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ROUTINE ARTICLE

Outcomes With Hybrid Catheter-Directed Therapy Compared With Aspiration Thrombectomy for Patients With Intermediate-High Risk Pulmonary Embolism

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Abstract

Purpose Intermediate-high-risk pulmonary embolism (IHR PE) is a challenging form of embolism obstruction that causes right ventricular (RV) dysfunction. The optimal management of IHR PE has not been established. This single-center prospective, observational study aimed to evaluate the efficacy and safety of complex catheter-directed therapy (CDT) — catheter-directed mechanical aspiration thrombectomy (CDMT) supplemented with catheter-directed thrombolysis (hybrid CDT) in comparison to CDMT alone for IHR PE.

Methods A propensity score based on the pulmonary embolism severity index class and Miller obstruction index (MOI) was calculated, and 21 hybrid CDT cases (mean age 54.8 (14.7) years, 9/21 women) were matched with 21 CDMT cases (mean age 58.8 (14.9) years, 13/21 women). The baseline demographics, clinical, and treatment characteristics were analyzed.

Results No significant differences were detected regarding baseline demographics and PE severity parameters. Hybrid CDT demonstrated a higher reduction in mean pulmonary artery pressure (mPAP) (hybrid CDT: median mPAP reduction 8 mmHg (IQR: 6–10 mmHg) vs CDMT: median mPAP reduction 6 mmHg (IQR: 4–7 mmHg); $P=0.019$), MOI score (hybrid CDT: median change − 5 points (IQR: 5–6 points) vs CDMT median change − 3 points (IQR: 3–5 points); $P=0.019$), and median RV: left ventricular ratio (hybrid CDT: median change 0.4 (IQR: 0.3–0.45) vs CDMT median change 0.26 (IQR: 0.2–0.4); $P=0.007$). No major bleeding was observed. Both the hybrid CDT and CDMT alone treatments are safe and effective in managing IHR PE.

Conclusions Hybrid CDT is a promising technique for the management of IHR PE with insufficient thrombus load reduction by CDMT.

Trial Registration NCT0447356—registration date 16 July 2020.

Keywords Catheter-directed mechanical thrombectomy · Catheter-directed thrombolysis · Right ventricular dysfunction · Pulmonary obstruction

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Introduction

Pulmonary embolism (PE) remains the third leading cause of cardiovascular mortality leading to hundreds of thousands of deaths worldwide every year [1–3]. PE is characterized by a wide spectrum of clinical presentations, which should be considered a disease severity continuum. More than half of PE cases are low-risk without hemodynamic consequences and may be initially treated with oral anticoagulants and early discharge. On the other side of the spectrum is the life-threatening high-risk PE accounting for approximately 5% of cases and causing rapid hemodynamic collapse which requires immediate reperfusion therapy [2]. The last one-third is the most challenging to manage intermediate-high risk (IHR) PE which includes patients with evidence of right ventricular dysfunction in imaging studies and increased concentration of biomarkers of myocardial injury due to obstruction of a significant part of the pulmonary vascular bed but without overt hypotension [3–5].

The optimal management strategy of IHR PE has not yet been well established. In IHR treatment, initial systemic thrombolysis (ST) is not recommended because the potential benefits do not outweigh the risk of serious bleeding [4, 5]. However, a significant percentage of IHR PE patients may suddenly deteriorate and become hemodynamically unstable. In such a clinical scenario, the current European Society of Cardiology (ESC) guidelines recommend ST, catheter-directed therapy (CDT), or surgical embolectomy (SE) as an alternative [5, 6]. Over the last few years, the management of IHR PE has changed significantly with the constantly growing interventional approach as part of the integrated treatment guided by PE Response Teams (PERTs); these therapies include catheter-directed mechanical thrombectomy (CDMT) and catheter-directed thrombolysis (CDL) or implantation of inferior vena cava filters in certain cases [5, 7–10]. Catheter-directed therapies aim to quickly decompress the pulmonary bed and allow blood to flow through local lytic drug delivery or mechanical fragmentation and aspiration of part of the embolic material while minimalizing bleeding risk [11, 12]. Early reduction of the pulmonary artery obstruction leads to improved patient hemodynamics and RV function.

Nevertheless, there is a lack of definitive data and consistent recommendations regarding the criteria indicating urgent CDT, the specific modality, or even the dose of drugs delivered locally into the thrombus leading decision at the operator's discretion. Therefore, we aimed to evaluate the acute efficacy and safety of CDMT and a hybrid strategy with CDMT complimented by CDL for IHR PE in a real-world population.

Methods

Study Design and Population

This prospective, observational study was conducted by institutional PERT (PERT-POZ) in a tertiary cardiology center between January 2019 and October 2022. The details concerning our institutional PERT organization were published elsewhere [7].

The protocol of this prospective observational study was in accordance with the current ESC guidelines and with respect to the principles of the Declaration of Helsinki. The institutional bioethics committee approved the study protocol (approval number 879/19). The study was also registered in the ClinicalTrials.gov.database (NCT04473560). All the patients accepted the treatment and provided informed consent to participate in the study.

All adult patients with acute IHR PE who were qualified for CDT by PERT were eligible for enrolment according to ESC guidelines and symptoms duration shorter than 7 days [7, 13]. Briefly, IHR PE was defined by the presence of right ventricular (RV) dysfunction assessed as RV-to-left ventricular diameter ratio (RV to LV ratio) ≥ 0.9 on imaging studies (transthoracic echocardiography (TTE) or computed tomography pulmonary angiography (CTPA)), elevated serum levels of troponin I and pulmonary embolism severity index (PESI) class III–V or simplified PESI (sPESI) score ≥ 1 [6]. Patients were enrolled if they (1) demonstrated at least one sign of clinically severe PE longer than 24 h including heart rate (HR) ≥ 100 bpm, systolic blood pressure (SBP) 90–100 mmHg, or arterial blood saturation (SaO_2) $\leq 90\%$ on room air; (2) had the central location of clots in main or lobar PAs on CTPA; and (3) were considered to be at increased risk of bleeding complications when treated with full-dose ST. In case of hemodynamic deterioration (sudden occurrence of one or more of the abovementioned signs of severe PE), the patient was also involved. Key exclusion criteria included unstable patients with high-risk PE, patients with absolute contraindications to thrombolysis, patients unable to receive anticoagulation, and those with a life expectancy of less than a month due to comorbidities (as determined by the physician). Details are provided in Supplementary Table 1. Follow-up assessments were performed at 48 h, 30 days (± 7 days), and 90 days (± 21 days).

Procedure

Catheter-directed mechanical thrombectomy procedures were performed as previously described [14] in the cardiac catheterization suite. Initially, the common femoral vein was

accessed with a 7-F vascular sheath, and a 7-F Swan-Ganz catheter was used to measure right heart and pulmonary pressures with the Fick method implementation for cardiac output and pulmonary vascular resistance assessment. Then, the main pulmonary arteries (PAs) were catheterized with a 6-F pigtail, and an initial selective angiogram was performed revealing detailed thrombi burden and location. Thrombi load was assessed according to the Miller obstruction index (MOI) score as previously described [15, 16]. On the angiographic assessment, 1 point was given in the case of partial (> 50%) or complete segmental artery occlusion. Nine segmental arteries were assigned to the right PA (three to the upper lobe, two to the middle lobe, and four to the lower lobe), while only seven segmental arteries to the left PA were assigned (two to the upper lobe, two to the lingula, and three to the lower lobe). If proximal arteries were involved (lobar or main), the awarded score was the sum of distally occluded segmental arteries, up to a maximal score of 16 points. Details are presented in Fig. 1.

Subsequently, a 115 cm, 8F CDMT catheter (Indigo CAT8 XTORQ; Penumbra, Alameda, California, USA) was placed in PA close to the clot through a 90 cm, 8F Flexor sheath (Cook; Bloomington, Indiana, USA) to perform the procedure. A direct-aspiration first-pass approach was performed to attach a large thrombus to the catheter tip by suction and then pull it out through the sheath. After that, a separator wire was repeatedly passed through the thrombus to break it up and facilitate aspiration. In case of anatomical difficulties, a Judkins right coronary diagnostic catheter or multi-purpose one catheter was used to simplify access to the lobar or segmental artery. Termination of the intervention was at the operator's discretion after careful evaluation of hemodynamical status (normalization of SBP, HR, or increase of SaO2 ≥ 92%), degree of clot clearance, and the total amount of aspirated blood (should not exceed 300 ml).

At the end of each procedure, PAP and the angiographic residual thrombus burden were assessed. If thrombus clearance was unsatisfactory, defined as a residual MOI of at least 12 points (number proved to be related to persistent RV dysfunction) [16], the procedure was extended by CDL with the infusion of alteplase at a dose of 1 mg/h/catheter for 8 h with initial bolus of 2 mg/catheter via a Fountain 4F or 5F catheter (Merit Medical, South, Jordan, Utah, USA). Based on the thrombus distribution during control angiography, the operating physician decided whether to perform unilateral or bilateral CDL. All patients were monitored in the cardiac intensive care unit throughout the CDL period and underwent repeat invasive PAP measurement and angiography at 12–24 h.

During the procedure, anticoagulation with therapeutic doses of unfractionated heparin (UFH) under activated clotting time control (therapeutic range: 200–300 s) was administered. After the hybrid CDL intervention, the weight-based UFH under the control of activated partial thromboplastin time (aPTT) (target aPTT of 1.5 to 2.5 times the control range) was continued for 24–48 h, while after CDMT alone, the weight-based UFH or weight-based low-molecular-weight heparin (LMWH) was given for 24–48 h, depending on the patient's clinical status, and the type of anticoagulation drug administered to each patient at discharge was at the physician's discretion.

Outcomes

The primary efficacy endpoints were the change in PAPs (systolic and mean) after the CDT and clot clearance assessed with the change in the MOI score. Secondary efficacy measures

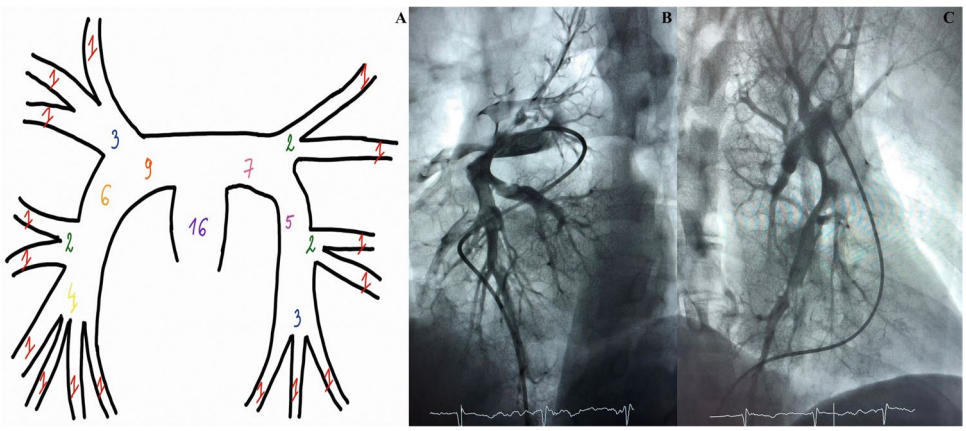

Fig. 1 Miller obstruction index (MOI) score assessment. **A** Scheme for MOI score calculation. Nine segmental arteries were assigned to the right pulmonary artery and seven to the left pulmonary artery. 1 point = partial (> 50%) or complete segmental artery occlusion. When the lobar or main artery was involved, the score was a sum of distally occluded segmental arteries, up to a maximal score of 16 points. **B**, **C** Selective pulmonary angiograms of **B** right and **C** left pulmonary arteries showing multiple emboli. MOI of the right pulmonary artery was assessed as 9 points, and of the left pulmonary artery as 5 points

were the change in the RV strain assessed in the TTE and/or CTPA assessed 24 h (± 12 h) after the index hybrid CDT/CDMT procedure, reduction of symptoms, HR, oxygen supplementation requirements, and change in SBP also evaluated 24 h (± 12 h) post index hybrid CDT/CDMT intervention.

The primary safety endpoints were death caused by PE (RV failure) during the index hospitalization or follow-up period and all-cause mortality during the index hospitalization or follow-up period. Secondary safety outcomes were major bleeding according to the Bleeding Academic Research Consortium (BARC) [17] classification and any procedure-related major adverse events. Major bleeding was defined as fatal bleeding, causing a hemoglobin drop of at leading to transfusion of at least 2 units of blood products, symptomatic bleeding in a critical area or organ, assessed as BARC type 3a or greater [17].

Statistical Analysis

Patients' characteristics are expressed as absolute and percentage frequencies for categorical variables and median with interquartile range (IQR) or mean with standard deviation (SD) for continuous variables. The normality distribution was assessed with the Shapiro–Wilk test. Continuous variables (nonparametric) were compared using the Mann–Whitney U-test or Student's *t*-test (parametric), and categorical variables were compared using the $\chi 2$ or Fisher's exact test, as appropriate. The significance of the change in continuous variables between the initial and final assessments was evaluated using the Wilcoxon signed-rank test for paired nonparametric variables. Friedman's rank test with post hoc Dunn-Bonferroni correction was used to compare hemodynamic parameters in the hybrid CDT group before and after the index CDMT procedure and after the completion of CDL therapy. As there was a concern that patients who received CDMT and hybrid CDT differed in unmeasured confounding factors, propensity score matching was performed using PESI and MOI scores before comparisons between the groups were made. Patients were matched at a ratio of 1:1 from the CDMT and hybrid CDT groups, according to their propensity to receive hybrid CDT. Patients were matched within a 10% probability window. A two-tailed alpha of 0.05 was considered statistically significant. Statistical analysis was performed using MedCalc Software Ltd. version 20.215 (Ostend, Belgium).

Results

Baseline Demographics and Clinical Characteristics

A total of 89 IHR PE patients' cases treated with CDT were analyzed. After exclusion, 76 patients remained with 21 in the hybrid group and 55 in the CDMT group. Details are presented in Fig. 2.

The mean age of patients who underwent hybrid CDT was 54.8 (14.7) years and 58.8 (14.9) years for those who underwent CDMT. There were no significant differences regarding baseline demographics and clinical parameters pertinent to PE severity between hybrid CDT and CDMT groups. Details are presented in Table 1. The median symptom duration before diagnosis in both groups was 3 days. PE severity on presentation was comparable, with a median PESI score of 115 points noted in the hybrid CDT (IQR: 109–125 points) and CDMT (IQR: 108–127 points) groups, respectively. Additional clinical features of RV dysfunction including cardiac biomarker concentrations and echocardiographic parameters were similar in both groups.

Procedural Characteristics

Procedural characteristics are summarized in Table 2. The total procedure duration time (89.2 ± 17.6 min vs 80.3 ± 23 min, $P = 0.17$), the total amount of contrast medium (170 ml (140–200 ml) vs 140 ml (IQR: 100–170 ml), $P = 0.13$), and the median estimated blood loss per procedure (320 ml (260–400 ml) vs 290 ml (IQR: 290–330 ml), $P = 0.37$) were comparable in both groups. The median length of post-procedure hospital stay was also parallel 5 days (IQR: 3–7) in hybrid CDT and 4 days (4–8) in the CDMT group.

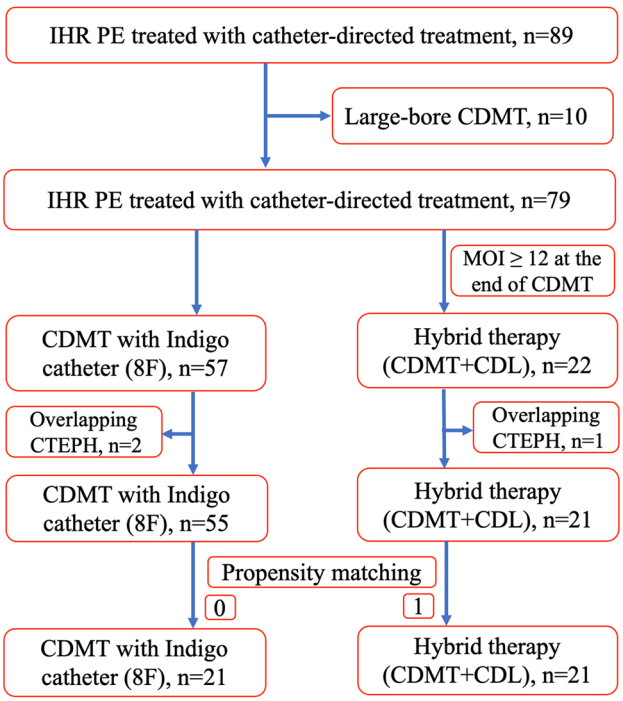

Fig. 2 Study population selection flowchart. Abbreviations: CDL, catheter-directed thrombolysis; CDMT, catheter-directed mechanical thrombectomy; CTEPH, chronic thromboembolic pulmonary hypertension; IHR, intermediate-high risk; PE, pulmonary embolism

Table 1 Baseline patients' and PE severity characteristics

Variables	Hybrid CDT (CDMT + CDL), $n = 21$	CDMT (matched cases), $n = 21$	*P* value
Male sex	12 (57.14)	8 (38.1)	0.35
Age, years[#]	54.8 (14.7)	58.8 (14.9)	0.38
BMI, kg/m^{2}[#]	29.4 (5.7)	29.2 (4.6)	0.89
Comorbidities			
Arterial hypertension	9 (42.9)	10 (47.6)	0.76
Congestive heart failure	2 (9.5)	-	0.49
Diabetes mellitus	4 (19)	2 (9.5)	0.66
Concomitant deep vein thrombosis	17 (81.0)	16 (76.2)	0.99
Coronary artery disease	2 (9.5)	1 (4.8)	0.99
Chronic obstructive pulmonary disease	2 (9.5)	-	0.49
COVID-19	-	2 (9.5)	0.49
Chronic kidney disease	5 (23.8)	2 (9.5)	0.41
Risk factors for PE			
Obesity, BMI ≥ 30 kg/m^{2}	7 (33.3)	8 (38.1)	0.99
Malignancy	5 (23.8)	5 (23.8)	1.0
Surgery within last 2 weeks	7 (33.3)	6 (28.6)	0.99
Immobilization	2 (9.5)	2 (9.5)	1
Thrombophilia	6 (28.6)	8 (38.1)	0.74
History of PE	4 (19.1)	3 (14.3)	0.99
Oral contraceptive	2 (9.5)	2 (9.5)	1
PE clinical presentation			
Syncope	-	2 (9.5)	
Dyspnea at rest	21 (100)	18 (85.7)	0.44
Chest pain	-	1 (4.8)	
Symptoms duration, days	3 (2–7)	3 (3–4)	0.28
PE severity			
PESI score	115 (108–127)	115 (109–125)	0.66
PESI class	4 (4–5)	4 (4–5)	0.34
PESI class			
I–II	2 (9.5)	2 (9.5)	
III	2 (9.5)	4 (19)	0.34
IV	8 (38.1)	11 (52.4)	
V	9 (42.9)	5 (23.8)	
Heart rate, bpm	115 (107–121)	110 (105–120)	0.41
Respiratory rate, pm	33 (30–34)	30 (30–32)	0.074
Arterial oxyhemoglobin saturation, %	90 (86–95)	92 (89–94)	0.47
Systolic blood pressure, mmHg	106 (104–120)	120 (98–140)	0.44
Diastolic blood pressure, mmHg	74 (70–80)	80 (68–87)	0.77
hs Troponin I level, ng/ml[$]	0.43 (0.03–0.79)	0.33 (0.19–0.78)	0.54
NT-proBNP level, pg/ml^	3987 (1734–7261)	2349 (1276–4767)	0.35
Lactate level, mmol/l	2.4 (2–3.1)	2.1 (1–2.4)	0.167
RV:LV ratio, mm/mm	1.5 (1.1–1.5)	1.2 (1.2–1.5)	0.5
TAPSE, mm	15 (13–16)	15 (13–16)	0.78
S′ wave, cm/s	13 (9–14)	12 (11–13)	0.54
RVSP, mmHg	58 (45–60)	54 (50–60)	0.95

Data are *n* (%) or median (IQR)

Abbreviations: see Figs. 2 and 3. *BMI*, body mass index; *hs*, high sensitive; *PESI*, pulmonary embolism severity index; *RVSP*, right ventricular systolic pressure; *TAPSE*, tricuspid annular plane systolic excursion

[#]Data presented as mean (SD)

[$]Normal range < 0.005 ng/ml

^Normal range < 125 pg/ml

Clinical Outcomes

The initial catheter-derived, MOI score medians, thrombus location, systolic, mean, and diastolic pulmonary arterial pressure medians were similar in both the hybrid CDT and the CDMT groups. All patients had bilateral central PE. Hemodynamic and vital outcomes are presented in Table 2. Immediately following the procedure, the mean PAP median change differed significantly between both groups; in the hybrid therapy, the mean PAP decreased from 29 (IQR: 27–33 mmHg) to 23 mmHg (IQR: 20–25 mmHg) (−8 mmHg (IQR: 6–10 mmHg) median change), while in the CDMT group, the mean PAP decreased from 34 (IQR: 29–36 mmHg) to 27 mmHg (IQR: 22–31 mmHg) (−6 mmHg (IQR: 4–7 mmHg) median change), $P=0.019$. The median systolic PAP change was also significantly higher in the hybrid CDT group, 17 mmHg (IQR: 12–20 mmHg) in the hybrid CDT vs 9 mmHg (IQR: 5–9 mmHg) in the CDMT group ($P=0.003$), respectively. When considering stages of the hybrid CDT therapy, the mean and systolic PAP decreased significantly after the index CDMT procedure with further significant reduction after implementation of the CDL. Details are presented in Fig. 3. The median MOI score decreased significantly from 14 points (IQR: 13–15 points) to 9 points (IQR: 8–9 points) (−5 points (IQR: 5–6 points) median change) in the hybrid CDT group in comparison to the CDMT group from 14 points (IQR: 13–15 points) to 11 points (IQR: 9–11 points) (−3 points (IQR: 3–5 points) median change), $P=0.019$. The median RV: LV ratio improved from 1.5 (IQR: 1.1–1.5) to 0.95 (IQR: 0.84–1.05), with the median change of 0.4 (IQR: 0.3–0.45) after hybrid CDT and from 1.5 (IQR: 1.1–1.5) to 1.05 (IQR: 0.9–1.2), with median change of 0.26 (IQR: 0.2–0.4)) after CDMT ($P=0.007$). The median arterial pO_2 improved from 60 (IQR: 47–72 mmHg) to 87 mmHg (IQR: 80–94 mmHg) (+27.8 mmHg (IQR: 14–34.6 mmHg) median change) after hybrid CDT and from 60 (IQR: 58–66 mmHg) to 69 mmHg (IQR: 65–78 mmHg) (+10.8 mmHg (IQR: 6–19.4 mmHg) median change) ($P=0.0039$). Key effectiveness outcomes are summarized in Fig. 4.

Safety Outcomes

There were no catheter-related complications. No major bleeding related to the hybrid CTD or CDMT procedure was observed. There were two minor bleeding complications in each group. All were access-related groin hematomas that resolved with manual compression. One patient in the CDMT group developed an ischemic stroke with aphasia and left-side paralysis several hours after the procedure due to paradoxical embolism through the patent foramen ovale. There were no intraprocedural deaths. One death in the hybrid CDT group at the 48-day follow-up was unrelated to the procedure. There were an additional two deaths at 30-day follow-up in both groups, all adjudicated as unrelated to the study procedure. These two deaths were due to pre-existing malignancies—ovarian cancers. The one 90-day all-cause readmission in the hybrid CDT group was related to the reoccurrence of DVT. There were no further complications within the following 90 days of anticoagulation. Safety outcomes are displayed in Table 3.

Discussion

Main Findings

This study demonstrated that both hybrid CDT with CDMT with 8F Indigo catheter complimented by CDL with a total dose of 10–20 mg of alteplase derived with an 8-h infusion and CDMT monotherapy performed with the same equipment was safe and effective treatment modalities for managing IHR PE. To our knowledge, this is the first study reporting on the acute hemodynamic effects of a hybrid CDT treatment strategy in IHR PE. Our study showed that hybrid CDT resulted in substantial thrombi removal and improvement in clinical status, pulmonary, and right heart hemodynamics as compared to CDMT alone in PE patients at IHR of early death.

RV Strain Improvement

The role of catheter-directed therapies in the treatment of acute PE is rapidly evolving. However, the optimal protocol for patients and CDT method selection, particularly for IHR PE, remains a matter of debate. The principal aim of CDMT is to rapidly restore the patency of occluded PAs by debulking central occlusive clots [12]. The efficient clot removal reduces the strain and afterload of the RV and increases pulmonary and systemic perfusion.

Increased RV: LV diameter ratio assessed by echocardiography or CTPA is a reproducible and validated tool for identifying patients with acute PE and increased risk of adverse events, particularly early mortality [18, 19]. In the present study, the median RV: LV diameter ratio change was significantly higher after hybrid CDT (0.4; IQR: 0.3–0.45) as compared to RV: LV diameter ratio change (0.26; IQR: 0.2–0.4) after standard CDMT. Regardless of the differences between the groups, our results align with the previous studies assessing the efficacy of different percutaneous therapies [20–22]. In the EXTRACT-PE study conducted on 119 patients who underwent CDMT with the 8F Indigo catheter the mean reduction of RV: LV diameter ratio was 0.43 48 h post-procedure [20]. In the FLASH registry patients treated with large-bore FlowTriever (Inari Medical, Irvine, California, US), CDMT had an average reduction in RV: LV

Table 2 Comparison of procedural characteristics and clinical outcomes

Variables	Hybrid CDT (CDMT + CDL), $n = 21$	CDMT (matched cases), $n = 21$	*P* value
Procedure duration time, min[#]	89.2 (17.6)	80.3 (23)	0.17
Radiation dose, mGy	184 (166–231)	126.5 (64–286)	0.055
Fluoroscopy time, min	27 (18–35)	17 (12.5–26)	0.01
Amount of contrast administrated, ml	170 (140–200)	140 (100–170)	0.13
Amount of blood loss, ml	320 (260–400)	290 (290–330)	0.37
Access site			
Right internal jugular vein	-	1	0.99
Right common femoral vein	20	21	
Left common femoral vein	1	-	
Length of hospitalization, days	7 (5–9)	6 (5–10)	0.76
Length of hospitalization after procedure, days	5 (3–7)	4 (4–8)	0.76
PE location			
Bilateral	21 (100)	21 (100)	
Saddle and main arteries	3 (14.3)	5 (23.8)	0.7
Lobar and segmental	18 (86.1)	16 (76.2)	
Segmental and subsegmental	-	-	
Initial MOI score, points	14 (13–15)	14 (13–15)	0.87
Final MOI score, points	9 (8–9)	11 (9–11)	0.0035
Change in MOI score, points	5 (5–6)	3 (3–5)	0.007
Initial systolic PAP, mmHg	59 (43–62)	54 (46–62)	0.94
Final systolic PAP, mmHg	39 (38–56)	44 (38–56)	0.007
Change in systolic PAP, mmHg	17 (12–20)	9 (5–10)	0.003
Initial diastolic PAP, mmHg	20 (19–24)	20 (19–25)	0.94
Final diastolic PAP, mmHg	14 (13–18)	14 (12–20)	0.94
Change in diastolic PAP, mmHg[#]	6 (5–8)	5 (4–8)	0.75
Initial mean PAP, mmHg	29 (27–33)	34 (29–36)	0.085
Final mean PAP, mmHg	23 (20–25)	27 (22–31)	0.001
Change in mean PAP, mmHg	8 (6–10)	6 (4–7)	0.019
Hemoglobin concentration before procedure, mmol/l	8.2 (7.5–9.6)	7.5 (7.1–9.3)	0.43
Hemoglobin concentration 24 h after procedure, mmol/l	7.35 (6.7–8.4)	7.4 (7.0–8.7)	0.84
Arterial pO_2 before procedure, mmHg	60 (47–72)	60 (58–66)	0.98
Arterial pO_2 after procedure, mmHg	87 (80–94)	69 (65–78)	0.0001
Change in arterial pO_2, mmHg	27.8 (14–34.6)	10.8 (6–19.4)	0.039
Time of switching to oral anticoagulation after interventional treatment, days	2 (1–2)	2 (1–2)	0.65
Type of anticoagulation administered in extended treatment			
DOAC*	19 (90.5)	19 (90.5)	
Rivaroxaban	5 (23.8)	6 (28.6)	
Apixaban	14 (66.7)	11 (52.4)	0.66
Dabigatran	-	2 (9.5)	
VKA	-	-	
LMWH	2 (9.5)	2 (9.5)	

Data are *n* (%) or median (IQR)

Abbreviations: see Figs. 2 and 3. *DOAC*, direct oral anticoagulant; *LMWH*, low molecular-weight heparin; *VKA*, vitamin K antagonist

[*]Edoxaban is not available in Poland

*is an additional information why edoxaban is not listed in doac category

[#]Data presented as mean (SD)

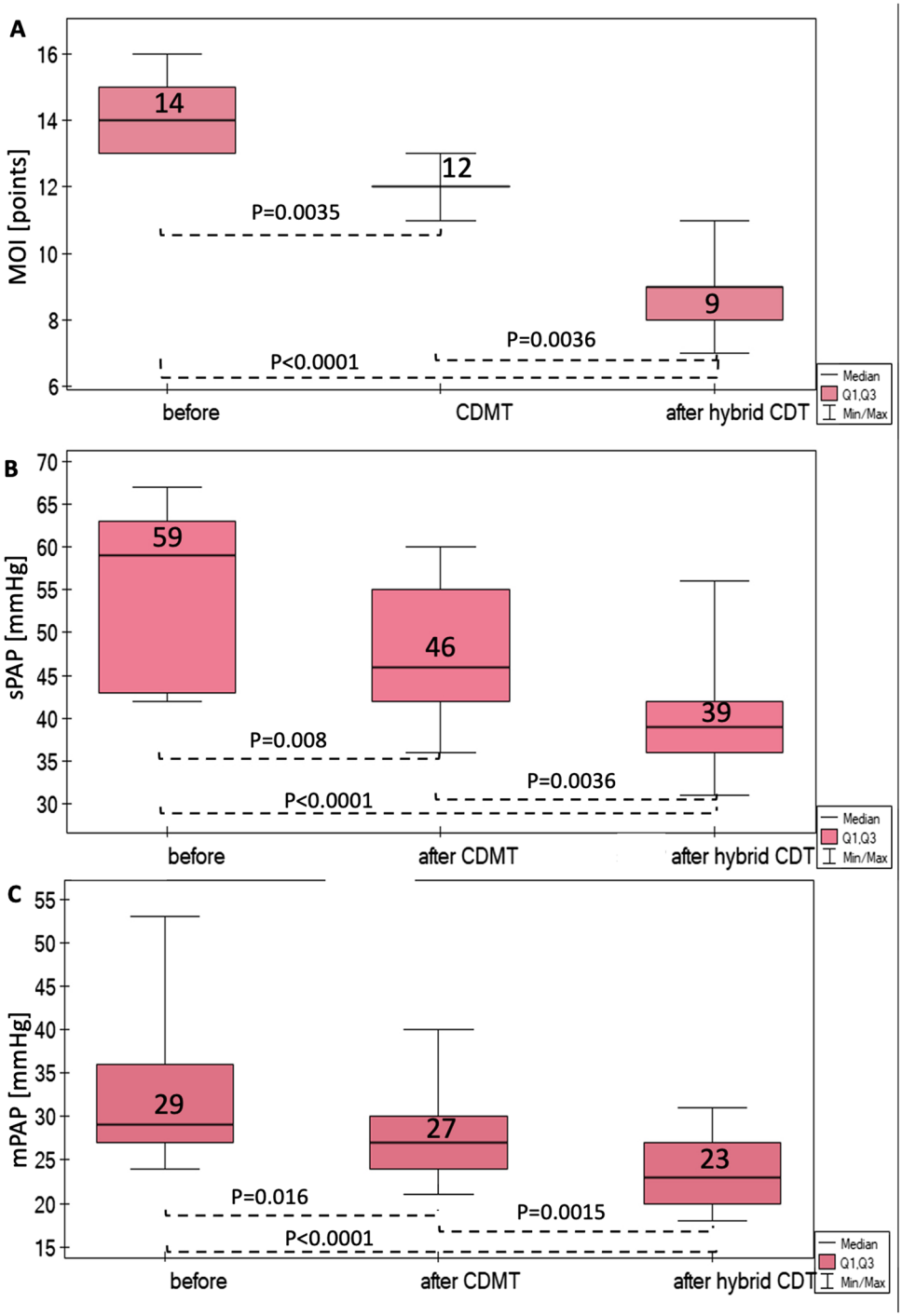

Fig. 3 Change in Miller obstruction index (MOI) and systolic, and mean pulmonary arterial pressures (sPAP and mPAP) in the hybrid therapy group baseline, after catheter-directed mechanical thrombectomy and after administration of local fibrinolysis. Abbreviations: see Fig. 1 and Table 2. mPAP, mean pulmonary arterial pressure; sPAP, systolic pulmonary arterial pressure

diameter ratio of 0.25 [21]. In the SEATTLE II study, which evaluated ultrasound-assisted catheter-directed thrombolysis (USAT) EkoSonic System (EKOS, Boston Scientific, Marlborough, USA), an average reduction in the RV: LV diameter ratio was 0.42 [22]. Interestingly, the SUNSET sPE randomized trial assessing the comparative effectiveness between standard CDL via a multi-hole catheter and USAT in patients with IHR showed a greater reduction in RV: LV diameter ratio after 48 h in standard CDL (0.37 ± 0.34 in the USAT group and 0.59 ± 0.42 in the standard CDL group) [23]. The RESCUE study with the Bashir catheter designed for pharmacomechanical local thrombolysis showed a mean RV: LV ratio change of 0.56, and initial results of mechanical-electric thrombectomy with Magneto 20F device demonstrated a mean RV: LV ratio change of 0.45 [24, 25]. What is more, the results of this study indicated a significant change in surrogate markers of RV dysfunction including tachycardia, troponin, NT-proBNP, and lactate levels 48 h

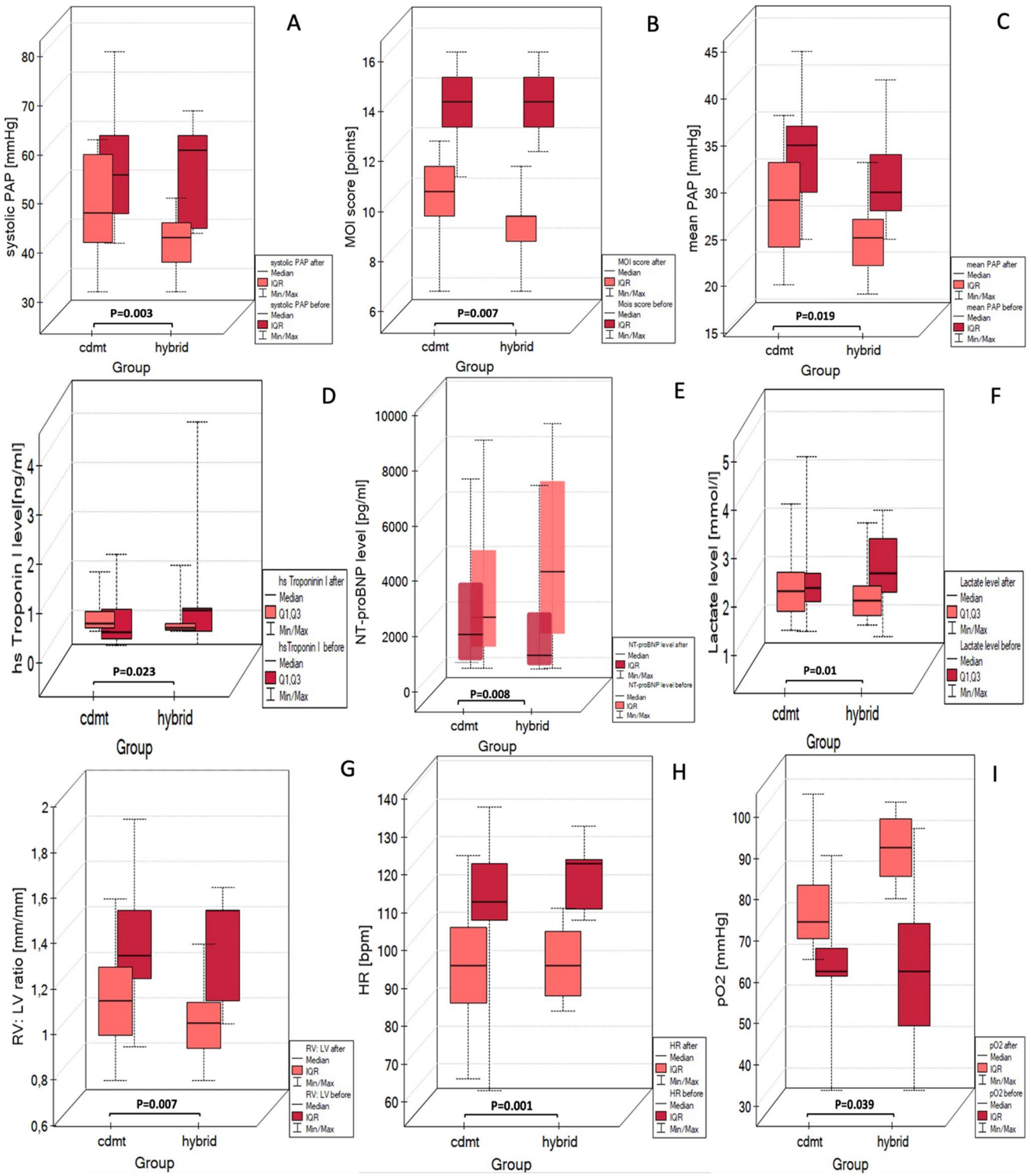

Fig. 4 Diagrams of key effectiveness outcomes. Abbreviations: see Fig. 1 and Table 2. HR, heart rate; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PAP, pulmonary arterial pressure; pO_2, partial oxygen pressure; RV:LV, right ventricular-to-left ventricular ratio

after CDMT. Of note, we also observed that surrogate markers of RV dysfunction HR, troponin, and NT-proBNP levels faster decreased after hybrid CDT treatment as compared to standard CDMT.

Hemodynamic and Angiographic Improvement

Importantly, PAPs have been demonstrated to serve as valuable prognostic markers in acute PE [26]. In this study, the

Table 3 Safety outcomes

Variables	Hybrid CDT (CDMT + CDL), $n = 21$	CDMT (matched cases), $n = 21$
Minor bleeding complication (BARC < 3)	2 (9.5)	2 (9.5)
Major bleeding complication (BARC ≥ 3a)	0 (0)	0 (0)
Cardiac arrest after the initial procedure	0 (0)	0 (0)
Stroke	0 (0)	1 (4.8)
Heparin-induced thrombocytopenia	0 (0)	1 (4.8)
All-cause 30-day mortality	1 (4.8)	1 (4.8)
PE-related 30-day mortality	0 (0)	0 (0)
All-cause 30-day readmission	0 (0)	0 (0)
PE or procedure-related 30-day readmission	0 (0)	0 (0)
All-cause 90-day mortality	0 (0)	0 (0)
PE-related 90-day mortality	0 (0)	0 (0)
All-cause 90-day readmission	1 (4.8)	0 (0)

Data are *n* (%)

Abbreviations: see Fig. 2. *BARC*, Bleeding Academic Research Consortium

reduction of mean PAP was significantly higher in hybrid CDT (17 mmHg (IQR: 12–20 mmHg)) in comparison to (9 mmHg (IQR: 5–9 mmHg)) in the CDMT group. Similarly, the change in mean PAP differed significantly between both groups, in favor of the hybrid CDT therapy (8 mmHg (IQR: 6–10 mmHg) vs 6 mmHg (IQR: 4–7 mmHg)). The change of systolic and mean PAPs in the hybrid group was comparable to those reported previously in the large cohort FLASH registry and SEATTLE II study, but lower than reported in the PERCECT registry [21, 22, 27]. Avgerinos et al. also found additional improvement in all assessed hemodynamic parameters after CDMT complemented with CDL [28]. Interestingly, a recent study by Feroze et al. comparing large-bore CDMT with CDL demonstrated no difference in the change of PAPs between those two therapies [29].

We found that supplementing CDMT with CDL was associated with an improvement in angiographic perfusion assessed by MOI. The median MOI score reduction in the hybrid CDT group was 5 points (IQR: 5–6 points) as compared to 3 points (IQR: 3–5 points) in the standard CDMT group. In contrast to other vascular beds, subtotal thrombectomy within the pulmonary artery tree is not accomplishable in most cases. Unfortunately, we were unable to discuss our results with other studies due to missing or inconsistent data regarding the change in the angiographic obstruction ratio. However, it seems reasonable that thrombus fragmentation with CDMT increases the surface area for thrombolysis and in combination with CDL delivered directly into the thrombus facilitates its dissolution [30]. Nonetheless, the SUNSET sPE trial showed that lysis alteplase dose or lysis time were not predictors of increased thrombus load reduction [23]. The administration of CDL improved the blood flow through PAs including distal arteries. It was previously reported that increased blood flow through the distal PAs correlated with the reduction in RV volume assessed in CT scans [28]. However, it was demonstrated that the thrombus load reduction was similar in the case of standard CDL with a multi-hole catheter or USAT applications [23]. Locally derived fibrinolysis can reach the distal lung perfusing branches, whereas the CDMT devices alone can remove mainly more proximally located thrombi [28]. Therefore, in case of difficult CDMT catheter placement into PA branches and increased risk of complications, CDL should be considered to improve outcomes by increasing thrombi clearance. The advantage of the hybrid CDT in treating patients with acute PE is its low profile (8F) and its ease of use compared to large-bore CDMT systems (up to 24F), which may be challenging to position and operate, especially in unstable patients with PE.

Safety Outcomes

This study demonstrated equivalent outcomes in terms of PE-related and all-cause mortality, bleeding complications, length of stay, and other safety outcomes between both groups. The all-cause 30-day mortality was 4.8% in both groups. None of the deaths were due to PE; all were related to advanced ovarian cancers. Although the analysis is limited owing to the small number of patients in each group, the results are like those previously reported. The SEATTLE II and PERFECT studies, which evaluated the use of CDT, reported 30-day mortality of 2.7% and 1.0%, respectively [22, 27]. In the SUNSET sPE study, the reported mortality was 1.25% (one patient in the USAT arm) [23]. In the EXTRACT-PE trial, the 30-day mortality was 2.5% [20]. Advanced oncological disease is reported to be the most common cause of death in the posthospital period [31–33]. A recent study indicated three times higher

mortality during 12 months after PE diagnosis as compared to non-oncological patients [34]. There was one case of ischemic stroke after the CDMT procedure in our cohort. Avgerinos et al. reported one episode of hemorrhagic transformation in a patient with a prior embolic stroke; therefore, ischemic stroke should be emphasized as an important contraindication to the administration of any thrombolytic drug even at a low dose [28].

There was no major bleeding in this study. In the other studies with a reduced dose of the locally administered lytic drug (total dose of alteplase ≤ 20 mg), the overall major bleeding rate was also low, 4.0% in the OPTALYSE study, 2.5% in the SUNSET sPE study, 2.1% in the CANARY study, and 0.9% in the RESCUE study, respectively [23, 24, 33–36].

One of the concerns of any kind of CDMT is the potential for increased blood loss, especially if not embedded in the thrombus. Both groups had no significant differences regarding the amount of blood loss during the procedure and the change in hemoglobin concentration 24 h after the intervention. No patients required a blood transfusion due to aspiration. These results are in line with other reports with the use of Penumbra 8F catheter with estimated overall blood loss < 400 ml [20, 31]. Similar results were obtained when comparing large-bore CDMT with CDL [37].

This study focused on the short-term outcomes of a hybrid strategy in IHR PE patients. Although some authors reported the application of a hybrid strategy, none of them indicated the clear criteria and detailed circumstances of its implementation [21, 38]. In the American nationwide analysis of CDT procedures in 3216 patients with high-risk PE, 27% received CDMT, 58% received CDL, and 15% received both procedures, which is a significant part of all procedures [38]. In this study, we used the MOI at the end of CDMT to guide the decision to apply or not the CDL after CDMT.

Limitations

The current study is burdened by several limitations. One of the study's limitations is its observational character, which may also be considered a strong point and reflects the real-life nature of our cohort. The study included a small number of patients from a single center. Despite the statistical significance observed in variables after the intervention, the small number of studied patients unpowered these results. The study is also limited by the lack of a single CDL procedure arm and the impossibility of comparison between different CDL approaches (i.e., USAT) and other interventional modalities. Another limitation is the lack of a matched control group that did not undergo intervention which would allow an evaluation of mortality outcomes with conservative therapies. Regardless of these limitations, the current study provides an initial glimpse into the outcomes of the comparison of endovascular techniques in PE treatment.

Conclusions

In our cohort, we have achieved significant improvements in RV dysfunction, decreased PAPs, and improved oxygenation in IHR PE patients after the implementation of transcatheter therapy; additional improvements in all assessed clinical and hemodynamic parameters were observed after complementation of CDMT with CDL, with similar safety outcomes between groups. Currently, experts have no consensus about the optimal method for CDT therapy of PE. Future randomized studies with long-term clinical outcome assessment are necessary to firmly establish an ideal catheter-based therapy protocol.

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Data Availability Data are available from the corresponding author upon reasonable request.

Declarations

Ethics Approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Poznan University of Medical Science (09.2019 No. 879).

Consent to Participate Informed consent was obtained from all individual participants included in the study.

Consent for Publication The authors affirm that human research participants provided informed consent for the publication of the images in Figs. 1b and c.

Competing Interests The authors have no relevant financial or non-financial interests to disclose.

References

1. Kochar A, Bergmark BA. Catheter-directed interventions for pulmonary embolism. Eur Heart J Acute Cardiovasc Care. 2022;11:721–7.
2. Silva BV, Calé R, Menezes MN, et al. How to predict the prognosis in patients with acute pulmonary embolism? Recent advances Kardiol Pol. 2023;81:684–91.
3. Huang W, Goldberg RJ, Anderson FA, Kiefe CI, Spencer FA. Secular trends in occurrence of acute venous thromboembolism: the Worcester VTE study (1985–2009). Am J Med. 2014;127:829-9.e5.
4. Meyer G, Vicaut E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med. 2014;370:1402–11.

5. Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA. 2014;311:2414–21.
6. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41:543–603.
7. Sławek-Szmyt S, Jankiewicz S, Smukowska-Gorynia A, Janus M, Klotzka A, Puślecki M, et al. Implementation of a regional multidisciplinary pulmonary embolism response team: PERT-POZ initial 1-year experience. Kardiol Pol. 2020;78:300–10.
8. Araszkiewicz A, Kurzyna M, Kopeć G, Sławek-Szmyt S, Wrona K, Stępniewski J, et al. Pulmonary embolism response team: a multidisciplinary approach to pulmonary embolism treatment. Polish PERT Initiative Report Kardiol Pol. 2021;79:1311–9.
9. Pasha AK, Siddiqui MU, Siddiqui MD, Ahmed A, Abdullah A, Riaz I, et al. Catheter directed compared to systemically delivered thrombolysis for pulmonary embolism: a systematic review and meta-analysis. J Thromb Thrombolysis. 2022;53:454–66.
10. Pruszczyk P, Klok FA, Kucher N, Roik M, Meneveau N, Sharp ASP, et al. Percutaneous treatment options for acute pulmonary embolism: a clinical consensus statement by the ESC Working Group on pulmonary circulation and right ventricular function and the European Association of Percutaneous Cardiovascular Interventions. EuroIntervention. 2022;18(8):e623–38.
11. Giri J, Sista AK, Weinberg I, Kearon C, Kumbhani DJ, Desai ND, et al. Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association. Circulation. 2019;140:e774–801.
12. Chandra VM, Khaja MS, Kryger MC, Sista AK, Wilkins LR, Angle JF, et al. Mechanical aspiration thrombectomy for the treatment of pulmonary embolism: a systematic review and meta-analysis. Vasc Med. 2022;27:574–84.
13. Kopeć G, Araszkiewicz A, Kurzyna M, et al. Role of catheter-directed therapies in the treatment of acute pulmonary embolism. Expert opinion of the Polish PERT Initiative, Working Group on Pulmonary Circulation, Association of Cardiovascular Interventions, and Association of Intensive Cardiac Care of the Polish Cardiac Society. Kardiol Pol. 2023;81:423–40.
14. Araszkiewicz A, Sławek-Szmyt S, Jankiewicz S, Żabicki B, Grygier M, Mularek-Kubzdela T, et al. Continuous aspiration thrombectomy in high- and intermediate-high-risk pulmonary embolism in real-world clinical practice. J Interv Cardiol. 2020;2020:4191079.
15. Miller GA, Sutton GC, Kerr IH, Gibson RV, Honey M. Comparison of streptokinase and heparin in treatment of isolated acute massive pulmonary embolism. Br Med J. 1971;2:681–4.
16. Wong LF, Akram AR, McGurk S, Van Beek EJ, Reid JH, Murchison JT. Thrombus load and acute right ventricular failure in pulmonary embolism: correlation and demonstration of a "tipping point" on CT pulmonary angiography. Br J Radiol. 2012;85:1471–6.
17. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123:2736–47.
18. Engelberger RP, Kucher N. Ultrasound-assisted thrombolysis for acute pulmonary embolism: a systematic review. Eur Heart J. 2014;35:758–64.
19. Meinel FG, Nance JW, Schoepf UJ, Hoffmann VS, Thierfelder KM, Costello P, et al. Predictive value of computed tomography in acute pulmonary embolism: systematic review and meta-analysis. Am J Med. 2015;128:747-59.e2.
20. Sista AK, Horowitz JM, Tapson VF, Rosenberg M, Elder MD, Schiro BJ, et al. Indigo aspiration system for treatment of pulmonary embolism: results of the EXTRACT-PE trial. JACC Cardiovasc Interv. 2021;14:319–29.
21. Toma C, Jaber WA, Weinberg MD, Bunte MC, Khandhar S, Stegman B, et al. Acute outcomes for the full US cohort of the FLASH mechanical thrombectomy registry in pulmonary embolism. EuroIntervention. 2023;18:1201–12.
22. Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, et al. A Prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. JACC Cardiovasc Interv. 2015;8:1382–92.
23. Avgerinos ED, Jaber W, Lacomis J, Markel K, McDaniel M, Rivera-Lebron BN, et al. Randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism: the SUNSET sPE trial. JACC Cardiovasc Interv. 2021;14:364–73.
24. Bashir R, Foster M, Iskander A, et al. Pharmacomechanical catheter-directed thrombolysis with the bashir endovascular catheter for acute pulmonary embolism: the RESCUE study. JACC Cardiovasc Interv. 2022;15:2427–36.
25. Andersen A, Musialek P, Araszkiewicz A, et al. First-in-human trial of mechanical-electric thrombectomy in acute pulmonary embolism. JACC Cardiovasc Interv. 2023;16:623–5.
26. Stępniewski J, Kopeć G, Musiałek P, Magoń W, Jonas K, Waligóra M, et al. Hemodynamic effects of ultrasound-assisted, catheter-directed, very low-dose, short-time duration thrombolysis in acute intermediate-high risk pulmonary embolism (from the EKOS-PL study). Am J Cardiol. 2021;141:133–9.
27. Kuo WT, Banerjee A, Kim PS, DeMarco FJ, Levy JR, Facchini FR, et al. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): initial results from a prospective multicenter registry. Chest. 2015;148:667–73.
28. Avgerinos ED, Abou Ali A, Toma C, Wu B, Saadeddin Z, McDaniel B, et al. Catheter-directed thrombolysis versus suction thrombectomy in the management of acute pulmonary embolism. J Vasc Surg Venous Lymphat Disord. 2019;7:623–8.
29. Rafey F, Shilpkumar A, Nour T, Robert S, Tony D, Rahul J, et al. Comparison of large-bore thrombectomy with catheter-directed thrombolysis for the treatment of pulmonary embolism. J Soc Cardiovasc Angiography Interv. 2023;2:100453.
30. Owens CA. Ultrasound-enhanced thrombolysis: EKOS EndoWave infusion catheter system. Semin Intervent Radiol. 2008;25:37–41.
31. Sławek-Szmyt S, Stępniewski J, Kurzyna M, et al. Catheter-directed mechanical aspiration thrombectomy in a real-world pulmonary embolism population - a multicenter registry. Eur Heart J Acute Cardiovasc Care. 2023;2023(12):584–93.
32. Sławek-Szmyt S, Puślecki M, Stefaniak S, et al. Emergent aspiration thrombectomy for thrombus in transit and pulmonary embolism using AngioVac. Pol Arch Intern Med. 2023;133:16433.
33. Szmyt K, Wierzbicki T, Borejsza-Wysocki M, et al. Adrenocortical carcinoma with tumor thrombus extension into the right atrium. Pol Arch Intern Med. 2023;133:16434.
34. Pietrasik A, Gąsecka A, Kurzyna P, et al. Cancer associated thrombosis: comparison of characteristics, treatment, and outcomes in oncological and non-oncological patients followed by pulmonary embolism response team. Pol Arch Intern Med. 2023:16421.
35. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE trial. JACC Cardiovasc Interv. 2018;11:1401–10.
36. Sadeghipour P, Jenab Y, Moosavi J, et al. Catheter-directed thrombolysis vs anticoagulation in patients with acute intermediate- high-risk pulmonary embolism: the CANARY randomized clinical trial. JAMA Cardiol. 2022;7:1189–97.

37. Graif A, Patel KD, Wimmer NJ, et al. Large-bore aspiration thrombectomy versus catheter-directed thrombolysis for acute pulmonary embolism: a propensity score-matched comparison. J Vasc Interv Radiol. 2020;31:2052–9.
38. Sedhom R, Elbadawi A, Megaly M, et al. Outcomes with catheter-directed thrombolysis vs. catheter-directed embolectomy among patients with high-risk pulmonary embolism: a nationwide analysis. Eur Heart J Acute Cardiovasc Care. 2023;12:224–31.