricular function, whereas the long-term outcomes were less certain.¹⁹⁻²² Most trials reported only up to 90-day outcomes, and they either had no control group or merely compared CDT with anticoagulation alone. There were even rare observational studies comparing these 2 strategies, and they were only in short- and intermediate-term prognosis⁶⁻⁹. In the current study, we clearly showed that the CDT group had both lower in-hospital mortality and 1-year mortality than the ST group. In fact, the survival benefit of CDT was maintained throughout the whole follow-up period (Figure 2A). In contrast, Konstantinides et al reported that ST had no impact on mortality or symptoms at 3 years with long-term follow-up.²³ This different outcome-related finding may come from the fundamental difference in the delivery of thrombolytic agents between CDT and ST. Because CDT can achieve a higher local concentration of thrombolytic agents, its efficacy in terms of thrombus resolution is greater. Our study showed that the CDT group had lower rates of recurrent PE and pulmonary hypertension, which were both important risk factors for mortality. It is important to treat acute PE as completely as possible at the first attack, or it may lead to grave cardiovascular outcomes.

Recurrent PE with subsequent pulmonary hypertension is another important issue after an acute PE episode. Recurrent PE may come from irregular or early termination of anticoagulation use. The latest European Society of Cardiology guideline now

suggests extended anticoagulation therapy in almost all patients with acute PE to reduce the risk of recurrent PE.³ However, Frederikus et al reported that the risk of recurrent PE events is still high even under longterm anticoagulation use, especially in patients with unprovoked venous thromboembolic events.²⁴ Other than anticoagulation maintenance, the resolution of thrombus as early as possible seems to be a reasonable strategy to prevent further PE episodes. Previous studies showed that there was considerable residual thrombus after acute PE treatment, even when patients were symptom free with normal right atrium/right ventricle size in echocardiography.^{25,26} The end point for acute PE treatment has yet to be standardized in current guidelines or the various previous studies.^{25,26} Theoretically, CDT has higher local concentration and efficiency to clear thrombus in the pulmonary artery. In our study, we found that the recurrence rate of PE was significantly lower in the CDT cohort than in the ST cohort throughout the follow-up period, which was similar to the finding with respect to all-cause mortality. It is thus reasonable to suppose that the early resolution of pulmonary thrombus may prevent further PE events.

Beyond the risk of death and recurrent PE, previous studies showed that chronic thromboembolic pulmonary hypertension (CTEPH) may develop in survivors of PE. Vitorrio et al reported that the cumulative incidence of symptomatic CTEPH after acute PE treated with either naticoagulation or thrombolysis was 3.1% at 1 year and 3.8% at 2 years.²⁷ It is generally believed that CTEPH comes from repeated PE, which finally leads to pulmonary hypertension. Although CTEPH is now regarded as a critical disease leading to grave



Figure 2. Fitted survival curves of all-cause mortality (A) and fitted cumulative incidence function of recurrent pulmonary embolism (PE) (B) of patients treated with catheter-directed thrombolysis or systemic thrombolytic therapy in the inverse probability of treatment weighting-adjusted cohort.

outcomes, it is important to treat patients early and even prevent them from developing CTEPH. We found that patients with acute PE accepting CDT not only had a lower recurrence of PE but also a lower rate of newonset pulmonary hypertension than those receiving ST. According to the definition of CTEPH, recurrent PE with pulmonary hypertension is not necessarily equivalent to but is highly associated with CTEPH. From the current study, it can be supposed that CDT may be an effective therapy for the prevention of CTEPH after

A 0 00 0											
A In-hospital death			. (0()	00 (050(01) (B 1-year mortality					-
	Favor catheter-	Favor No. of	event (%)	OR (95% CI) of	P value for		Favor catheter-	Favor systemic	No. of event (%)	HR (95% CI) of	P value for
	directed	systemic Cathete	er Systemic	catheter-directed	interaction		directed	thrombolytic C	atheter Systemic	catheter-directed	interaction
Age group		thrombolytic			0.218	Age group					0.105
<65 years	⊢ →	14.6	17.7	0.60 (0.39-0.94)		<65 years	⊢ ◆	•	25.9 26.7	0.81 (0.65-1.02)	
≥65 years		11.2	25.0	0.40 (0.26-0.63)		≥65 years	→		20.2 36.4	0.63 (0.51-0.78)	
Sex					0.649	Sex					0.028
Female	→	14.2	22.0	0.52 (0.34-0.78)		Female			25.1 31.2	0.62 (0.51-0.75)	
Male		10.5	20.7	0.45 (0.27-0.73)		Male	· · · · ·		19.1 32.2	0.89 (0.69-1.15)	
Chronic kidney disease					0.001	Chronic kidney disease					0.018
No.	_	11.6	177	0 66 (0 46-0 95)	01001	No.			20 7 27 2	0.70 (0.66-0.95)	0.010
Voc		10.5	20.6	0.00 (0.40-0.33)		Vec			20.7 27.3	0.73 (0.00-0.33)	
·				0.20 (0.10-0.37)					33.332.8	0.51 (0.57=0.70)	
Cancer					0.15	Cancer					<0.001
No		10.8	19.8	0.55 (0.39-0.80)		No			19.1 27.3	0.86 (0.72-1.03)	
Yes		26.6	32.4	0.32 (0.17-0.61)		Yes			49.5 59.9	0.39 (0.29-0.52)	
CCI score					0.127	CCI score					0.004
0-2	·+	9.6	15.7	0.61 (0.40-0.94)		0-2		-	16.0 21.7	0.90 (0.72-1.13)	
≥3		19.5	32.4	0.37 (0.24-0.59)		≥3	→ → · · · · · · · · · · · · · · · · · ·		37.5 50.6	0.57 (0.46-0.71)	
Cardiogeneric shock					0.001	Cardiogeneric shock					0.143
No	·	• 2.3	2.0	1.34 (0.61-2.93)		No	· •		10.1 13.3	0.82 (0.61-1.10)	
Yes		31.3	53.2	0 28 (0 19-0 42)		Yes	→		45.4 61.5	0.63 (0.52-0.76)	
Intubation					<0.001	Intubation					0.496
No		c o	7 5	0.00 (0.65 1.61)	-0.001	No			120 192	0 66 (0 52-0 94)	0.450
NU	· · · ·	0.0	7.5	0.35 (0.03-1.31)		Yes			12.5 10.2	0.00 (0.00-0.04)	
Yes	•	35.4	63.3	0.21 (0.13-0.34)		res			60.7 72.1	0.74 (0.60-0.91)	
0.1 0	.2 0.4 0.8	1.6				0.3	0.5 1.4	0 2.0			
		(CI)					Hazard ratio (95	5% CI)			
	Odds ratio (957	6 CI)					1182810 1810 (55	J/J CIJ			
	1					D All-cause mortality					
C Recurrent PE	Favor catheter-	Favor systemic No. c	f event (%)	SHR (95% CI) of	P value for	D All-cause mortality	Favor	Favor	No. of event (%)	HR (95% CI) of	P value for
C Recurrent PE	Favor catheter- directed	Favor systemic No. o thrombolytic Cathet	f event (%) er Systemic	SHR (95% CI) of catheter-directed	P value for interaction	D All-cause mortality	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic	HR (95% CI) of catheter-directed	P value for interaction
C Recurrent PE	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet	f event (%) er Systemic	SHR (95% CI) of catheter-directed	P value for interaction 0.274	D All-cause mortality	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic	HR (95% CI) of catheter-directed	P value for interaction 0.507
C Recurrent PE	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 13.8	f event (%) er Systemic 20.9	SHR (95% CI) of catheter-directed 0.69 (0.51–0.94)	P value for interaction 0.274	D All-cause mortality Age group	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0	HR (95% CI) of catheter-directed 0.86 (0.71–1.04)	P value for interaction 0.507
C Recurrent PE	Favor catheter- directed	Favor systemic No. o thrombolytic Cathet 13.8	f event (%) er Systemic 20.9 27 2	SHR (95% CI) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08)	P value for interaction 0.274	All-cause mortality Age group <55 years >65 years	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1	HR (95% CI) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93)	P value for interaction 0.507
C Recurrent PE Age group <65 years ≥65 years	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 13.8 → 28.9	f event (%) er Systemic 20.9 27.2	SHR (95% Cl) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08)	P value for interaction 0.274	D All-cause mortality Age group <65 years 265 years	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.257.1 _	HR (95% CI) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93)	P value for interaction 0.507
C Recurrent PE	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 13.8 28.9	f event (%) er Systemic 20.9 27.2 23.6	SHR (95% Cl) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08)	P value for interaction 0.274	D All-cause mortality Age group <65 years _65 years _5ex years	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1	HR (95% Cl) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93)	P value for interaction 0.507
C Recurrent PE	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet → 28.9 → 19.2 26.6	f event (%) er Systemic 20.9 27.2 23.6 24.2	SHR (95% Cl) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08) 0.90 (0.70–1.17) 0.74 (0.5.0 03)	P value for interaction 0.274 0.249	D All-cause mortality Age group <65 years 265 years Sex Female	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4	HR (95% Cl) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 0.70 (0.60–0.82)	P value for interaction 0.507
C Recurrent PE	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 13.8 28.9 19.2 26.6	f event (%) er Systemic 20.9 27.2 23.6 24.3	SHR (95% Cl) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08) 0.90 (0.70–1.17) 0.74 (0.58–0.93)	P value for interaction 0.274	D All-cause mortality Age group <65 years ≥65 years Sex Female Male	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9	HR (95% Cl) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 0.70 (0.60–0.82) 1.01 (0.83–1.23)	P value for interaction 0.507
C Recurrent PE Age group <55 years 265 years Female Amaie Chronic kidney disease	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet → 28.9 → 19.2 26.6	f event (%) er Systemic 20.9 27.2 23.6 24.3	SHR (95% Cl) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08) 0.90 (0.70–1.17) 0.74 (0.58–0.93)	P value for interaction 0.274 	D All-cause mortality Age group <65 years 265 years 5ex Female Male Chronic kidney disease	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9	HR (95% Cl) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 0.70 (0.60–0.82) 1.01 (0.83–1.23)	P value for interaction 0.507
C Recurrent PE Age group <55 years	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 13.8 → 28.9 → 19.2 26.6 4 23.7	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0	SHR (95% Cl) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08) 0.90 (0.70–1.17) 0.74 (0.58–0.93) 0.87 (0.72–1.05)	P value for interaction 0.274 0.249 0.063	D All-cause mortality Age group <65 years 265 years Sex Female Male Chronic kidney disease No	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 34.2 42.6	HR (95% Cl) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 0.70 (0.60–0.82) 1.01 (0.83–1.23) 0.88 (0.77–1.02)	<i>P</i> value for interaction 0.507 0.004 0.003
C Recurrent PE Age group -65 years 265 years Fernale Maie Chronic kidney disease No Yes	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 28.9 	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6	SHR (95% Cl) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08) 0.90 (0.70–1.17) 0.74 (0.58–0.93) 0.87 (0.72–1.05) 0.51 (0.30–0.87)	<i>P</i> value for interaction 0.274 0.249 0.063	D All-cause mortality Age group <65 years	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 34.2 42.6 63.9 69.7	HR (95% Cl) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 1.01 (0.83–1.23) 0.88 (0.77–1.02) 0.57 (0.44–0.74)	P value for interaction 0.507
C Recurrent PE Age group <55 years Sex Female Male Chronic kidney disease No Yes Cancer	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 13.8 28.9 19.2 26.6 4 23.7 12.1	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6	SHR (95% Cl) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08) 0.90 (0.70–1.17) 0.74 (0.58–0.93) 0.87 (0.72–1.05) 0.51 (0.30–0.87)	P value for interaction 0.274 0.249 0.063 <0.001	D All-cause mortality Age group <65 years Sex Female Male Chronic kidney disease No Yes Cancer	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 34.2 42.6 63.9 69.7	HR (95% Cl) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 0.70 (0.60–0.82) 1.01 (0.83–1.23) 0.88 (0.77–1.02) 0.57 (0.44–0.74)	P value for interaction 0.507 0.004 0.003
C Recurrent PE Age group <55 years 265 years Sex Female Male Chronic kidney disease No Yes Cancer No So Yes Chronic kidney disease No	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 38.9 19.2 26.6 23.7 12.1 24.6	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 24.0 23.6 22.7	SHR (95% Cl) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08) 0.90 (0.70–1.17) 0.74 (0.58–0.93) 0.87 (0.72–1.05) 0.51 (0.30–0.87) 0.97 (0.80–1.17)	P value for interaction 0.274 0.249 0.063 <0.001	D All-cause mortality Age group <65 years	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 34.2 42.6 63.9 69.7 33.6 43.7	HR (95% CI) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 1.01 (0.83–1.23) 0.88 (0.77–1.02) 0.57 (0.44–0.74) 0.90 (0.78–1.03)	P value for interaction 0.507 0.004 0.003 0.003
C Recurrent PE Age group <55 years Sex Female Male Chronic kidney disease No Yes Cancer No Yes	Favor catheter- directed	Favor systemic No. o thrombolytic Cathet 3.8.9 	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 23.6 22.7 33.1	SHR (95% CI) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.90 (0.70-1.17) 0.74 (0.58-0.93) 0.87 (0.72-1.05) 0.51 (0.30-0.87) 0.97 (0.80-1.17) NA	P value for interaction 0.274 0.249 0.063 <0.001	D All-cause mortality Age group <65 years Sex Female Male Chronic kidney disease No Yes Cancer No Yes Yes	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 34.2 42.6 63.9 69.7 33.6 43.7 74.0 69.6	HR (95% Cl) of catheter-directed 0.86 (0.71–1.04) 79 (0.67–0.93) 10 (0.60–0.82) 10 (0.60–0.82) 01 (0.60–0.82) 01 (0.60–0.82) 02 (0.70–0.92) 00 (0.60–0.82) 00 (0.60–0.82) 00 (0.60–0.82) 00 (0.70–0.92) 00 (0.70–0.92)00 (0.70–0.92)00 (0.70–0.92	P value for interaction 0.507
C Recurrent PE Age group c45 years 265 years Sex Female Male Chronic kidney disease No Yes Cancer No Yes CCI score	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 13.8 28.9 19.2 26.6 4 23.7 12.1 1.2 1 24.6 0.0	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1	SHR (95% CI) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08) 0.90 (0.70–1.17) 0.74 (0.58–0.93) 0.87 (0.72–1.05) 0.51 (0.30–0.87) 0.97 (0.80–1.17) NA	P value for interaction 0.274 0.249 0.063 <0.001	D All-cause mortality Age group <65 years	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 34.2 42.6 63.9 69.7 33.6 43.7 74.0 69.6	HR (95% Cl) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 1.01 (0.83–1.23) 0.88 (0.77–1.02) 0.57 (0.44–0.74) 0.90 (0.78–1.03) 0.54 (0.42–0.71)	P value for interaction 0.507 0.004 0.003 0.003 0.001
C Recurrent PE Age group <55 years Sex Female Male Chronickidney disease No Yes Cancer No Yes CCI score 0-2	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 13.8 2.2 26.6 4 23.7 12.1 24.6 0.0 28.4 28.4 28.4 28.4 28.4 28.4 28.4 28.4	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0	SHR (95% CI) of catheter-directed 0.69 (0.51–0.94) 0.86 (0.69–1.08) 0.87 (0.58–0.93) 0.87 (0.72–1.05) 0.57 (0.80–1.17) 0.97 (0.80–1.17) 0.97 (0.80–1.17) 0.97 (0.80–1.17)	P value for interaction 0.274 0.249 0.063 <0.001 <0.001	D All-cause mortality Age group <5 years Sex Female Male Chronic kidney disease No Yes Cancer No Yes Cal soore 0-2	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 3 34.2 42.6 63.9 69.7 33.6 43.7 74.0 69.6 45.7 25.9 35.8	HR (95% C)) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 0.70 (0.60–0.82) 1.01 (0.83–1.23) 0.88 (0.77–1.02) 0.57 (0.44–0.74) 0.90 (0.78–1.03) 0.54 (0.42–0.71) 0.54 (0.42–0.71)	P value for interaction 0.507 0.004 0.003 0.001 0.613
C Recurrent PE Age group c55 years 265 years Sex Female Male Chronic kidney disease No Yes Cancer No Yes CCI score 0-2 23	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 28.9 19.2 26.6 23.7 24.2 24.2 24.0 0.0 24.2 24.0 0.0 24.2 24.0 0.0 24.2 24.0 0.0	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0 26.1	SHR (95% CI) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.90 (0.70-1.17) 0.74 (0.58-0.93) 0.87 (0.72-1.05) 0.51 (0.30-0.87) 0.97 (0.80-1.17) NA 1.17 (0.95-1.43) 0.23 (0.15-0.36)	P value for interaction 0.274 0.249 0.063 0.063 0.001	D All-cause mortality Age group <65 years	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 34.2 42.6 63.9 69.7 33.6 43.7 74.0 69.6 25.9 35.8	HR (95% CI) of catheter-directed 0.86 (0.71-1.04) 0.79 (0.67-0.93) 101 (0.83-1.23) 0.88 (0.77-1.02) 0.57 (0.44-0.74) 0.57 (0.44-0.74) 0.90 (0.78-1.03) 0.54 (0.42-0.71) 0.83 (0.70-0.99) 0.78 (0.66-0.93)	P value for interaction 0.507 0.004 0.003 0.001 0.613
C Recurrent PE Age group <55 years 265 years Sex Female Male Chronic kidney disease No Yes Cancer No Yes Cancer Oc Cascre Oc 2 aga	Favor catheter- directed	Favor systemic No. 0 thrombolytic Cathet 13.8 - 28.9 - 19.2 26.6 - 23.7 - 24.6 0.0 - 28.4 - 29.4 -	f event (%) 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0 26.1	SHR (95% CI) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.87 (0.69-1.08) 0.57 (0.30-0.87) 0.57 (0.30-0.87) 0.97 (0.80-1.17) 0.97 (0.80-1.17) 0.97 (0.80-1.17) 0.97 (0.80-1.17) 1.17 (0.95-1.43) 0.23 (0.15-0.36)	P value for interaction 0.274 0.249 0.063 0.063 <0.001 <0.001	D All-cause mortality Age group <5 years 5ex Female Male Chronic kidney disease No Yes Cancer No Yes Cancer Oc2 23 23 Cardingeneric shorts	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 34.2 42.6 63.9 69.7 33.6 43.7 74.0 69.6 25.9 35.8 65.9 69.0	HR (95% C)) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 0.70 (0.66–0.82) 1.01 (0.83–1.23) 0.88 (0.77–1.02) 0.57 (0.44–0.74) 0.90 (0.78–1.03) 0.54 (0.42–0.71) 0.83 (0.70–0.99) 0.78 (0.66–0.93)	P value for interaction 0.507 0.004 0.003 0.001 0.613 0.613
C Recurrent PE Age group c55 years 265 years Sex Female Male Chronic kidney disease No Yes Cancer No Yes CCI score 0-2 23 Ccrofugeneric shock No	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 28.9 19.2 26.6 4 23.7 12.1 2.4 2.6 4 23.7 2.6 4 23.7 2.6 4 23.7 2.6 4 23.7 2.6 4 23.7 2.6 2.6 2.6 2.6 2.6 2.6 2.6 2.6 2.6 2.6	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0 26.1 25.4	SHR (95% CI) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.90 (0.70-1.17) 0.74 (0.58-0.33) 0.87 (0.72-1.05) 0.51 (0.30-0.87) 0.51 (0.30-0.87) 0.51 (0.30-0.87) 0.51 (0.30-0.87) 0.51 (0.30-0.87) 0.51 (0.51-1.13) 0.23 (0.15-0.36) 0.92 (0.75-1.11)	P value for interaction 0.274 0.249 0.063 	D All-cause mortality Age group <65 years 265 years Sex Female Male Chronic kidney disease No Yes Yes Cancer Cance	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 34.2 42.6 63.9 69.7 33.6 43.7 74.0 69.6 25.9 35.8 65.9 69.0	HR (95% CI) of catheter-directed 0.86 (0.71-1.04) 0.79 (0.67-0.93) 101 (0.83-1.23) 0.88 (0.77-1.02) 0.57 (0.44-0.74) 0.57 (0.44-0.74) 0.56 (0.77-0.22) 0.54 (0.42-0.71) 0.83 (0.70-0.99) 0.78 (0.66-0.93) 0.56 (0.71-1.23)	P value for interaction 0.507 0.004 0.003 0.001 0.613 0.613
C Recurrent PE Age group <55 years 265 years Sex Female Male Chronic kidney disease Cancer No Yes Cancer O.2 additional Cardiogeneric shock No Yes	Favor catheter- directed	Favor systemic No. 0 thrombolytic Cathet 13.8 - 28.9 - 19.2 26.6 - 23.7 - 24.6 0.0 - 28.4 7.0 - 28.4 7.0 - 27.9 7.7	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0 26.1 25.4 18.8	SHR (95% CI) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.90 (0.70-1.17) 0.74 (0.58-0.93) 0.87 (0.72-1.05) 0.51 (0.30-0.87) 0.97 (0.80-1.17) 0.97 (0.95-1.43) 0.92 (0.76-1.13) 0.92 (0.76-1.13)	P value for interaction 0.274 0.249 0.063 0.063 0.001 0.013	D All-cause mortality Age group <5 years 5ex Female Male Chronic kidney disease No Yes Cancer No No Yes No Yes No No Yes No No Yes No Y	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 35.2 46.9 34.2 42.6 63.9 69.7 33.6 43.7 74.0 69.6 25.9 59.6 25.9 53.8 65.9 90.0 24.7 31.4	HR (95% C)) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 0.70 (0.60–0.82) 1.01 (0.83–1.23) 0.88 (0.77–1.02) 0.57 (0.44–0.74) 0.90 (0.78–1.03) 0.54 (0.42–0.71) 0.54 (0.62–0.73) 0.83 (0.70–0.99) 0.78 (0.66–0.93) 0.37 (0.67–0.03)	P value for interaction 0.507 0.004 0.003 0.001 0.613 0.162
C Recurrent PE Age group c55 years 265 years Sex Female Male Chronic kidney disease No Yes Ccl score 0-2 23 Ccl score 0-2 23 crafigeneric shock No Yes Insubation	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 28.9 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.9 19.2 26.6 19.2 26.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.0 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.0 20.9 10.0 20.0 20.0 20.0 20.0 20.0 20.0 20.0	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0 26.1 25.4 18.8	SHR (95% CI) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.90 (0.70-1.17) 0.74 (0.58-0.33) 0.87 (0.72-1.05) 0.51 (0.30-0.87) 0.51 (0.30-0.87) 0.51 (0.30-0.87) 0.37 (0.80-1.17) 0.32 (0.15-0.36) 0.32 (0.15-0.36) 0.32 (0.76-1.11) 0.45 (0.27-0.76)	P value for interaction 0.274 0.249 0.063 <0.001 <0.001 0.013	D All-cause mortality Age group <65 years	Favor catheter-directed	Favor systemic C	No. of event (%) stheter Systemic 35.1 37.0 41.2 57.1 40.5 47.4 32.2 46.9 43.2 46.9 43.2 42.6 63.9 69.7 33.6 43.7 4.0 69.6 55.9 69.0 25.9 35.8 65.9 69.0 25.9 35.8 65.9 69.0	HR (95% CI) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 101 (0.83–1.23) 0.88 (0.77–1.02) 0.57 (0.44–0.74) 0.57 (0.44–0.74) 0.54 (0.42–0.71) 0.84 (0.70–0.99) 0.78 (0.66–0.93) 0.71 (0.60–0.84)	P value for interaction 0.507 0.004 0.003 0.001 0.613 0.613
C Recurrent PE Age group <55 years 265 years Sex Female Male Chronic kidney disease No Yes Cancer No Yes Cancer No Yes Cacore O-2 23 Cardiogeneric shock No Yes Intubation No Yes	Favor catheter- directed	Favor systemic No. 0 thrombolytic Cathet 13.8 4 28.9 19.2 26.6 4 23.7 12.1 4 24.6 19.2 26.6 4 23.7 12.1 4 24.6 0.0 0 4 28.4 7.0 12.7 7.0 24.6 28.4 7.0 24.9 24.9 24.9 24.9 24.9 24.9 24.9 24.9	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0 26.1 25.4 18.8 25.0	SHR (95% C) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.90 (0.70-1.17) 0.74 (0.58-0.93) 0.87 (0.72-1.05) 0.51 (0.30-0.87) 0.97 (0.80-1.17) NA 1.17 (0.95-1.43) 0.23 (0.15-0.36) 0.92 (0.76-1.11) 0.45 (0.27-0.76)	P value for interaction 0.274 0.249 0.063 0.063 0.063 0.001 0.013	D All-cause mortality Age group <5 years 5ex Female Male Chronic kidney disease No Yes Cancer No Yes Cancer No Yes Cancer No Yes Colscore Colscore Colscore Colscore No Yes Includation	Favor catheter-directed	Favor systemic C	No. of event (%) sheter Systemic 35.1 37.0 41.2 57.1 45.2 46.9 44.2 46.6 33.6 47.7 43.2 46.9 43.2 46.9 43.2 46.9 43.2 46.9 43.7 40.6 95.6 52.9 35.8 65.9 69.0 24.7 31.4 63.0 73.0	HR (95% C)) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 1.01 (0.83–1.23) 0.88 (0.77–1.02) 0.57 (0.44–0.74) 0.57 (0.44–0.74) 0.54 (0.42–0.71) 0.54 (0.42–0.71) 0.54 (0.66–0.93) 0.78 (0.66–0.93) 0.71 (0.66–0.84)	P value for interaction 0.507 0.004 0.003 0.001 0.613 0.162 0.339
C Recurrent PE Age group c55 years 265 years Sex Female Male Chronic kidney disease No Yes Cancer No Yes Ccl score 0-2 3 a_a_carlogeneric shock No Yes Intrubation No Yes	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 28.9 19.2 26.6 4 23.7 12.1 19.2 26.6 4 23.7 12.1 19.2 26.6 4 23.7 12.1 19.2 26.6 4 23.7 12.1 19.2 26.6 4 23.7 19.2 26.6 4 23.7 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 26.6 19.2 20.9 19.2 26.6 19.2 20.9 19.2 26.6 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.9 19.2 20.0 19.2 20.9 19.2 20.9 19.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 20.9 10.2 10.2 10.2 10.2 10.2 10.2 10.2 10.2	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0 26.1 25.4 18.8 25.0 15.5	SHR (95% CI) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.90 (0.70-1.17) 0.74 (0.58-0.33) 0.87 (0.72-1.05) 0.51 (0.30-0.87) 0.51 (0.30-0.87) 0.37 (0.80-1.17) 0.37 (0.95-1.43) 0.23 (0.15-0.36) 0.32 (0.75-1.11) 0.45 (0.27-0.76) 0.85 (0.71-1.01) 0.55 (0.71-1.01)	P value for interaction 0.274 0.249 0.063 <0.001 <0.001 0.013	D All-cause mortality Age group <65 years	Favor catheter-directed	Favor systemic C	No. of event (%) atheter Systemic 35.1 37.0 40.5 47.4 35.2 45.9 44.2 45.6 45.9 69.7 33.6 43.7 74.0 69.6 25.9 35.8 65.9 69.0 24.7 31.4 35.0 73.0 29.4 35.8	HR (95% CI) of catheter-directed 0.86 (0.71–1.04) 0.97 (0.67–0.93) 101 (0.83–1.23) 0.88 (0.77–1.02) 0.57 (0.44–0.74) 0.57 (0.44–0.74) 0.54 (0.42–0.71) 0.83 (0.70–0.99) 0.78 (0.66–0.93) 0.71 (0.66–0.84) 0.71 (0.66–0.84)	P value for interaction 0.507 0.004 0.003 0.001 0.613 0.613 0.162
C Recurrent PE	Favor catheter- directed	Favor systemic No. 0 thrombolytic Cathet 13.8 28.9 19.2 26.6 4 23.7 12.1 24.6 0.0 0 4 28.4 7.0 12.1 24.6 0.0 0 4 28.4 7.0 24.8 0.0 0 7.7 24.8 0.0 7.7 24.8 0.0 7.7 24.8 0.0 24.9 24.9 24.9 24.9 24.9 24.9 24.9 24.9	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0 26.1 25.4 18.8 25.0 15.9	SHR (95% CI) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.90 (0.70-1.17) 0.74 (0.58-0.93) 0.87 (0.72-1.05) 0.51 (0.30-0.87) 0.97 (0.80-1.17) NA 1.17 (0.95-1.43) 0.23 (0.15-0.36) 0.92 (0.76-1.11) 0.45 (0.27-0.76) 0.85 (0.71-1.01) 0.56 (0.26-1.18)	P value for interaction 0.274 0.249 0.063 0.063 0.063 0.063 0.013	D All-cause mortality Age group <5 years 5ex Female Male Chronic kidney disease No Yes Cancer No Yes Cancer No Yes Calcore Co 2 2 2 Cardiogeneric shock No Yes Intubation No Yes Yes	Favor catheter-directed	Favor systemic C	No. of event (%) sheter Systemic 35.1 37.0 41.2 57.1 45.2 46.9 44.2 42.6 63.9 69.7 33.6 43.7 74.0 69.6 52.9 35.8 63.9 73.0 24.7 31.4 63.0 73.0 29.4 35.8 73.8 15.8	HR (95% (C)) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 0.70 (0.60–0.82) 1.01 (0.83–1.23) 0.85 (0.77–1.02) 0.57 (0.44–0.74) 0.57 (0.44–0.74) 0.54 (0.42–0.71) 0.54 (0.64–0.79) 0.78 (0.66–0.93) 0.71 (0.60–0.84) 0.71 (0.60–0.84) 0.76 (0.65–0.89)	P value for interaction 0.507 0.004 0.003 0.001 0.613 0.613 0.162
C Recurrent PE	Favor catheter- directed	Favor systemic No. c thrombolytic Cathet 28.9 19.2 26.6 4 23.7 12.1 4 24.6 0.0 4 24.6 0.0 4 24.6 0.0 4 24.8 7.0 12.1 24.8 7.7 24.8 7.7	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0 26.1 25.4 18.8 25.0 15.9	SHR (95% CI) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.90 (0.70-1.17) 0.74 (0.58-0.33) 0.87 (0.72-1.05) 0.51 (0.30-0.87) 0.51 (0.30-0.87) 0.51 (0.30-0.87) 0.37 (0.88-1.17) 0.37 (0.95-1.43) 0.23 (0.15-0.36) 0.32 (0.76-1.11) 0.45 (0.27-0.76) 0.85 (0.71-1.01) 0.56 (0.26-1.18)	P value for interaction 0.274 0.249 0.063 0.063 0.063 0.001 0.013 0.289	D All-cause mortality Age group <pre><65 years 265 years 265 years Sex Female Male Chronic kidney disease No Yes Cancer No Yes Cancer Cancer No Yes Cardiogeneric shock No Yes Intubation No Yes</pre>	Favor catheter-directed	Favor systemic C 	No. of event (%) atheter Systemic 35.1 37.0 40.5 47.4 35.2 45.9 44.2 45.6 45.9 69.7 33.6 43.7 74.0 69.6 25.9 35.8 65.9 69.0 24.7 31.4 63.0 73.0 24.4 35.8 73.3 81.4	HR (95% C)) of catheter-directed 0.86 (0.71–1.04) 	P value for interaction 0.507 0.004 0.003 0.001 0.613 0.613 0.162 0.339
C Recurrent PE	Favor catheter- directed	Favor systemic No. 0 thrombolytic Cathet 13.8 - 28.9 - 19.2 26.6 - 23.7 - 24.6 - 24.6 - 27.9 - 7.7 - 27.9 - 7.7 - 24.6 - 7.2 - 7.9 - 7.7 - 24.6 - 7.2 - 7.9 - 7.7 - 24.8 - 7.2 - 24.8 - 7.2 - 24.8 - 7.2 - 24.8 - 7.2 - 24.8 - 7.2 - 7.2	f event (%) er Systemic 20.9 27.2 23.6 24.3 24.0 23.6 22.7 33.1 23.0 26.1 25.4 18.8 25.0 15.9	SHR (95% CI) of catheter-directed 0.69 (0.51-0.94) 0.86 (0.69-1.08) 0.90 (0.70-1.17) 0.74 (0.58-0.93) 0.87 (0.72-1.05) 0.51 (0.30-0.87) 0.97 (0.80-1.17) NA 1.17 (0.95-1.43) 0.32 (0.76-1.11) 0.45 (0.27-0.76) 0.85 (0.71-1.01) 0.56 (0.26-1.18)	P value for interaction 0.274 0.249 0.063 0.063 0.063 0.063 0.063 0.063 0.063 0.063	All-cause mortality	Favor catheter-directed	Favor systemic C	No. of event (%) sheter Systemic 35.1 37.0 41.2 57.1 45.2 46.9 44.2 42.6 63.9 69.7 33.6 43.7 74.0 69.6 25.9 35.8 65.9 69.0 24.7 31.4 63.0 73.0 29.4 35.8 73.3 81.4	HR (95% C)) of catheter-directed 0.86 (0.71–1.04) 0.79 (0.67–0.93) 0.70 (0.66–0.82) 1.01 (0.83–1.23) 0.57 (0.44–0.74) 0.57 (0.44–0.74) 0.57 (0.44–0.74) 0.57 (0.74–0.74) 0.53 (0.77–0.59) 0.78 (0.66–0.93) 0.71 (0.66–0.84) 0.71 (0.66–0.84) 0.76 (0.65–0.89) 0.86 (0.71–1.04)	P value for interaction 0.507 0.004 0.003 0.001 0.613 0.613 0.162 0.339
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Figure 3. Subgroup analysis comparing catheter-directed thrombolysis with systemic thrombolytic therapy in terms of the risks of in-hospital death (A), 1-year mortality, including in-hospital death (B), all-cause mortality by the end of follow-up (C), and recurrent pulmonary embolism (PE) (D) in the inverse probability of treatment weighting-adjusted cohort. CCI indicates charlson comorbidity index; HR, hazard ratio; OR, odds ratio; and SHR, subdistribution HR.

acute PE, but this should be validated in future prospective studies.

Surprisingly, the expected superiority of CDT to ST in patients with PE in terms of bleeding events was not observed in our study. As mentioned above, the current guidelines reserve CDT for patients with PE requiring reperfusion therapy with higher bleeding risk. In our study, all the uses of CDT were performed with multi-side-hole catheters, but the use of ultrasound-assisted thrombolysis (USAT) was allowed in the PERFECT (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis) trial.²⁰ USAT is a modified CDT using a proprietary system of local ultrasound waves to dissociate the thrombus, allowing for deeper penetration of lytic medication. Kuo et al reported that USAT was more efficient with reduced dosages of thrombolytic agents and shorter CDT courses than traditional CDT in treating patients with acute PE. Therefore, a lower major bleeding rate among patients with PE treated with USAT is expected, which may explain the difference between our study and the PERFECT trial.

Current guidelines suggest systemic thrombolytic therapy, not CDT, as the first-line therapy for patients

with PE requiring reperfusion therapy. In the current study, there was significant interaction in the subgroup analysis for in-hospital mortality in certain critical circumstances, including chronic kidney disease, intubation, and shock. On the basis of our results, the application of CDT could be considered more often than the current guidelines suggest. There were similar benefits of CDT in the subgroup analysis for chronic kidney disease and cancer with respect to 1-year and all-cause mortality. Previous studies showed that there were 5 to 7 times the risk of venous thromboembolism and 3 times the rate of fatal PE in patients with cancer than in those without cancer.²⁸⁻³¹ Furthermore, thrombosis was confirmed to be one of the leading complications and the second leading cause of death in patients with cancer.32,33

Limitations

This study had several limitations. First, the diseases in the NHIRD were identified using *ICD-9-CM* codes, and the database does not provide hemodynamic data, laboratory test, or image information. Accordingly, we could not stratify our patients into distinct risk groups

as current guidelines suggest. However, we still detected cardiogenic shock, extracorporeal membrane oxygenation use, and intubation, which are related to the severity of PE. Second, there was no standard protocol of CDT with respect to the dosage and infusion time of thrombolytic agents, and it was impossible to extract the drug dosing data from our database. The different dosages and infusion times of thrombolytic agents might influence the efficacy and safety of CDT. Third, all the uses of CDT were performed with multiside-hole catheters, and there were no cases involving USAT included in our study. Meanwhile, given that newer generations of CDT devices for acute PE have propagated rapidly, our results may not truly reflect the current status of CDT. Moreover, the subgroup analysis may be underpowered because of the small sample size of patients undergoing CDT. Last, this was a retrospective observational database study, and the existence of numerous confounding factors in our study cohort may have influenced the results.

CONCLUSIONS

In our analysis, we found that for patients with PE, CDT might be more effective than ST in terms of reducing in-hospital mortality, all-cause mortality, and recurrent PE, whereas the bleeding risk of both forms of treatment is essentially equal. This result should be cautiously validated in further randomized trials to confirm our findings and guide clinical practice.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material Table S1

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SUPPLEMENTAL MATERIAL

Variable	ICD-9 CM Code
Pulmonary embolism	415.1x
Deep vein thrombosis	453.xx
Hypertension	401.xx-405.xx
Diabetes mellitus	250.xx
Hyperlipidemia	272. xx
Peripheral arterial	440.0.xx, 440.2x, 440.3x, 440.8x, 440.9x, 443.xx, 444.0x,
disease	444.22, 444.8x, 447.8x, 447.9x
Chronic obstructive	491.xx, 492.xx, 496.xx
pulmonary disease	
Gouty arthritis	274.xx
Liver disease	070.xx, 456.0-456.2, 570.xx, 571.xx, 572.2-572.8,
	573.xx, V42.7
Ischemic heart disease	410.xx-414.xx
Myocardial infarction	410.xx, 412.xx
Congestive heart failure	410.xx-414.xx
Atrial fibrillation	427.3x
Stroke	430.xx-437.xx
Paralysis	334.1, 342.xx, 343.xx, 344.xx
(Immobilization)	
Chronic kidney disease	580.xx-589.xx, 403.xx-404.xx 016.0x, 095.4x, 236.9x,
	250.4x, 274.1x, 442.1x, 447.3x, ,440.1x, 572.4x, 642.1x,
	646.2x, 753.1x, 283.11, 403.01, 404.02, 446.21
Pulmonary	416.0x, 416.8x
hypertension	
Autoimmune disease	7100, 7101, 7100, 7101, 7102, 7140, 7104, 7103, 4460,
	4464, 4465, 4431, 4467, 4461, 1361, 6944, 555.xx, 556,
	5560, 5561, 5562, 5563, 5564, 5565, 5566, 5568, 5569,
	446.2x (Catastrophic illness certificate)
Cancer	140.xx-208.xx (Catastrophic illness certificate)
Trauma injury	800.xx-959.xx
Heart failure	428.xx
Acute myocardial	410.xx
infarction	
Major bleeding	3361, 3636, 37272, 37632, 37742, 37923, 4230, 430,
	431, 4320, 4321, 4329, 531, 5312, 5314, 5316, 532,
	5322, 5324, 5326, 5307, 533, 5332, 5334, 5336, 534,

Table S1. ICD-9 CM diagnostic codes.

	5342, 5344, 5346, 5693, 53501, 53511, 53521, 53531,
	53541, 53551, 53561, 53571, 53783, 53784, 56202,
	56203, 56212, 56213, 56985, 578, 59381, 7191, 72992,
	7725, 8520, 8522, 8524, 8530, 86601, 86602, 86611,
	86612
Gastrointestinal	530.21, 530.7, 530.82, 531.xx-535.xx, 537.83, 537.84,
bleeding	578.xx
Intracranial hemorrhage	430.xx-432.xx

ICD-9 CM, International Classification of Diseases, Ninth Revision, Clinical Modification.