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ORIGINAL ARTICLE

Time trends of catheter-directed treatment in acute pulmonary embolism in Germany

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Abstract

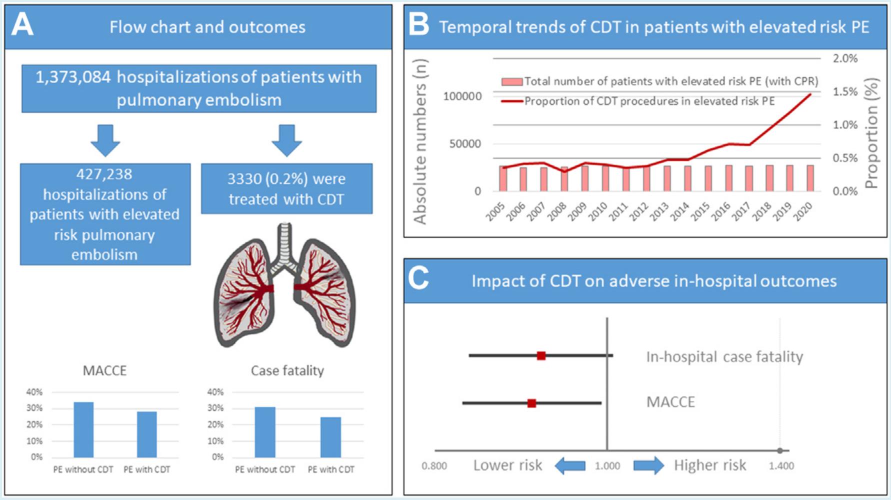
Background: Catheter-directed treatment (CDT) is an innovative treatment for patients with elevated risk pulmonary embolism (PE) to resolve embolus and restore pulmonary perfusion.

Objectives: We aimed to analyse the use and the benefit of CDT in PE patients in Germany.

Methods: The German nationwide inpatient sample was used to include all hospitalizations of patients with PE from 2005 to 2020 in Germany. PE patients were stratified for CDT usage. Temporal trends and the impact of CDT on case fatality and other outcomes were investigated.

Results: Overall, 1,373,084 hospitalizations of patients with PE (55.9% aged ≥70 years; 53.0% females) were included in this study from 2005 to 2020, and among these, 427,238 (31.1%) patients were categorized as having elevated-risk PE and 3330 (0.2%) were treated with CDT with annual increase from 0.17% (2005) to 0.51% (2020). PE patients of younger age, male sex, with previous surgery, and elevated-risk PE were more often treated with CDT. In patients with elevated risk-PE, CDT attributed to a lower observed rate of major adverse cardiac and cerebrovascular events (major adverse cardiac and cerebrovascular events [MACCE]; 28.2% vs 34.2%; $P < .001$) and in-hospital case fatality (24.9% vs 31.0%; $P < .001$). CDT was associated with reduced MACCE (OR, 0.91; 95% CI, 0.83-0.99) and with a trend toward lower case fatality (OR, 0.92; 95% CI, 0.84-1.01). The benefit of CDT regarding case fatality was age-dependent.

Conclusion: Although the annual rate of CDT increased in Germany between 2005 and 2020, only 0.2% of the PE patients were treated with CDT. Selection criteria for CDT treatment were younger age, male sex, previous surgery, and elevated risk-PE. CDT treatment was associated with reduced MACCE and case-fatality rate in PE patients with elevated-risk PE.



(A) We studied 1,373,084 hospitalizations of patients with pulmonary embolism (PE) admitted to German hospitals during 2005 to 2020. Of these 427,238 had an elevated-risk PE and 3330 (0.2%) were treated with catheter-directed treatments (CDTs). Major adverse cardiac and cerebrovascular events and case fatality were lower in elevated-risk PE patients treated with CDT than without. (B) Usage of CDT increased slowly in patients with elevated-risk PE over time. (C) The benefit of CDT in patients with elevated-risk PE was independent of age, sex, and comorbidities. CDT, catheter-directed treatment; PE, pulmonary embolism.

KEYWORDS
catheter-directed treatment, local lysis, local therapy, pulmonary embolism, thrombectomy

Essentials

- CDT is an innovative treatment for elevated-risk PE.
- We analyzed the German NIS to observe the trends regarding CDT in PE.
- Usage of CDT increased in Germany between 2005 and 2020 at a low level.
- CDT was associated with reduced MACCE and a trend of lower case fatality in elevated-risk PE.

1 | INTRODUCTION

Pulmonary embolism (PE) is a potentially life-threatening condition representing the third most common cardiovascular cause of death after myocardial infarction and stroke [1–3]. While annual incidence of PE increased in the past decades, case fatality decreased anti-proportionally [2–5]. PE occurs when venous thrombi embolize to the pulmonary circulation and result in vascular occlusion with impaired circulation and gas exchange [3,5]. Initial risk stratification of acute PE is based on clinical symptoms, cardiac adaptations, comorbidities, and in particular, signs of hemodynamic instability [3,5]. The primary treatment aim is to restore blood flow to the affected areas of the lungs, resolving or removing the embolus burden and preventing further clot formation [3,5]. Since acute right ventricular failure with resulting low systemic output is the leading cause of death in patients with elevated-risk PE comprising high-risk PE (hemodynamic instability) and also selected patients with imminent hemodynamic compromise (intermediate high-risk), immediate reperfusion is recommended in this crucial patient group [5]. Systemic thrombolysis and surgical embolectomy are established treatment options for acute PE with hemodynamic deterioration [5,6]. In addition, catheter-directed treatments (CDTs) are an emerging option for the management of PE and include catheter-directed thrombolysis and catheter-based thrombectomy [5,6]. Catheter-directed thrombolysis involves the administration of a thrombolytic agent directly into the clot via a catheter, whereas catheter-based thrombectomy mechanically removes the clot using a catheter-based device [5,6]. These procedures are less invasive than surgical embolectomy and have a lower risk of bleeding complications than systemic thrombolysis [5]. Recent studies have shown that CDT are safe and effective treatment options for PE, with lower complication rates and shorter in-hospital stay than traditional therapies, which might also lead to reduced health care costs [5,7]. Besides these reperfusion treatments, anticoagulation treatment with heparins, vitamin-K antagonists, or new oral anticoagulation drugs is recommended for early and long-term treatment in PE patients [5].

While the standard reperfusion treatment of systemic thrombolysis is established, the new CDTs must demonstrate their non-inferiority and benefit regarding patients' outcome in a real-world setting.

2 | METHODS

2.1 | Data source

The Research Data Center (RDC) of the Federal Bureau of Statistics (Wiesbaden, Germany) calculated the intended statistical analysis on our behalf. For this objective, we supplied SPSS codes (IBM Corp Released 2011; IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA) to the RDC, and the RDC performed the statistics and afterwards provided the aggregated results to us (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005-2020, own calculations) [3,8].

With this data analysis of the German nationwide inpatient sample (NIS), we aimed to investigate the impact of CDT on outcomes and especially on case-fatality rate in acute PE (International Classification of Diseases [ICD]-code I26), as well as trends regarding usage of CDT during the observational period between 2005 and 2020.

2.2 | Study oversight and support

Since our study did not include any direct access by us—as the investigators—to individual patient data but only an access to summarized results provided by the RDC, approval by an ethics committee as well as patients' informed consent were not required, in accordance with the German law [3,8].

2.3 | Coding of diagnoses, procedures, and definitions

Four years after the turn of the millennium (in 2004), the introduction of diagnosis- and procedure-related remuneration was implemented in the German health care system. The coding of patients' data on diagnoses, coexisting conditions, and on surgeries as well as on procedures or interventions according the German Diagnosis Related Groups (G-DRGs) system and the transfer of these patient-related codes to the Institute for the Hospital Remuneration System are mandatory for German hospitals to get their remuneration [3,8]. Patients' diagnoses are coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, with German modification (ICD-10-GM) [3,8]. The surgical, diagnostic and interventional procedures are coded according to Operationen- und Prozedurenschlüssel (OPS) codes.

With our present analysis of the real-world data of the German NIS, we identified all hospitalizations of patients with PE in Germany during the observational period between 2005 and 2020.

Elevated-risk PE was defined as tachycardia (ICD-10 codes I47 and R00.0), right ventricle dysfunction (I26.0), or shock (R57) [7]. Hemodynamic instability was defined as shock (R57) or cardiopulmonary resuscitation (OPS code 8-77). The following reperfusion treatment procedures were included in the analysis: systemic thrombolysis (OPS code 8-020.8), surgical embolectomy (5-380.42), and CDT comprising catheter-directed thrombolysis (8-838.d0, 8-838.50, 8-838.60, 8-838.70), or catheter-based thrombectomy (8-83b.j).

2.4 | Study endpoints

The primary study outcome was death of all-causes during in-hospital stay (in-hospital death). In addition, we analyzed the prevalence of major adverse cardiovascular and cerebrovascular events (major adverse cardiac and cerebrovascular events [MACCE], composite of all-cause in-hospital death, acute myocardial infarction [ICD-code I21], and/or ischemic stroke [ICD-code I63]) [9].

2.5 | Statistical analysis

PE patients with and without performed CDT were compared with Wilcoxon-Whitney *U*-test for continuous variables and Fisher's exact or chi-squared test for categorical variables, as appropriate. Temporal trends regarding the usage of CDT in PE patients' hospitalizations were shown as figures. We provided information regarding total numbers of PE patients and proportion of PE patients treated with CDT. Univariate and multivariate logistic regression models were analyzed to investigate the impact of CDT on adverse in-hospital events and on in-hospital death in PE patients. Results are presented as OR and 95% CI. The multivariate regression models were adjusted for age, sex (as the reported patient's sex), obesity, diabetes mellitus, cancer, coronary artery disease, heart failure, chronic obstructive pulmonary disease, essential arterial hypertension, acute and chronic kidney failure, surgery, chronic anemia, and atrial fibrillation or flutter. We identified in previously published studies of the German NIS important risk factors for increased case fatality [3,10–15]. This information was used to select parameters for the adjustment of the multivariable logistic regression models. Therefore, we used this conservative and epidemiologic approach regarding adjustment to test the widespread independence of these outstanding influencing factors on the case-fatality rate during hospitalization.

All statistical analyses were carried out using the SPSS software (IBM Corp Released 2011; IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA). Only P values of $< .05$ (two-sided) were considered to be statistically significant. No adjustment for multiple testing was applied.

3 | RESULTS

Overall, 1,373,084 hospitalizations of patients with PE (767,907 [55.9%] aged ≥70 years; 727,484 [53.0%] females) from 2005 to 2020 were detected in Germany and were finally included in the present analysis. Among these 3330 (0.2%) were treated with CDT. Overall, 427,238 (31.1%) were categorized as elevated-risk PE (Tables 1 and 2).

3.1 | Temporal trends of CDT in PE patients

Total annual number of hospitalization cases of patients with PE increased from 70,393 in 2005 to 97,718 in 2020 (Figure 1A). During the observational period, absolute numbers of CDT rose from 118 (0.17%) in 2005 to 503 in 2020 (0.51%) (Figure 1A). The proportion of CDT increased distinctly in patients with elevated-risk PE, whereas the rate was widely constant in low-risk patients (Figure 1B). The highest incidence of PE was identified for PE patients in the seventh, eighth, and ninth decades of life, whereas highest relative number of CDT was detected in the first decade of life and decreased with increasing age (Figure 1C). Highest absolute numbers of CDT were found in the sixth to eighth decades of life (Figure 1D). Notably, the case-fatality rate was highest in patients treated with CDT at both ends of the age spectrum in PE patients <10 years of age and in those aged ≥80 years (Figure 1D).

3.2 | Patient characteristics in PE patients with and without *CDT*

PE patients treated with CDT were in median 6 years younger, less often female, but more often obese (Table 1). While surgery—as an important venous thromboembolism (VTE) risk factor—was more prevalent in PE patients with CDT, cancer was more common in those patients without CDT treatment. Patients treated with CDT more often had heart failure but less often peripheral artery disease, atrial fibrillation/flutter, and chronic obstructive pulmonary disease (Table 1). Elevated-risk PE (78.6% vs 31.0%) as well as hemodynamic instability (27.2% vs 8.9%) were substantially more frequent in PE patients with CDT therapy than in those without (Table 1).

When focusing on 427,238 hospitalizations of patients with elevated-risk PE, patients treated with CDT were also younger, less often female, but more often obese (Table 2). Patients with elevated-risk PE treated with CDT less often had comorbidities such as cancer, peripheral artery disease, atrial fibrillation or flutter, and chronic obstructive pulmonary disease (Table 2).

3.3 | CDT technologies

Overall, 2919 (87.7%) of the PE patients with CDT therapy were treated with catheter-directed thrombolysis, and among them 1163 (34.9%) with additional ultrasound assistance, 780 (23.4%) with catheter-based defragmentation and/or 849 (25.5%) with catheter-based thrombectomy (Table 1). Thus, some of the PE patients were treated with more than one CDT. Of the PE patients with CDT, 54.9% were admitted to an intensive care unit, 15.3% were treated with systemic thrombolysis, and 1.1% with surgical embolectomy (Table 1).

3.4 | Adverse events during hospitalization in patients with elevated-risk PE

In patients with elevated-risk PE, CDT was attributed to lower MACCE (28.2% vs 34.2%; $P < .001$) and in-hospital case-fatality rate (24.9% vs 31.0%, $P < .001$) (Table 2, Graphical abstract). CDT therapy in patients with elevated-risk PE was accompanied by a significant reduction regarding MACCE (OR, 0.91; 95% CI, 0.83-0.99; $P = .03$) and a trend toward lower case fatality (OR, 0.92; 95% CI, 0.84-1.02; $P = .068$) (Table 3, Figure 2B, Graphical abstract). The impact of CDT on in-hospital case fatality of patients with elevated-risk PE was more pronounced in later years 2013-2020 (multivariable logistic regression: OR, 0.90 [0.81-1.02]; $P = .096$) than in former years 2005 to 2012 (multivariable logistic regression: OR, 1.06 [0.90-1.24]; $P = .466$).

In addition, the influence of CDT on the case fatality of patients with elevated-risk PE was similar in patients with additional COVID-19 (multivariable logistic regression: OR, 0.39 [0.10-1.46]; $P = .16$) and those patients without additional COVID-19 (multivariable logistic regression: OR, 0.92 [0.84-1.00], $P = .06$).

We detected an age-dependent benefit of CDT in different age decades of patients with elevated-risk PE. The largest benefit regarding the independent reduction of case fatality was observed for patients with elevated-risk PE in the eighth and ninth decades of life (Figure 2C).

In contrast, MACCE (24.3% vs 18.4%; $P < .001$) and case-fatality rate (21.4% vs 15.3%; $P < .001$) were higher when the influence of CDT usage was analyzed in all included PE patients regardless of PE severity (Table 1), which was confirmed in the logistic regressions (MACCE [OR, 1.72; 95% CI, 1.58-1.87; $P < .001$] and case fatality [OR, 1.91; 95% CI, 1.76-2.09); $P < .001$]) (Table 4, Figure 2A).

4 | DISCUSSION

CDT is an innovative treatment option for patients with elevated-risk PE including those patients with impending decompensation or decompensation to resolve embolus and restore pulmonic perfusion [5, 16–18]. Since these CDT procedures are less invasive than systemic thrombolysis or surgical embolectomy, they are supposed to have a low risk of complications, adverse events, and especially

TABLE 1 Patient characteristics, treatment and course of 1,373,084 hospitalizations of patients with pulmonary embolism during 2005-2020 in Germany, stratified by use of catheter-directed treatments.

Parameters	PE without CDT (*n* = 1,369,754; 99.8%)	PE with CDT (*n* = 3330; 0.2%)
Age, median (IQR)	72.0 (60.0-80.0)	66.0 (53.0-75.0)
Age ≥70 y	766,556 (56.0%)	1351 (40.6%)
Female sex	725,901 (53.0%)	1583 (47.5%)
Days in hospital, median (IQR)	9.0 (5.0-16.0)	6.0 (10.0-17.0)
Cardiovascular risk factors		
Obesity	130,138 (9.5%)	502 (15.1%)
Essential arterial hypertension	601,303 (43.9%)	1427 (42.9%)
Diabetes mellitus	255,626 (18.7%)	603 (18.1%)
Hyperlipidemia	171,650 (12.5%)	490 (14.7%)
VTE risk factors		
Cancer	278,800 (20.4%)	357 (10.7%)
Surgery	709,906 (51.8%)	1949 (58.5%)
Pregnancy	1771 (0.13%)	5 (0.15%)
Thrombophilia	16,000 (1.2%)	70 (2.1%)
Comorbidities		
Coronary artery disease	187,135 (13.7%)	445 (13.4%)
Heart failure	299,748 (21.9%)	1034 (31.1%)
Peripheral artery disease	39,609 (2.9%)	67 (2.0%)
Atrial fibrillation/ flutter	206,642 (15.1%)	403 (12.1%)
Chronic obstructive pulmonary disease	138,227 (10.1%)	170 (5.1%)
Acute or chronic renal failure	293,637 (21.4%)	819 (24.6%)
Anemia	120,057 (8.8%)	270 (8.1%)
Clinical findings		
Deep venous thrombosis and/or thrombophlebitis	487,423 (35.6%)	1596 (47.9%)
Syncope	33,197 (2.4%)	117 (3.5%)
Elevated risk pulmonary embolism (without cardiopulmonary resuscitation)	424,620 (31.0%)	2618 (78.6%)
Tachycardia	40,717 (3.0%)	199 (6.0%)
RV dysfunction	378,713 (27.6%)	2532 (76.0%)
Shock	56,070 (4.1%)	571 (17.1%)

(Continues)

TABLE 1 (Continued)

Parameters	PE without CDT (*n* = 1,369,754; 99.8%)	PE with CDT (*n* = 3330; 0.2%)
Hemodynamic instability (Shock and/or cardiopulmonary resuscitation)	122,264 (8.9%)	907 (27.2%)
Treatment		
Admission to intensive care unit	244,154 (17.8%)	1827 (54.9%)
Mechanical ventilation	34,131 (2.5%)	2.5% (218)
Systemic thrombolysis	56,666 (4.1%)	509 (15.3%)
Surgical embolectomy	1973 (0.1%)	37 (1.1%)
CDTs		
Catheter-directed thrombolysis	0 (0%)	2919 (87.7%)
Catheter-directed thrombolysis with ultrasound-assistance	0 (0%)	1163 (34.9%)
Catheter-based defragmentation	0 (0%)	780 (23.4%)
Catheter-based thrombectomy	0 (0%)	849 (25.5%)
Adverse events during hospitalization		
MACCE[a]	251,394 (18.4%)	809 (24.3%)
In-hospital mortality	209,843 (15.3%)	711 (21.4%)
Stroke	40,421 (3.0%)	158 (4.7%)
Pneumonia	329,921 (24.1%)	898 (27.0%)
Acute renal failure	89,897 (6.6%)	457 (13.7%)

[a]Defined as all-cause in-hospital death, acute myocardial infarction, or stroke. CDT, catheter-directed treatment; MACCE, major adverse cardiac and cerebrovascular events; PE, pulmonary embolism; RV, right ventricle; VTE, venous thromboembolism.

bleeding complications compared to systemic thrombolysis or surgical embolectomy [5,17].

The key findings of our study can be summarized as follows:

I) More than 1.3 million hospitalizations of patients with PE were counted during the years 2005 to 2020 in Germany; among them only 3330 (0.2%) PE patients were treated with CDT with an increased use from 0.17% to 0.51%.
II) The highest absolute numbers of CDT use were found in the sixth to eighth decades of life.
III) Selection criteria for CDT in PE patients were younger age, male sex, obesity, recently performed surgery and elevated-risk PE, while cancer was less prevalent in these patients.

TABLE 2 Patient characteristics, treatment, and course of 427,238 hospitalizations of patients with elevated-risk pulmonary embolism (without cardiopulmonary resuscitation) during 2005 to 2020 in Germany, stratified by use of catheter-directed treatments.

Parameters	PE without CDT (*n* = 424,620; 99.4%)	PE with CDT (*n* = 2618; 0.6%)
Age, median (IQR)	73.0 (62.0-81.0)	66.0 (54.0-76.0)
Age ≥70 y	254,746 (60.0%)	1096 (41.9%)
Female sex	231,518 (54.5%)	1240 (47.4%)
Days in hospital, median (IQR)	10.0 (5.0-17.0)	9.0 (5.0-17.0)
Cardiovascular risk factors		
Obesity	47,655 (11.2%)	414 (15.8%)
Essential arterial hypertension	177,701 (41.8%)	1097 (41.9%)
Diabetes mellitus	89,292 (21.0%)	491 (18.8%)
Hyperlipidemia	51,475 (12.1%)	388 (14.8%)
VTE risk factors		
Cancer	65,176 (15.3%)	278 (10.6%)
Surgery	212,676 (50.1%)	1528 (58.4%)
Pregnancy	558 (0.1%)	5 (0.2%)
Thrombophilia	4458 (1.0%)	44 (1.7%)
Comorbidities		
Coronary artery disease	63,897 (15.0%)	364 (13.9%)
Heart failure	140,297 (33.0%)	911 (34.8%)
Peripheral artery disease	13,937 (3.3%)	56 (2.1%)
Atrial fibrillation or flutter	82,926 (19.5%)	338 (12.9%)
Chronic obstructive pulmonary disease	46,933 (11.1%)	132 (5.0%)
Acute or chronic renal failure	120,289 (28.3%)	710 (27.1%)
Chronic anemia	39,365 (9.3%)	217 (8.3%)
Clinical findings		
Deep venous thrombosis and/or thrombophlebitis	145,028 (34.2%)	1190 (45.5%)
Syncope	12,922 (3.0%)	101 (3.9%)
Parameters of elevated risk pulmonary embolism (without cardiopulmonary resuscitation)		
Tachycardia	40,717 (9.6%)	199 (7.6%)
RV dysfunction	378,713 (89.2%)	2532 (96.7%)
Shock	56,070 (13.2%)	571 (21.8%)
Hemodynamic instability (Shock and/or cardiopulmonary resuscitation)	102,166 (24.1%)	866 (33.1%)
Cardiopulmonary resuscitation	68,423 (16.1%)	568 (21.7%)
Treatment		
Admission to intensive care unit	125,217 (29.5%)	1501 (57.3%)
Mechanical ventilation	15,628 (3.7%)	186 (7.1%)
Systemic thrombolysis	46,112 (10.9%)	433 (16.5%)
Surgical embolectomy	1572 (0.4%)	31 (1.2%)
Catheter-directed treatments		
Catheter-directed thrombolysis without ultrasound-assistance	0 (0%)	2307 (88.1%)
Catheter-directed thrombolysis with ultrasound-assistance	0 (0%)	889 (34.0%)
Catheter-based defragmentation	0 (0%)	654 (25.0%)
Catheter-based thrombectomy	0 (0%)	693 (26.5%)
Adverse events during hospitalization		
MACCE[a]	145,246 (34.2%)	737 (28.2%)
In-hospital mortality	131,563 (31.0%)	653 (24.9%)
Stroke	14,497 (3.4%)	136 (5.2%)
Pneumonia	113,435 (26.7%)	730 (27.9%)
Acute renal failure	49,838 (11.7%)	421 (16.1%)

[a]Defined as all-cause in-hospital death, acute myocardial infarction, or stroke. CDT, catheter-directed treatment; MACCE, major adverse cardiac and cerebrovascular events, PE, pulmonary embolism; RV, right ventricle; VTE, venous thromboembolism.

IV) Rates for MACCE and in-hospital case fatality were lower in PE patients with elevated-risk PE who were treated with CDT.

V) The benefit of CDT was age-dependent in patients with elevated-risk PE. The largest benefit regarding independent reduction of case fatality was particularly observed for patients with elevated-risk PE in the eighth and ninth decade of life.

It is well known that PE patients with decompensation or intended decompensation (intermediate high-risk and high-risk

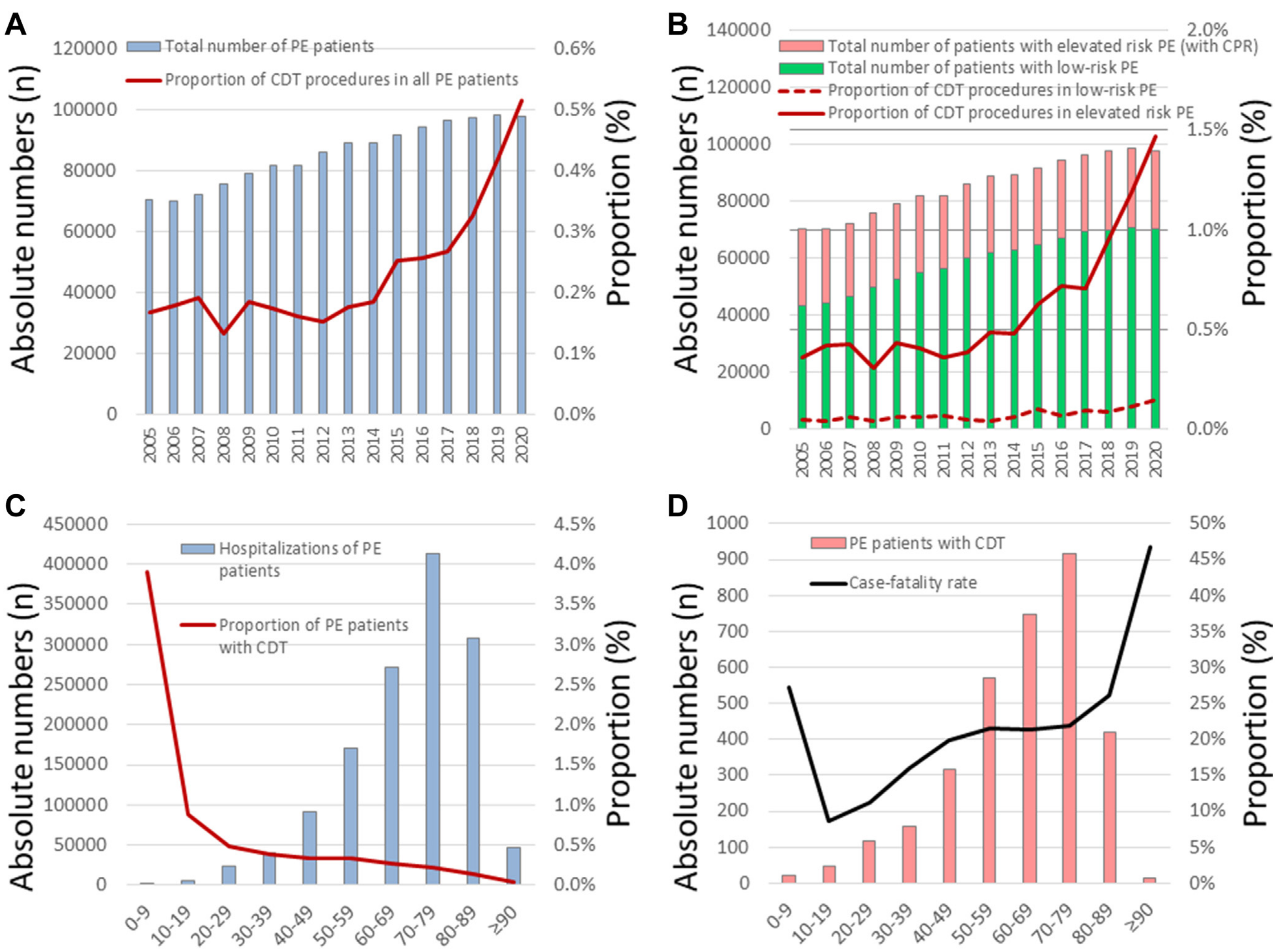


FIGURE 1 Time trends of hospitalization cases of patients with pulmonary embolism (PE) and rate of catheter-directed treatments in Germany. (A) Annual trends of hospitalization cases of patients with PE and rate of catheter-directed treatments in Germany. (B) Annual trends of hospitalization cases of patients with PE with low-risk status (green bars) and elevated-risk PE with cardio-pulmonary resuscitation (red bars) and rate of catheter-directed treatments in low-risk group and elevated-risk PE group (without cardio-pulmonary resuscitation) in Germany. (C) Age-dependent trends of hospitalization cases of patients with PE and rate of catheter-directed treatments in Germany. (D) Age-dependent trends of hospitalization cases of PE patients treated with catheter-directed treatments and related case-fatality rate of these patients treated with catheter-directed treatments in Germany. PE, pulmonary embolism.

corresponding to the terms submassive and massive PE in Anglo-American countries) are afflicted by a substantially increased risk of death due to right ventricle failure [5,19–21]. In these cases, CDT has emerged as an alternative treatment option to systemic thrombolysis for patients with acute PE, necessitating advanced reperfusion treatment if systemic thrombolysis failed or is contraindicated [5,20,22]. CDT comprises catheter-directed thrombolysis and catheter-based thrombectomy approaches [5,6,23]. While catheter-directed thrombolysis involves the administration of a thrombolytic agent into or in the direct surrounding of the clot via a catheter, catheter-based thrombectomy consists of the mechanical disintegration and removal of the clot using a catheter-based device [5,6,17]. Thus, CDT can rapidly decrease PE thrombus burden in the pulmonary artery bed [18]. An increasing number of CDT systems, applying various pharmaco-mechanical or aspiration-based thrombus removal, have already been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [20,22,24].

Our real-world data of the German NIS analyzing more than 1.3 million hospitalizations of patients with PE during the years 2005 to 2020 demonstrated a steady rise of the annual usage rate of CDT in PE patients increasing from 0.17% in the year 2005 to 0.51% in 2020. As expected, this annual rise was substantially accelerated in patients with elevated-risk PE and widely constant in low-risk patients. Similarly to our results, Raghupathy et al. [25] reported in their study an increase in the rate of performed catheter-directed mechanical thrombectomy from 0.20% in 2010 to 0.87% in 2018 in the NIS of the United States (US). In contrast, an analysis of the Nationwide Readmissions Database of the US (years 2016-2020) revealed a higher usage of CDT in the US, but also with a significant increase in the utilization of CDT from 2.9% in 2016 to 7.1% 2020 [26]. These data of the US underline a faster increase in the usage of CDT in the US than in Germany, which is also evident in the very low (0.2%) rate of CDT usage in all hospitalized PE patients of Germany during the observational period from 2005 to 2020 [20,25–28]. This might be driven by

TABLE 3 Logistic regression analysis regarding impact of catheter-directed treatments on adverse in-hospital events and outcomes in patients with elevated-risk pulmonary embolism (without cardiopulmonary resuscitation).

	Univariate regression OR (95% CI)	Multivariable regression (adjustment level[a]) OR (95% CI)
Treatment escalation		
Admission to intensive care unit	3.21 (2.97-3.47)	2.92 (2.69-3.17)
Mechanical ventilation	2.00 (1.72-2.32)	1.65 (1.41-1.92)
Surgical embolectomy	3.22 (2.25-4.61)	1.77 (1.23-2.55)
Adverse events during hospitalization		
MACCE[b]	0.75 (0.69-0.82)	0.90 (0.83-0.99)
In-hospital death	0.74 (0.68-0.81)	0.92 (0.84-1.01)

MACCE, major adverse cardiac and cerebrovascular event.
[a]Adjustment level: age, sex, obesity, diabetes mellitus, cancer, coronary artery disease, heart failure, chronic obstructive pulmonary disease, essential arterial hypertension, acute and chronic kidney failure, surgery, chronic anemia, and atrial fibrillation or flutter.
[b]Defined as all-cause in-hospital death, acute myocardial infarction, or stroke.

the reservation of the European scientific societies and health care systems, which have been cautious for a long time to implement CDT in daily PE management in the German hospitals [5,6,20]. In accordance with literature [25], highest absolute numbers of CDT were identified in the sixth to eighth decade of life.

Our study support the recommendation of the European Society of Cardiology guidelines that CDT should be performed only in selected PE patients with decompensation or intended decompensation (intermediate high-risk and high-risk corresponding to the terms submassive and massive PE in the Anglo-American countries) and not in low-risk PE patients [5,6,22]. Reperfusion treatments are aggressive treatments, which are accompanied by complications as confirmed in our study with increased rate of MACCE and case fatality in unselected patients [3,5,6,22]. This finding pronounces the importance of patient selection and evaluation of contraindications for each patient regarding choosing one of the different reperfusion treatments. In accordance, Sadar et al. [29] reported that in particular, patients with more severe and especially life-threatening PE revealed the greatest benefits from ultrasound-assisted, catheter-directed thrombolysis.

In contrast, our study demonstrated a benefit regarding the use of CDT in PE patients with elevated-risk PE with reductions of MACCE and in-hospital case-fatality rates. These results are in accordance with other studies: In the US NIS, CDT was associated with reduced in-hospital mortality compared to systemic thrombolysis [23,30]. A study investigating the Taiwan National Health Insurance Research Database revealed that the in-hospital mortality rate was significantly lower in the CDT group than in patients with systemic thrombolysis. Interestingly, no significant differences between the groups were observed for the safety (bleeding) outcomes [31]. One previously published study of our research group about the German NIS showed, that among patients with shock, catheter-directed thrombolysis was associated with lower in-hospital mortality than systemic thrombolysis [32]. In addition, another study of our research group, focusing on cost drivers in PE, detected also a rise in CDT usage between 2016 and 2020 in Germany and CDT was accompanied by 7.1% lower in-hospital case-fatality rate in patients with elevated-risk PE during this observational period [7]. Although these studies emphasize in accordance with our study results, the benefit of CDT treatment in selected patients, it has to be mentioned that the selection of the patients with elevated-risk PE who underwent CDT has to be questioned. Since we are not aware that other important selection criteria (eg, as approaching end of life in cancer disease, high risk of complications and bleeding, and multi-morbid condition) might significantly impacted the decision to use or not to use CDT in these patients, the selection of the PE patients with elevated risk might influenced the beneficial effect of CDT in patients with elevated-risk PE. This marks the urgent need for large trials regarding CDT in these vulnerable patients. Nevertheless, this is a real-world NIS, which mirrors the temporal trends of CDT use in PE in the observational period. Beyond that, our study identified some important particularities regarding the usage of CDT in PE patients: First, the case-fatality rate in PE patients treated with CDT was highest in the very young and very old patients. These PE patients should be considered as critical patient groups prone for crucial complications. Second, the benefit of CDT was age-dependent of patients with elevated-risk PE. The largest benefit regarding the independent reduction of case fatality was observed for patients with elevated-risk PE in the eighth and ninth decade of life. Third, selected PE patients for and with performed CDT were younger, more often of male sex, obese, and had undergone more frequently surgery as an important VTE risk factor, while cancer was less prevalent in these patients. Elevated-risk PE as well as hemodynamic instability were selection criteria for CDT and therefore more frequently identified in patients with CDT. An admission rate of 55% of patients with elevated-risk PE, let us suggest that these patients were in part already stabilized in the emergency room and afterwards monitored on normal ward instead of intensive care unit.

In summary, the selection of PE patients and evaluation of these patients regarding the occurrence of life-threatening complications for CDT is of outstanding importance. Since the field of CDT for acute PE remains evolving and the total numbers are growing, it becomes increasingly obvious that the decision to pursue CDT needs to be personalized/individualized by factors that go beyond currently accepted risk stratification schemes [18]. In this context, the PE response teams (PERT) play an exceptional role [33–35].

5 | LIMITATIONS

There are certain limitations of our study which need to be mentioned. First, study data were based on ICD discharge codes and OPS codes, which might be prone for underreporting or miscoding. Second, detailed baseline data such as concomitant medications, cardiac

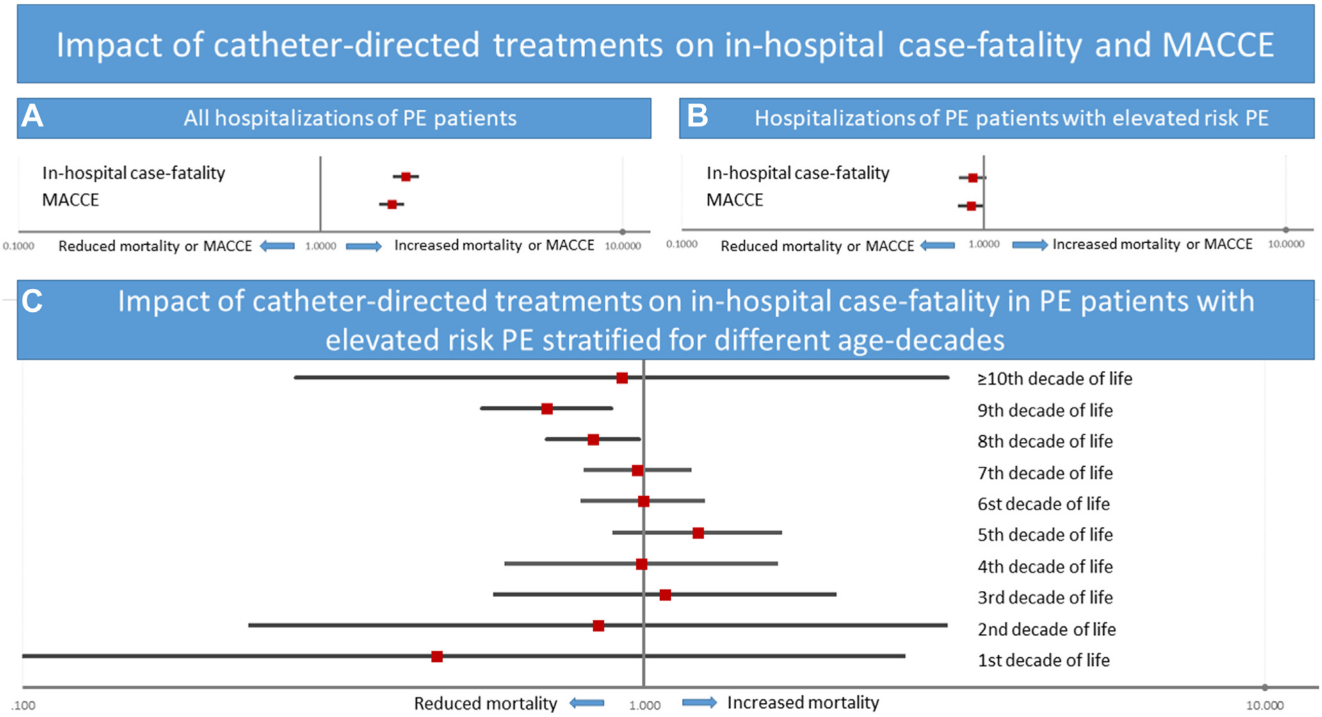


FIGURE 2 Impact of catheter-directed treatments on case fatality and major adverse cardiac and cerebrovascular events in pulmonary embolism (PE) patients. (A) All hospitalized PE patients. (B) PE patients with elevated-risk PE. (C) PE patients with elevated-risk PE. PE, pulmonary embolism.

troponin plasma concentrations, and echocardiographic parameters were unavailable. Moreover, for vital signs recorded as continuous variables, exact values (of heart rate or systolic blood pressure, for example) were not available in the German NIS; however, ICD coding allows categorical analysis of those variables (such as tachycardia and shock). Third, the exact timing and course of hemodynamic instability and elevated-risk PE (ie, whether it was present on admission or a complication during the hospital stay) could not be determined. Fourth, we acknowledge that the exact cause of death cannot be obtained from the German NIS. However, previous studies have impressively demonstrated that the majority of in-hospital deaths are related to the acute PE episode (or to complications of its treatment) [36,37]. Fifth, another main limitation of our study regarding the benefit of CDT is the selection of the PE patients for the different treatments. Since we analyzed the nationwide German inpatient statistics and no randomized trial, the selection of patients for the different treatment groups are inconsistent and could not controlled by our group. However, we tried to overcome this problem in part by adjusting the multivariable regressions for age, sex, and several comorbidities. Nevertheless, we could not be aware that additional important selection criteria others than these we have adjusted for, for example, approaching end of life in cancer disease, high risk of complications and bleeding and multi-morbid condition might significantly impacted the decision not to use/choose CDT in these patients. Therefore, these additional selection criteria for not performing a CDT, might have influenced the beneficial effect of CDT in patients with elevated-risk PE. Sixth, due to the nature of these administrative data regarding hospitalization, we can only provide data from the timeframe of hospitalization and have no data about later follow-ups. Thus, we cannot provide data about 30-day mortality. Seventh, the term "elevated-risk PE" is only an approximation toward the categorization of the European Society of Cardiology guideline, but mirrors

TABLE 4 Logistic regression analysis regarding impact of catheter-directed treatments on adverse in-hospital events and outcomes in patients with pulmonary embolism.

	Univariate regression OR (95% CI)	Multivariable regression (adjustment level[a]) OR (95% CI)
Treatment escalation		
Admission to intensive care unit	5.60 (5.23-6.00)	5.14 (4.78-5.52)
Mechanical ventilation	2.74 (2.39-3.15)	2.13 (1.85-2.46)
Surgical embolectomy	7.79 (5.62-10.80)	3.15 (2.25-4.43)
Adverse events during hospitalization		
MACCE[b]	1.43 (1.32-1.54)	1.72 (1.58-1.87)
In-hospital death	1.50 (1.38-1.63)	1.91 (1.76-2.09)

[a]Adjustment level: age, sex, obesity, diabetes mellitus, cancer, coronary artery disease, heart failure, chronic obstructive pulmonary disease, essential arterial hypertension, acute and chronic kidney failure, surgery, chronic anemia, and atrial fibrillation or flutter.
[b]Defined as all-cause in-hospital death, acute myocardial infarction, or stroke. MACCE, major adverse cardiac and cerebrovascular event.

patients who are on an elevated risk to die. The data included in the German NIS represent all population parts of Germany. However, information on the socio-cultural determinants of health and race/ethnicity of the study population are unavailable in the data set provided by the RDC. Thus, the transferability of the study results to other populations might not unaffectedly be possible with certainty.

6 | CONCLUSION

In conclusion, our extensive study on over 1.3 million cases of PE in Germany from 2005 to 2020 highlights the increasingly significant role of CDT. Demonstrating a steady rise in adoption, particularly for elevated-risk PE cases; CDT offers a less invasive alternative with potentially lower complication rates than traditional methods like systemic thrombolysis or surgical embolectomy. The data underscore the importance of careful patient selection to optimize outcomes and minimize risks, reinforcing CDT's value in modern PE management strategies. However, randomized clinical trials are needed and are on their way to provide more definite answers regarding the role of CDT in PE.

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AUTHOR CONTRIBUTIONS

K.K. and L.H. were responsible for the conception of the study and for acquisition as well as analysis of the data. All authors were responsible for interpretation of the data. K.K. drafted the article and all other authors revised it critically for important intellectual content.

RELATIONSHIP DISCLOSURE

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DATA AVAILABILITY

All codes used in this study are publicly available online. The data/results are available at the Federal Statistical Office of Germany (Statistisches Bundesamt, DEStatis) (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2005-2020, and own calculations).

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