


Initial results of investigator initiated international database on catheter directed therapy of acute pulmonary embolism

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Abstract

Background: Catheter directed therapies (CDT) are widely used in the treatment of acute pulmonary embolism (PE). A multicenter registry was organized to evaluate their application in real life and to determine efficacy and safety of these procedures. Local experience of participating centers in percutaneous techniques for PE treatment was assessed.

Methods: An internet-based registry was designed to collect clinical, echocardiographic and laboratory data of consecutive PE patients treated with CDT in participating centers between 2017 and 2022.

Results: Under analysis were 145 consecutive patients with acute PE, aged 61 ± 15 years, treated with CDT in 7 centers: 50 (34.5%) patients with high-risk PE (HRPE), and 95 (65.5%) patients with intermediate-high risk PE (IHRPE). 100 (69%) patients were treated with dedicated devices, in 45 (31%) subjects a pigtail catheter was used. Total PE or CDT related in-hospital mortality in HRPE reached 14% (7 patients), while in IHRPE 3.2% (3 patients) ($p = 0.032$). 50% of PE or CDT related deaths occurred in patients treated with a pigtail catheter. All-cause mortality in 145 patients was 9.7%, and it was higher in HRPE than in IHRPE (18% vs. 5.3%, $p = 0.019$). The use of pigtail catheters compared to dedicated systems was associated with higher mortality (20% vs. 5%, $p = 0.01$).

Conclusions: Catheter directed therapies is a real option of treating PE. It was used as primary therapy also in patients without contraindication for thrombolysis suggesting that clinical practice does not always follow current PE guidelines. Patients treated with dedicated CDT systems had a higher survival rate than subjects treated with pigtail catheters. (Cardiol J 2024; 31, 3: 390–397)

Keywords: pulmonary embolism, catheter-directed therapy, registry

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Introduction

Acute pulmonary embolism (PE) is a potentially life-threatening cardiovascular emergency. According to the 2019 European Society of Cardiology (ESC) guidelines on acute PE, reperfusion therapy, preferably systemic thrombolysis (sTL), is recommended as the first-line treatment in hemodynamically unstable patients, and also should be considered in initially normotensive PE subjects who deteriorate despite anticoagulation [1]. However, due to high bleeding risk at least half of hemodynamically unstable patients do not receive sTL [2–4]. There is growing clinical evidence on catheter-directed therapies (CDT) for the treatment of acute PE. Currently a wide range of systems and techniques for CDT are available including clot fragmentation, mechanical embolectomy, local thrombolysis, and combined pharmaco-mechanical thrombus fragmentation [5–7]. A multicenter, investigator initiated European Database on Catheter Directed Therapy of Pulmonary Embolism (EuroPE-CDT) has been organized in order to assess the currently applied CDT techniques in real life and to determine in-hospital mortality, efficacy and safety of this invasive procedure. Moreover, the aim was to assess how local experience in percutaneous techniques for PE treatment of participating centers impacts CDT results.

Methods

Study design

Seven centers from 3 European countries (Poland, Serbia, and Spain) participated in an internet-based registry which collected anonymized clinical, echocardiographic and laboratory data of consecutive PE patients treated with CDT in these centers between 2017 and 2022. Patients who at the time of PE diagnosis were hemodynamically unstable according to current ESC guidelines formed the group with high-risk pulmonary embolism (HRPE) [1]. Intermediate-high risk pulmonary embolism (IHRPE) was diagnosed when patients with systolic blood pressure (SBP) ≥ 90 mmHg presented with right ventricle dysfunction at computed tomography pulmonary angiogram or echocardiography, and elevated plasma troponin levels [1]. The following four groups defined were the studied PE patients. Group 1: HRPE patients who were submitted to CDT as a primary form of pulmonary reperfusion; group 2: HRPE patients who underwent CDT after unsuccessful sTL; group 3: IHRPE

who underwent CDT as an initial therapy; group 4: IHRPE patients who, while on anticoagulation, met criteria of HRPE or did not improve (persistent tachycardia, no increase of systemic SBP) despite at least 12-hour parenteral anticoagulation and/or sTL [2]. We recorded device type used for CDT and contraindications for sTL. As a primary end-point 30-day all-cause mortality was considered. Moreover, in-hospital mortality related to PE was analyzed (sudden death or death in shock state which cannot be explained by other causes) and to CDT procedure, major complications of CDT procedure which included periprocedural mortality and major vascular complications. Non-PE related death was diagnosed when an alternative unequivocal cause of death was diagnosed including sepsis or progression of neoplastic disease.

In order to assess how the experience in percutaneous techniques for PE treatment impacts CDT results we compared the outcomes between two groups of centers. We identified more experienced centers with the number of CDT procedures above the median of reported CDT procedures of all precipitating centers and less experienced ones with the median or below this value.

Statistics

Data with a normal distribution are expressed as a mean followed by standard deviation. Parameters without such a distribution are expressed as median followed by 25–75 percentile. T-Student or Mann–Whitney tests were used for comparisons between the two groups. The Fisher exact test was used to compare discrete variables. All tests were two-sided. Analyses were considered significant at $p < 0.05$.

Protocol of the current study was accepted by the Local Ethics Committee.

Results

Patient characteristics

Data of 145 consecutive patients with confirmed acute PE (females 70), aged 61 ± 15 years were included in the analysis (Fig. 1). Their clinical characteristics are presented in Table 1. All patients had elevated plasma troponins and right ventricle enlargement or dysfunction at computed tomography pulmonary angiogram or echocardiography. Fifty (34.5%) of all studied patients were hemodynamically unstable at PE diagnosis (HPRE group). Four of them required cardiopulmonary resuscitation (2.8%), 13 (9%) were intubated, and 26 (18%) patients received intravenous vasopres-

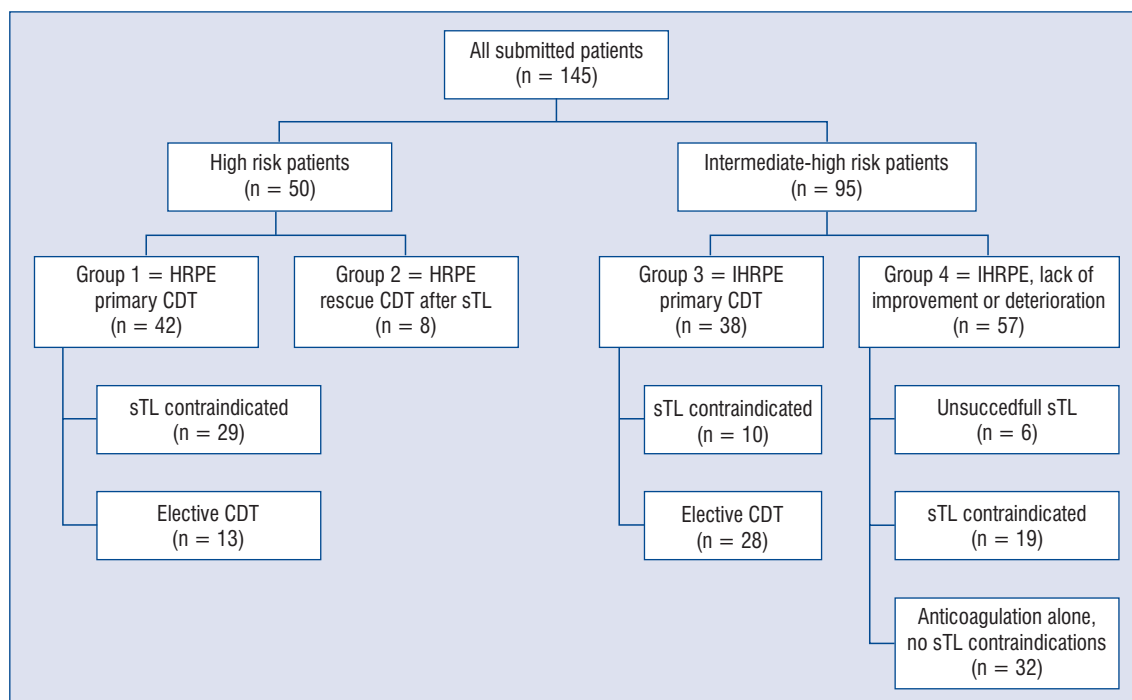


Figure 1. Characteristics of submitted patients; CDT — catheter-directed therapy; HRPE — high risk pulmonary embolism; IHRPE — intermediate-high risk pulmonary embolism; sTL — systemic thrombolysis.

sors. Eight (16%) patients with HRPE underwent CDT after unsuccessful systemic thrombolysis. In the remaining 84% of HRPE subjects CDT was a method of primary reperfusion, although 13 (31%) among these patients there were no reported significant contraindications for sTL.

The remaining 95 (65.5%) patients were hemodynamically stable at the PE diagnosis and were diagnosed with IHRPE. Anticoagulation was a primary treatment in 57 (60%) of IHRPE patients. However, after median duration of anticoagulation of 24 hours (12–48 hours) 21 patients deteriorated and were urgently submitted to CDT. Non-improvement of hemodynamic status (persistent tachycardia, need for oxygen supply) despite anticoagulation was also observed in 36 other patients. Interestingly, 6 of them before CDT received additionally urgent sTL without a significant hemodynamic improvement. Of note 40% (38 patients) of IHRPE patients were referred for CDT as the primary reperfusion option. In this group time between PE diagnosis and CDT was 5 (3–20) hours.

Bleeding risk

In 59 (41%) patients absolute or relative contraindications for systemic thrombolysis were reported. Absolute contraindications were found

in 51 (35%) patients and included recent major surgery or severe trauma with bone fractures in 27 (63%) patients, active malignancy in 13 (30%) subjects [1]. Recent ischemic stroke was diagnosed in 4 cases, while acute intracranial hemorrhage was present in 3 other subjects. History of intracranial hemorrhage was found in 5 other patients. Recent or active major extracranial bleeding was diagnosed in 7 (16%). Moreover, in 8 other patients individually assessed bleeding risk by managing physician was found to be high and was regarded as a contraindication for sTL (erosive esophagitis, HAS-BLED score > 3, recent childbirth, recent mild head trauma, surgery more than 3 weeks before). In 86 subjects who were submitted to CDT no significant contraindications for sTL were reported; only 13 of them (7 HRPE patients and 6 IHRPE patients who deteriorated despite anticoagulation) underwent systemic, unsuccessful thrombolysis. There was one HRPE patient who received sTL despite relative contraindications; he was subsequently treated with CDT and was discharged without serious complications.

Periprocedural anticoagulation

Initially 59% (82 patients) of patients received unfractionated heparin, while 42% (58 patients) were treated with body weight adjusted or pro-

Table 1. Clinical characteristics at pulmonary embolism (PE) diagnosis and results of catheter directed therapy (CDT) in 145 patients with acute PE.

	All patients (n = 145)	HRPE (n = 50)	IHRPE (n = 95)	HRPE		IHRPE	
				pCDT (n = 42)	rCDT (n = 8)	pCDT (n = 38)	rCDT (n = 57)
Gender: female/male (%F)	70/75 (48)	28/22 (56)	42/53 (44)	23/19 (55)	5/3 (63)	12/26 (32)	30/27 (53)
Age [years]	63.5 (53–70)	61.5 (52–69)	64 (54–72)	61.5 (53–70)	59.5 (38–68.5)	67 (56–72)	62 (54–71.5)
Blood pressure [mmHg] at diagnosis	110 (90–130)	88 (80–90)	120 (110–135)	89 (80–90)	86.5 (80–90)	121.5 (110–130)	120 (110–140)
Heart rate [bpm] at diagnosis	110 (97.5–120)	120 (100–131.5)	106 (95–120)	120 (100–134)	120 (112.5–130)	109 (99–120)	104.5 (91–116)
Hours from PE diagnosis to CDT	13 (5–24)	10 (3–24)	16.5 (5–24)	7.5 (3–18)	22 (7–30)	5 (3–20)	24 (12–48)
RV/LV ratio	1.02 (0.84–1.20)	1.04 (0.89–1.31)	1.00 (0.78–1.14)	1.08 (0.93–1.31)	1.00 (0.89–1.06)	0.90 (0.75–1.09)	1.02 (0.89–1.26)
Periprocedural deaths	4 (2.7%)	3 (6%)	1 (1.1%)	2 (4.8%)	1 (12.5%)	1 (2.6%)	0 (0%)
PE and CDT related mortality	10 (6.9%)	7 (14%)	3 (3.2%)	5 (11.9%)	2 (25%)	1 (2.6%)	2 (3.5%)
All-cause in-hospital deaths	14 (9.7%)	9 (18%)	5 (5.3%)	7 (16.7%)	2 (25%)	2 (5.2%)	3 (5.2%)

HRPE — high risk pulmonary embolism; IHRPE — intermediate-high risk pulmonary embolism; pCDT — primary catheter directed therapy; rCDT — rescue catheter directed therapy; RV/LV ratio — right to left ventricle size ratio

phylactic dose of low molecular weight heparin. Interestingly 3 (2%) IHRPE subjects were initially treated with non-vitamin K antagonist oral anti-coagulants and 2 patients due to active bleeding received no anticoagulation before CDT.

CDT technique

The most frequently used dedicated devices were: EKOS (34%, n = 50), followed by AngioJet (21%, n = 30), Indigo Penumbra (12%, n = 17) and FlowTriever (1%, n = 2) and Cardiva/Nautilus (1%, n = 1). In the remaining 31% subjects (n = 45) intervention with a pigtail catheter was used for mechanical thrombi fragmentation and/or aspiration, without (38 patients) or with (7 patients) local thrombolysis. In total, local thrombolysis was administered in 72% (n = 104) cases, including 33 patients with contraindications for sTL. Doses of recombinant tissue plasminogen activator differed depending on the device, i.e.: Pigtail 25 mg (16–50 mg), EKOS 50 mg (50–50 mg), AngioJet 20 mg (10–20 mg), Indigo Penumbra 12 mg (9–12 mg). Of note, among 59 patients who had contraindications for sTL, 33 (56%) subjects received alteplase locally during CDT. Moreover, 7 patients received low dose local thrombolysis during CDT despite previous systemic thrombolysis.

Results of catheter directed treatment

Periprocedural results

Four patients died during the CDT procedure including 3 HRPE patients who deteriorated despite percutaneous therapy and 1 IHRPE patient with an absolute contraindication for systemic thrombolysis, who experienced fatal intrapulmonary bleeding caused by pulmonary artery injury with a pigtail catheter. Periprocedural mortality was 2.7% in the whole group, 6% in HRPE, and 1.1% in IHRPE. However, within the first 24 hours after the CDT procedure there were 3 additional deaths. All of them occurred in patients who, before the beginning of CDT met criteria of HRPE, including 1 death caused by fatal massive bleeding from the vascular access site. Moreover, there were 3 additional delayed deaths caused by severe post cardiopulmonary resuscitation brain damage and occurred at least 14 days after CDT. Eventually, they were also regarded as PE related fatalities. Thus, PE or CDT related in-hospital mortality in the whole group was 6.9% (10 patients), and in HRPE reached 14% (7 patients), while in IHRPE was 3.2% (3 patients) (p = 0.032). Of note, 5 (50%) of 10 PE or CDT related deaths occurred in patients treated with pigtail fragmentation,

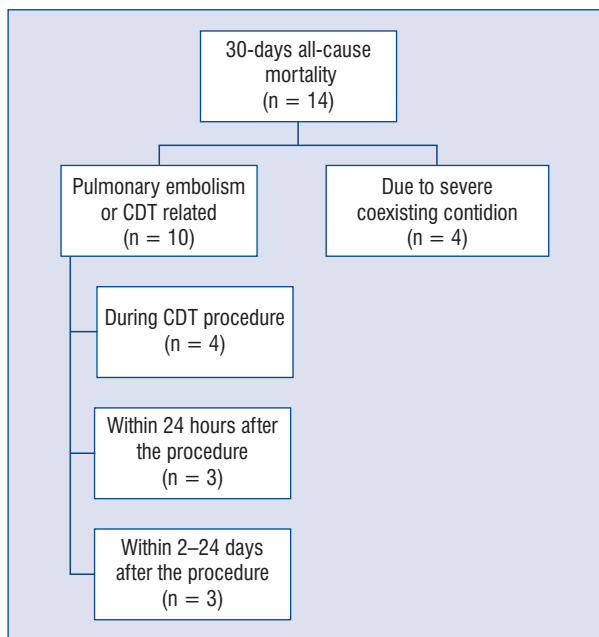


Figure 2. Characteristics of death in 30-day follow-up; CDT — catheter-directed therapy.

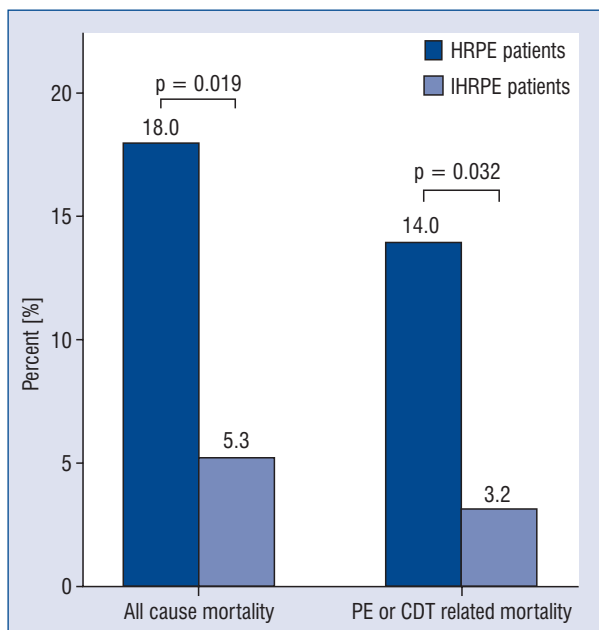


Figure 3. Distribution of all-cause and pulmonary embolism (PE) or catheter-directed therapy (CDT) related mortality in 145 PE patients, depending on the pulmonary embolism risk group; HRPE — high risk pulmonary embolism; IHRPE — intermediate-high risk pulmonary embolism.

including pulmonary artery injury and a fatal bleeding from the vascular access site. Moreover, there were additional 4 in-hospital deaths not related to

PE, nor to CDT complications. These fatalities were caused by underlying severe coexisting diseases including advanced cancer, unfavorable delayed neurologic sequel of major ischemic stroke which occurred before PE, severe COVID-19 infection, and in-hospital pneumonia with sepsis. In a 30-day follow-up, 14 patients had died (Fig. 2). Therefore, the all-cause mortality in the whole group analyzed was 9.7%, and it was higher in HRPE when compared to IHRPE group 18% vs. 5.3%, $p = 0,019$, respectively (Fig. 3). Interestingly, out of 8 HRPE patients in whom systemic thrombolysis failed 6 patients were successfully treated with rescue CDT and were discharged home.

Patient outcomes according to local expertise and the dedicated system for CDT

Across participating centers, in the current registry the median number of reported CDT procedures was 14 per center. Three centers reported at least 20 CDT procedures (mean 39.9 patients per center), while 4 others reported a lower CDT number (mean 6.5 patients per center). There were 2 (7.7%) deaths related to PE or CDT procedure in low volume centers and 8 (6.7%) deaths related to PE or CDT procedure in high volume centers, $p > 0.05$.

In total, dedicated CDT systems were used for CDT in 100 cases while pigtail catheters were used in the remaining 45 cases. Of note, pigtail catheters were used for CDT more frequently in less experienced centers than in centers with more expertise 61.5% vs. 24.4%, $p < 0.01$. The use of pigtail catheters compared to dedicated systems was associated with higher overall mortality (20% and 5%, $p = 0.01$). Highly significant difference was observed in the group of IHRPE where all-cause mortality and PE or CDT mortality were significantly higher in the pigtail treated group (21%; 5 deaths vs. 0%, $p < 0.01$, and 13%; 3 deaths vs. 0%, $p = 0.01$, respectively) (Fig. 4).

Discussion

According to the current ESC guidelines, optimal management of acute PE depends on adequate risk assessment of PE-related early death which in high-risk PE exceeded 15% [1, 8, 9]. Currently, primary reperfusion using CDT is not the first-line treatment in patients with high-risk acute PE, nor for any of the other PE risk categories. However, CDT should be considered for patients with high-risk PE, in whom thrombolysis is contraindicated or has failed [10]. CDT should also be considered

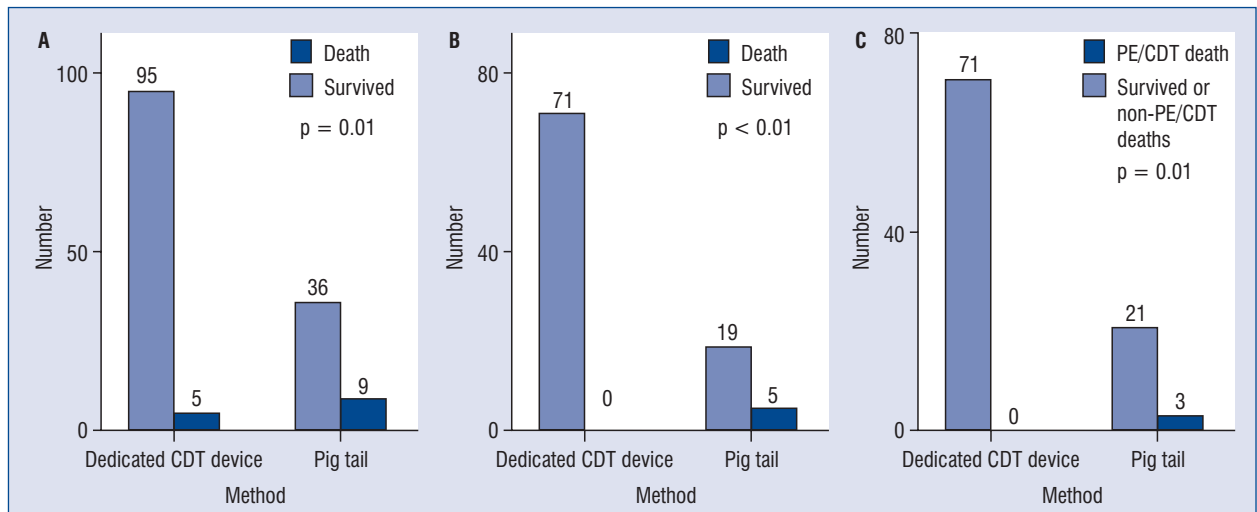


Figure 4. Mortality in pulmonary embolism (PE) patients depending on the applied method; **A.** All cause mortality in all PE patients; **B.** All cause mortality in all IHRPE patients; **C.** PE and CDT-related mortality in IHRPE patients; CDT — catheter-directed therapy; IHRPE — intermediate-high risk pulmonary embolism.

as rescue treatment for initially stable patients in whom anticoagulant treatment fails, i.e., those who experience haemodynamic deterioration despite adequate-dose initial anticoagulation [1]. However, it should be underlined that ESC guidelines on acute PE did not provide a definition of hemodynamic deterioration, and it should be elaborated. Although various dedicated CDT systems are widely available, pigtail catheters are still used. There has been no randomized trial or even large observational series in acute PE patients with pigtail catheters, but they are still widely used and they are inexpensive in comparison with CDT dedicated systems. The registry used included 145 consecutive PE patients treated with CDT in 7 European centers. At PE diagnosis 34.5% of them were hemodynamically unstable and high-risk PE was diagnosed. Interestingly, in 16% (8 patients) of HRPE patients CDT was performed after unsuccessful systemic thrombolysis and eventually 6 of them after successful CDT were discharged home in a good general condition.

The opinion herein, is that this is a very important observation, because there are very limited data on the efficacy of CDT after unsuccessful systemic thrombolysis suggesting that percutaneous techniques could be a real therapeutic option in such settings. In the remaining 84% subjects with HRPE CDT was the primary reperfusion method mostly due to coexisting contraindications for systemic thrombolysis. However, of note in 20 (40%) HRPE patients no significant contraindications

for systemic thrombolysis were present. It seems that local, low dose thrombolysis could be used safely in patients with relative contraindications for systemic thrombolysis.

Two-thirds of patients included into the registry were hemodynamically stable at the PE diagnosis and were initially diagnosed with IHRPE. In IHRPE patients' therapeutic anticoagulation alone, without reperfusion treatment, is sufficient in most cases. On the other hand, it was reported that early mortality in this group may reach up to 5–10% [11]. Moreover, Pulmonary Embolism International Thrombolysis (PEITHO) trial showed that 5% of initially anticoagulated patients suffered hemodynamic decompensation and/or died, mostly within the first 72 hours after admission, and required rescue reperfusion treatment [12]. It should be underlined that in the PEITHO trial, systemic thrombolysis resulted in major bleedings in 11.5% of patients and what is even more important intracranial hemorrhage was experienced by 2% of them, while in patients who were only anticoagulated these complications occurred significantly less frequently (2.4% and 0.2%, respectively). In the present cohort anticoagulation was a primary treatment in 57 (60%) of IHRPE. Eventually, they were referred to CDT due to lack of hemodynamic improvement after the mean of 24 hours of anticoagulation or even hemodynamic deterioration despite full dose anticoagulation. Of note, 40% (38 patients) of IHRPE patients were referred for CDT as the primary treatment option even despite the

lack of contraindications to systemic thrombolysis in 28 of them. Interestingly, in the group when CDT was the treatment of choice median time between PE diagnosis and CDT was only 5 hours.

Pulmonary embolism- or CDT-related in-hospital mortality in the whole group was 6.9% (10 patients), and in HRPE reached 14% (7 patients), while in IHRPE was 3.2% (3 patients) ($p = 0.032$). It is worth underlining that if the group of 90 patients who had remained hemodynamically stable until the beginning of CDT analysis and still fulfilled the criteria of IHRPE, only 2 PE or CDT related deaths occurred (in-hospital PE or CDT related mortality 2.2%). It should be noted that both of them were treated with pigtail catheters and had not previously received sTL. It was reported that the overall efficacy of catheter-directed treatment, defined as stabilization of hemodynamic and blood gas parameters and survival to hospital discharge, approaches 90% [7, 13–17]. However, in the meta-analysis of 16 studies which included 860 patients, in-hospital mortality was 12.9% in patients with HRPE, and 0.74% in the IHRPE group [18]. The recently published FLASH registry showed that among 800 patients treated with FlowTriever 76.7% patients had IHRPE and 7.9% had HRPE. Importantly, only less than one third of invasively treated patients had thrombolytic contraindications. All-cause mortality was 0.3% at 48-hour follow-up and 0.8% at 30-day follow-up. No device-related deaths were observed. These data indicated that mechanical thrombectomy with the FlowTriever system shows a favorable safety profile, improvements in hemodynamic outcomes, and low 30-day mortality for intermediate- and high-risk PE [19]. Recently published single center experience with EKOS in 161 PE patients showed that not only all patients survived, but no hemodynamic decompensation occurred after CDT. Of note only 2 (1.2%) patients experienced major bleeding events. These data suggest that USAT with EKOS resulted in a rapid improvement of hemodynamic parameters among patients with intermediate-high risk acute PE and selected ones with high-risk acute PE [20]. Percutaneous mechanical embolectomy with Penumbra Indigo aspiration system was reported to be associated with a significant reduction in the right ventricle/left ventricle ratio in patients and a low major adverse event rate in IHRPE patients. Of note intraprocedural thrombolytic drugs were avoided in 98.3% of patients [21]. There is very limited data comparing short-term outcomes of CDT performed with various CDT devices. Recent analysis of over 3000 HRPE patient from

The Nationwide Readmissions Database showed that 27% received mechanical CDT, 58% local thrombolysis, while 15% of other patients were treated with combined procedures. No differences were found in mortality rate and major bleedings between these groups [22].

Of note in the present registry, pigtail catheters were used for CDT more frequently in less experienced centers than in centers with more expertise 61.5% vs. 24.4% ($p < 0.01$). The use of pigtail catheters compared to the use of dedicated systems was associated with higher mortality in all patients (20% vs. 5%, $p < 0.01$). This was primarily due to a reduction in mortality in the IHRPE patients, both overall (21% vs. 0%, $p < 0.01$) and due to PE and CDT related complications (13% vs. 0%, $p < 0.01$). In HRPE, the choice of intervention had no effect either on all-cause mortality (19% vs. 17%, $p = 1.0$) or PE and CDT related mortality (10% vs. 17%, $p = 0.68$).

Limitations of the study

The organized registry includes a relatively small number of patients. Importantly, causes of death were not adjudicated.

Conclusions

It was convincing that CDT is a safe and effective option for treating HRPE, or IHRPE when patients deteriorate despite anticoagulation and have contraindications for systemic thrombolysis. However, local low dose thrombolysis was frequently used even in patients with absolute contraindications for systemic thrombolysis. On the other hand, CDT was used in HRPE and IHRPE as primary therapy also in patients without contraindication for thrombolysis, suggesting that clinical practice does not always follow current PE guidelines. Interestingly, a higher overall survival rate was found in cases when dedicated CDT systems were used, compared to pigtail catheters. These observations indicate the need for use of dedicated CDT systems and underlines the role of training in CDT.

Conflict of interest: None declared.

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