Catheter-Directed Thrombolysis in Submassive Pulmonary Embolism and Acute Cor Pulmonale

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Treatment of submassive (intermediate-risk) pulmonary embolism (PE), defined as hemodynamically stable with right ventricular (RV) dysfunction, showed lower in-hospital all-cause mortality with intravenous thrombolytic therapy than with anticoagulants, but at an increased risk of major bleeding. The present investigation was performed to test whether catheter-directed thrombolysis reduces mortality without increasing bleeding in submassive PE. This was a retrospective cohort study based on administrative data from the Nationwide Inpatient Sample. In 2016, 13,130 patients were hospitalized with PE and acute cor pulmonale, were stable, and treated with catheter-directed thrombolysis in 1,500 (11%) or anticoagulants alone in 11,630 (89%). Mortality was lower with catheter-directed thrombolysis than with anticoagulants in unmatched patients, 35 of 1,500 (2.3%) compared with 755 of 11,630 (6.5%; p <0.0001) and in matched patients, 30 of 1,260 (2.4%) compared with 440 of 6,910 (6.4%; p <0.0001). Time-dependent analysis showed catheter-directed thrombolysis reduced mortality if administered within the first 3 days. Patients with saddle PE treated with anticoagulants had lower mortality than non-saddle PE, 75 of 1,730 (4.3%) compared with 680 of 9,900 (6.9%; p < 0.0001) in unmatched patients and 45 of 1,305 (3.4%) compared with 395 of 5,605 (7.0%; p < 0.0001) in matched patients. Mortality was not lower with inferior vena cava filters either in those who received catheter-directed thrombolysis or those treated with anticoagulants. There were no fatal or nonfatal adverse events associated with catheter-directed thrombolysis. In conclusion, patients with submassive PE appear to have lower in-hospital all-cause mortality with catheter-directed thrombolysis administered within 3 days than with anticoagulants, and risks are low. **(Am J Cardiol 2020;131:109−114)**

Pooled data from 8 randomized trials of treatment of submassive (intermediate-risk) acute pulmonary embolism (PE), defined as hemodynamically stable with right ventricular (RV) dysfunction, showed lower in-hospital all-cause mortality with intravenous thrombolytic therapy than with anticoagulants, 1.4% compared with 2.9%.[1] There was, however, increased risk of major bleeding with intravenous thrombolytic therapy, 7.7% compared with 2.3% with anticoagulants.[1] In view of the decreased mortality with intravenous thrombolytic therapy in patients with submassive PE, although accompanied by increased bleeding, the safety and efficacy of catheter-directed low-dose fibrinolysis was explored.[2−4] Data on mortality with catheter-directed thrombolysis compared with anticoagulants, however, are sparse.[3,4] All-cause mortality at 90 days was 0 of 30 (0%) in patients with RV dilatation treated with ultrasound-assisted catheter-directed thrombolysis which did not differ significantly in patients treated with anticoagulants, 1 of 29 (3.4%).[3] Pulmonary embolism-related death occurred in 1 of 64 (1.6%) in patients with submassive PE treated with catheter-directed thrombolysis and it was the same with anticoagulants.[4] Clearly more data would be useful. Therefore, this investigation of data from the Nationwide Inpatient Sample was undertaken.

Methods

This was a retrospective cohort study based on administrative data from the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality, 2016.[5] The Nationwide Inpatient Sample in 2016 is a sample of discharge records from all United States non-Federal, short-term, general, and other specialty hospitals participating in the Healthcare Cost and Utilization Project.[5] This investigation was determined by the institutional review board not to meet the definition of "human subjects" because the database includes only de-identified patients.

In-hospital all-cause mortality in patients with acute submassive PE was assessed according to treatment with catheter-directed thrombolysis or anticoagulants. The effects on mortality of inferior vena cava filters were also assessed. We identified stable patients with acute PE and acute cor pulmonale. Stable patients were defined as not in shock and not on ventilator support. Stable patients with PE and acute cor pulmonale were stratified according to whether or not they had saddle PE. We excluded patients who underwent pulmonary embolectomy or received intravenous thrombolytic therapy. We assumed that patients with PE and acute cor pulmonale were treated with anticoagulants if they did

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not receive intravenous thrombolytic therapy, catheter-directed thrombolytic therapy, or pulmonary embolectomy. We assumed that patients treated with catheter-directed thrombolysis also received anticoagulants.

Patients were identified by International Classification of Diseases-10-Clinical Modification (ICD-10-CM) Codes. The ICD-10-CM codes that we used are shown in Table 1. Included patients were adults (≥18 years of age) of both genders and all races hospitalized in short-stay hospitals from all regions of the United States. In all instances, "mortality" refers to in-hospital all-cause mortality (case fatality rate).

Co-morbid conditions in the updated Charlson co-morbidity index that showed good-to-excellent discrimination in predicting in-hospital mortality were assessed.[6] Co-morbidities that we used had updated weights that range from 1 to 6 depending on the risk-adjusted hazard ratio.[6] We did not assess co-morbidities with updated weights of 0. The ICD-10-CM codes used in identifying these co-morbid conditions and updated weights were shown previously.[7] We performed an analysis of unadjusted data and an analysis of data adjusted by matching age, gender, and co-morbid conditions using normal matching procedures.

To control for immortal time bias, we performed a time-dependent analysis. In our study, immortal time refers to the time between admission and treatment with catheter-directed thrombolysis. This wait period was considered immortal because individuals who received catheter-directed thrombolysis had to be alive to receive it. We studied only survivors of the immortal period by moving the start of follow-up of anticoagulant-treated patients to the end of the immortal period and moving the time of follow-up of those who received catheter-directed thrombolysis to the day of treatment.[8,9] Anticoagulant-treated patients who died before the day of catheter-directed thrombolysis were excluded from the analysis.[9] The number at risk at the end of each day was the preceding number less both the preceding day's deaths and discharges.[10] The day of admission was defined as day 1.

Table 1
International Classification of Disease-10th clinical modification codes used

Condition	ICD-10-CM code
Pulmonary embolism, no acute cor pulmonale	I26.92, I26.99
Saddle pulmonary embolism with acute cor pulmonale	I26.02
Other (not saddle) pulmonary embolism with acute cor pulmonale	I26.09
Thrombolytic therapy, catheter-tip	3E06317
Thrombolytic therapy, intravenous	3E03317
Shock	R57.0, R57.9
Ventilator dependence	Z99.11
Pulmonary embolectomy	02CP0ZZ, 02CQ0ZZ, 02CQ4ZZ, 02CR0ZZ, 02CP4ZZ, 02CR4ZZ
Inferior vena cava filter	06H03DZ
Adverse effects of thrombolytic drugs	T45.615A
Adverse effects of anticoagulants	T45.515A
Intracerebral hemorrhage	I61

Differences of categorical variables were calculated by the 2-tailed Fisher exact test or chi-square with Yates' correction using Graphpad Quickcalcs (Graphpad, San Diego, CA) or MedCalc statistical software, Osland, Belgium [medcalcviewersetup.msi (19.9 MB]. Odds ratios and their 95% confidence intervals (CI) were calculated with MedCalc statistical software version 19.1.3 [medcalcviewersetup.msi (19.9 MB]. The 95% CIs were calculated by the modified Wald method using Graphpad Quickcalcs. Continuous variables were expressed as mean ± standard deviation and differences were calculated with an unpaired t-test using Graphpad Quickcalcs. A p value ≤0.05 was considered statistically significant.

Results

In 2016, 13,130 patients had PE with acute cor pulmonale, were stable, and were treated with catheter-directed thrombolysis or anticoagulants (Figure 1). Treatment was with catheter-directed thrombolysis in 1,500 (11%) or with anticoagulants alone in 11,630 (89%). Mortality was lower with catheter-directed thrombolysis than with anticoagulants in unmatched patients, 2.3% compared with 6.5% (p <0.0001) and in matched patients, 2.4% compared with 6.4% (p <0.0001; Table 2).

Saddle PE with acute cor pulmonale was present in 2,345 (18%) and non-saddle PE with acute cor pulmonale was present in 10,785 (82%). Characteristics and co-morbid conditions in unmatched patients and matched patients with saddle PE and with non-saddle PE are shown in Tables 3 and 4.

A higher proportion of patients with saddle PE had catheter-directed thrombolysis than patients who had non-saddle PE, 615 of 2,345 (26%) compared with 885 of 10,785 (8.2%; p <0.0001). Patients with saddle PE treated with anticoagulants, however, were not at greater risk of death than patients with non-saddle PE when treated with anticoagulants. To the contrary, they were at lower risk of death (Table 2). In patients with saddle PE and patients with non-saddle PE, mortality in both unmatched and matched patients treated with catheter-directed thrombolysis was lower than in patients treated with anticoagulants (Table 2).

Mortality was not lower with inferior vena cava filters in unmatched patients either in those who received catheter-directed thrombolysis or those treated with anticoagulants (Table 5).

Most patients treated with catheter-directed thrombolysis, 1,195 of 1,500 (80%), received it on day 1. All who were treated with catheter-directed thrombolysis received it on days 1 to 5. Time-dependent analysis showed that patients who received catheter-directed thrombolysis within the first 3 days of hospitalization had a lower mortality than patients treated with anticoagulants.

There were no fatal or nonfatal adverse events due to catheter-directed thrombolysis in 1,500 patients. Nonfatal adverse events due to anticoagulants occurred in 135 of 11,630 (1.2%) patients treated with anticoagulants alone, and nonfatal adverse events due to anticoagulants occurred in 20 of 1500 (1.3%) who received anticoagulants in addition to catheter-directed thrombolysis

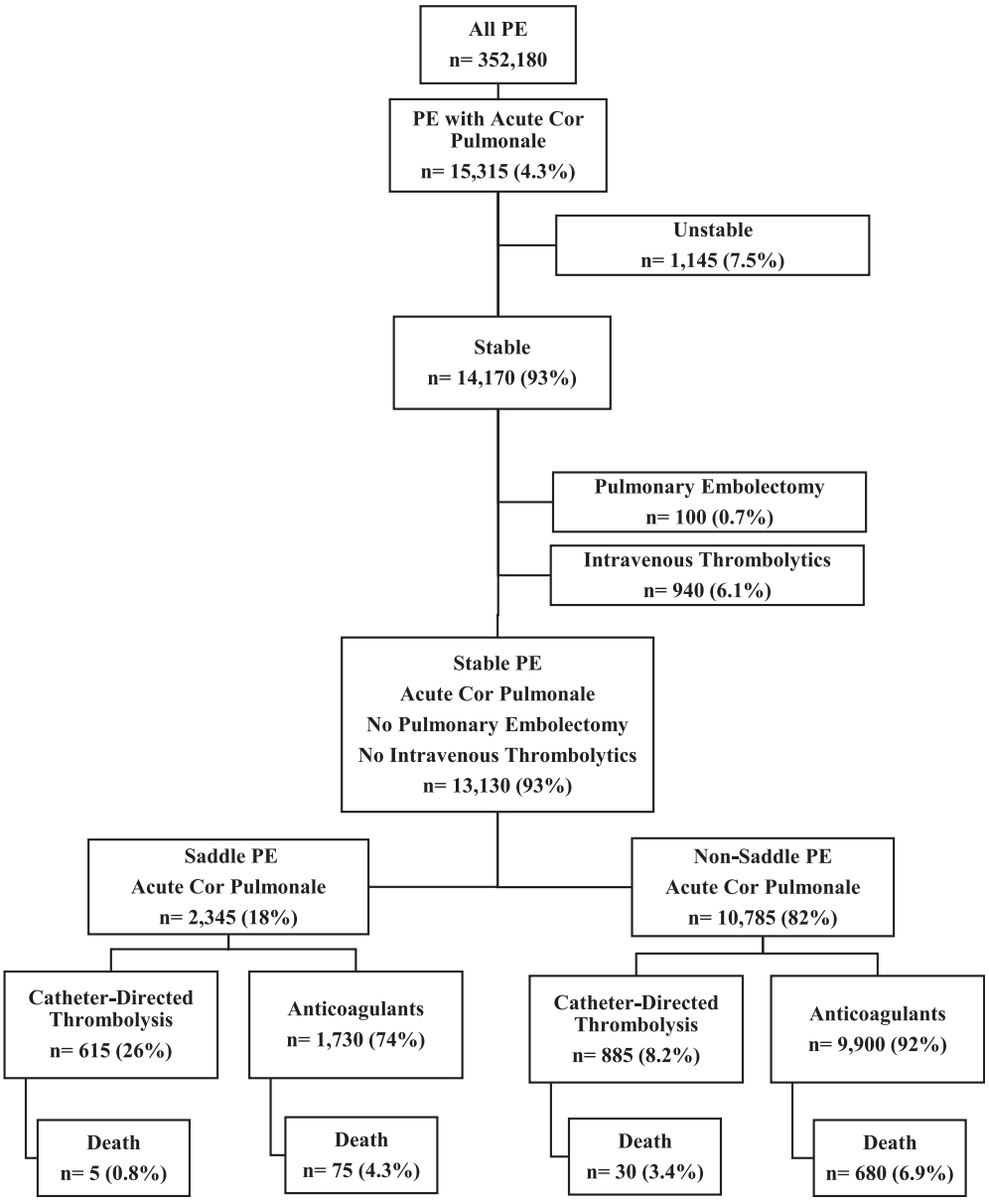

Figure 1. Flow diagram. PE = pulmonary embolism.

Table 2
Mortality according to treatment

Group	Catheter-directed thrombolysis mortality n/N (%)	95% CI	Anticoagulants mortality n/N (%)	95% CI	p	Odds ratio (95% CI)
Unmatched						
Saddle PE	5/615 (0.8%)	0.3-2.0%	75/1730 (4.3%)	3.5-5.4%	<0.0001	0.02 (0.01-0.04)
Non-Saddle PE	30/885 (3.4%)*	2.2 - 4.6%	680/9,900 (6.9%)†	6.4-7.4%	<0.0001	0.48 (0.33-0.69)
All submassive PE	35/1,500 (2.3%)	1.7-3.2%	755/11,630 (6.5%)	6.0-7.0%	<0.0001	0.01 (0.009-0.02)
Matched						
Saddle PE	0/525 (0%)	0-0.7%	45/1305 (3.4%)	2.6-4.6%	<0.0001	0.03 (0.002-0.43)
Non-saddle PE	30/735 (4.1%)†	2.9 - 5.8%	395/5,605 (7.0%)†	6.4-7.8%	0.0017	0.56 (0.38-0.82)
All submassive PE	30/1,260 (2.4%)	1.7-3.4%	440/6,910 (6.4%)	5.9-7.0%	<0.0001	0.36 (0.25-0.52)

CI = confidence interva1; PE = pulmonary embolism.
* p <0.0008 saddle PE vs non-saddle PE,
† p <0.0001 saddle PE vs non-saddle PE.

Table 3
Characteristics and co-morbid conditions in patients with saddle pulmonary embolism

Variable	Unmatched saddle PE			Matched saddle PE		
	Catheter-directed thrombolysis (n = 615)	Anticoagulants (n = 1,730)	p	Catheter-directed thrombolysis (n = 525)	Anticoagulants (n = 1,305)	p
Age (years) Mean ± SD	61 ± 14	63 ± 15	0.004	60 ± 14	60 ± 14	1.00
Male	350 (57%)†	940 (55%)§	0.2	310 (60%)**	760 (58%)‡‡	0.67
Female	260 (43%)†	785 (45%)§	0.2	210 (40%)**	540 (42%)‡‡	0.67
White	445 (76%)‡	1280 (78%)¶	0.6	380 (77%)††	920 (73%)§§	0.15
Congestive heart failure	65 (11%)	100 (5.8%)	<0.0001	15 (2.9%)	30 (2.3%)	0.51
Chronic pulmonary disease	55 (8.9%)	200 (12%)	0.08	50 (9.5%)	95 (7.3%)	0.13
Dementia	5 (0.8%)*	70 (4.0%)	-	0 (0%)	0 (0%)	1.00
Rheumatologic disease	5 (0.8%)*	40 (2.3%)	-	0 (0%)	0 (0%)	1.00
Liver disease, mild to severe	0 (0%)	15 (0.9%)	0.02	0 (0%)	0 (0%)	1.00
Diabetes mellitus, complicated	100 (16%)	255 (15%)	0.36	70 (13%)	175 (13%)	0.94
Hemiplegia, hemiparesis, paraplegia	5 (0.8%)*	65 (3.8%)	-	0 (0%)	0 (0%)	1.00
Renal disease (renal failure)	65 (11%)	155 (9.0%)	0.26	40 (7.6%)	95 (7.3%)	0.84
Neoplasms, leukemia, lymphoma	85 (14%	325 (19%)	0.005	75 (14%)	155 (12%)	0.16
Metastatic cancer	5 (0.8%)*	85 (4.9%)	-	0 (0%)	0 (0%)	1.00
HIV and AIDS	0 (0%)	0 (0%)	1.00	0 (0%)	0 (0%)	1.00

HIV = human immunodeficiency virus, AIDS = acquired immune deficiency syndrome.
* Values <10 are insufficient for calculation.
† Gender based on 610 patients.
‡ Race based on 585 patients.
§ Gender based on 1,725 patients.
¶ Race based on 1,645 patients.
** Gender based on 520 patients.
†† Race based on 495 patients.
‡‡ Gender based on 1,300 patients.
§§ Race based on 1,255 patients.

Table 4
Characteristics and co-morbid conditions in patients with non-saddle pulmonary embolism

Variable	Unmatched non-saddle PE			Matched non-saddle PE		
	Catheter-directed thrombolysis (n = 885)	Anticoagulants (n = 9,900)	p	Catheter-directed thrombolysis (n = 735)	Anticoagulants (n = 5,605)	p
Age (years) mean ± SD	62 ± 14	66 ± 15	<0.0001	60 ± 13	60 ± 11	1.00
Male	435 (49%)	4,610 (47%)†	0.14	345 (47%)	2,520 (45%)	0.32
Female	450 (51%)	5,285 (53%)†	0.15	390 (53%)	3,085 (55%)	0.32
White	610 (73%)*	6,805 (72%)‡	0.59	500 (72%)§	3,850 (72%)¶	0.96
Congestive heart failure	95 (11%)	1,880 (19%)	<0.0001	0 (0%)	0 (0%)	1.0
Chronic pulmonary disease	155 (18%)	3,250 (33%)	<0.0001	105 (14%)	785 (14%)	0.91
Dementia	15 (1.7%)	370 (3.7%)	0.002	15 (2.0%)	95 (1.7%)	0.55
Rheumatologic disease	30 (3.4%)	235 (2.4%)	0.06	25 (3.4%)	125 (2.2%)	0.07
Liver disease, mild to severe	0 (0%)	280 (2.8%)	<0.0001	0 (0%)	0 (0%)	1.0
Diabetes mellitus, complicated	155 (18%)	1,745 (18%)	0.97	145 (20%)	1,010 (18%)	0.31
Hemiplegia, hemiparesis, paraplegia	0 (0%)	170 (1.7%)	0.0002	0 (0%)	0 (0%)	1.0
Renal disease (renal failure)	125 (14%)	2,315 (23%)	<0.0001	65 (8.8%)	530 (9.5%)	0.59
Neoplasms, leukemia, lymphoma	155 (18%)	1,760 (18%)	0.88	125 (17%)	895 (16%)	0.52
Metastatic cancer	40 (4.5%)	510 (5.2%)	0.46	35 (4.8%)	260 (4.6%)	0.93
HIV and AIDS	0 (0%)	55 (0.6%)	0.048	0 (0%)	0 (0%)	1.0

HIV = human immunodeficiency virus, AIDS = acquired immune deficiency syndrome.
* Race based on 835 patients.
† Gender based on 9,895 patients.
‡ Race based on 9,435 patients.
§ Race based on 690 patients.
¶ Race based on 5,325 patients.

Table 5
Mortality according to use of inferior vena cava filters in unmatched patients

Group	Catheter-directed thrombolysis IVC filter Mortality (%)	Catheter-directed thrombolysis No IVC filter Mortality (%)	p	Anticoagulants IVC filter Mortality (%)	Anticoagulants No IVC filter Mortality (%)	p
Saddle PE	0/125 (0%)	5/490 (1.0%)	0.58	5/235 (2.1%)	70/1,495 (4.7%)	0.08
Non-saddle PE	15/200 (7.5%)	15/685 (2.2%)	0.001*	50/735 (6.8%)	630/9,165 (6.9%)	1.00
All PE	15/325 (4.6%)	20/1,175 (1.7%)	0.006*	55/970 (5.7%)	700/10,660 (6.6%)	0.31

IVC = inferior vena cava. PE = pulmonary embolism.
* Mortality higher with IVC filter.

(p = 0.65). There were no fatal adverse events associated with anticoagulant therapy and there were no intracerebral hemorrhages.

Discussion

Mortality in patients with submassive PE was lower with catheter-directed thrombolysis than with anticoagulants, based on unadjusted data and based on data from patients matched for age, gender, and co-morbid conditions providing treatment was administered within the first 3 days. Patients with saddle PE were not at greater risk of death when treated only with anticoagulants. Even so, a higher proportion of patients with saddle PE than non-saddle PE received catheter-directed thrombolysis. Inferior vena cava filters did not reduce mortality in patients treated with catheter-directed thrombolysis or with anticoagulants. There were no adverse events associated with catheter-directed thrombolysis**.** Presumably, therefore, treatment with catheter-directed thrombolysis was with low-dose thrombolytic agents.

Mortality that we report in patients with submassive PE is higher than reported in a meta-analysis of patients with submassive PE treated with intravenous thrombolytic agents (1.4% mortality) compared with anticoagulants (2.9% mortality).[1] Patients with PE who had acute cor pulmonale in our study population may have had more severe right ventricular dilatation than patients with submassive PE studied by others who could have had any amount of right ventricular enlargement without being considered as having acute cor pulmonale. Therefore, patients in our investigation may have been at higher risk than most patients with submassive PE studied by others.

We assumed that patients were treated with anticoagulants if they did not receive intravenous thrombolytic therapy, catheter-directed thrombolytic therapy or pulmonary embolectomy. In a prospective multicenter registry, 98.5% of patients with nonmassive PE received anticoagulant therapy.[11] In the RIETE investigation (Computerized Registry of Patients with Venous Thromboembolism), 0.9% of patients with acute venous thromboembolism underwent inferior vena cava filter insertion because of bleeding risk.[12] It may be, therefore, that approximately 0.9% to 1.5% of patients assumed to be treated with anticoagulants did not receive it.

In patients who received catheter-directed thrombolysis, we do not know the dose or agent used or duration of infusion or if standard catheter-directed thrombolysis or ultrasound-assisted thrombolysis was used. However, standard catheter-directed thrombolysis and ultrasound-assisted thrombolysis have been shown to achieve similar benefits in hemodynamics, right ventricular strain, and clinical outcome.[13]

Strengths of this investigation include the power afforded by the National Inpatient Sample database which includes adults of all ages and races and both genders from all regions of the United States. This is by far the largest investigation of patients with submassive PE in which mortality with catheter-directed thrombolysis was compared with anticoagulants. Stratification according to whether or not the patients had saddle PE has not been done previously. Assessment of the effects on mortality of inferior vena cava filters also has not been done previously. The time-dependent analysis that we performed eliminated immortal time bias.[9] Matching age, gender, and co-morbid conditions helped reduce the likelihood of spurious results.

Weaknesses are that the investigation is retrospective and based on administrative data. We do not know the positive predictive value of the codes for PE with acute cor pulmonale. Intuitively, it would seem that the codes for PE with acute cor pulmonale have few false positives.

In conclusion, patients with submassive PE appear to have lower in-hospital all-cause mortality with catheter-directed thrombolysis administered within 3 days than with anticoagulants, and risk of bleeding is low. Although clinical implication is that catheter-directed thrombolysis would lower mortality in patients with submassive PE providing expertise is available, it would be useful to have confirmatory data.

Author Contribution

All authors had access to the data and participated in preparation of the manuscript.

Disclosures

The authors have no conflicts of interest to disclose.

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