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Comparison of catheter-directed thrombolysis and anticoagulation in intermediate-risk pulmonary embolism: A retrospective analysis

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Abstract:

BACKGROUND AND OBJECTIVES: The selection of escalation of care strategies for the treatment of intermediate-risk pulmonary embolism (PE) is a matter of debate. Here, we aimed to assess the features of our population treated either with anticoagulation (AC) alone or catheter-directed thrombolysis (CDT). We also sought to identify a relationship between high residual systolic pulmonary artery pressure (sPAP) and demographic and clinical variables.

PATIENTS AND METHODS: The retrospective data of 30 intermediate-high-risk PE patients were analyzed. CDT was used in 14 (46.7%) cases. Enoxaparin (b. i. d) injections were administered in the AC group. In the CDT group, patients received 5 mg bolus dose of alteplase followed by 1 mg/h infusion for 24 h. Estimated sPAP at presentation and discharge was recorded. A value equal to or greater than 40 mmHg in the latter was accepted as a significant rise.

RESULTS: The patients in the CDT group had a lower HAS-BLED score (2 [0–3] vs. 1 [0–3], $P = 0.03$). Although initial sPAP values were comparable among treatment arms, sPAP at discharge was significantly lower in the CDT group (mmHg, 42 ± 11.2 vs. 33.6 ± 9.7 , $P = 0.04$). The reduction in sPAP at discharge was also significantly higher in this group. The degree of reduction in sPAP was considerably correlated with baseline sPAP ($r = 0.632$, $P < 0.001$). Finally, the baseline sPAP measurement and HAS-BLED score of the patients with high residual sPAP were significantly higher (56.6 ± 13.1 vs. 67.3 ± 11.3 , $P = 0.02$, and 1 [0–3] vs. 2 [0–3], $P = 0.02$, respectively).

CONCLUSION: CDT was preferred over AC when lower bleeding risk was anticipated for intermediate-high-risk PE patients in our sample population. Eventually, CDT provided lower discharge sPAP levels and a greater reduction in sPAP. However, the factors associated with high sPAP at discharge were only high baseline sPAP measurement and HAS-BLED score.

Keywords:

Anticoagulants, pulmonary embolism, pulmonary hypertension, thrombolytic therapy

Introduction

Acute pulmonary embolism (PE) is one of the leading causes of in-hospital mortality. It may also result in a reduction of functional capacity and quality of

life during long-term follow-up mainly but not invariably via development of chronic thromboembolic pulmonary hypertension (CTEPH).^[1,2] Regarding the enhanced awareness of the disease, widespread access to imaging modalities in health facilities, and formation of local disease-specific assemblies, namely

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response teams, PE has been increasingly diagnosed recently.^[3-5]

Risk modeling is the mainstay of management in PE by influencing not only the prognosis but also the level of care and selection of aggressive treatment modalities such as administration of thrombolytics, percutaneous techniques, and surgical embolectomy.^[6,7] Relevant guidelines define intermediate-risk PE as the presence of findings indicating increased right ventricular (RV) afterload in subjects without hypotension.^[8,9] European guidelines further classify this group into two: intermediate-low risk, designating the signs suggestive of RV dilation and/or dysfunction or increased biomarkers, and intermediate-high risk, expressing the existence of both.^[9] The intermediate-risk group constitutes 20%–25% of all PE cases with a mortality rate ranging between 3% and 5%.^[6,7,10,11]

CTEPH is the major long-term complication of PE which had been reported with an estimated frequency varying between 0.5% and 4.6% in different registries related to the population selected for investigation.^[7,12-14] Currently, precise risk factors for the development of CTEPH have not been fully established.^[14] However, even intermediate-risk PE was documented to be associated with an increased incidence of CTEPH.^[7,15]

In line with these data, escalation of care strategies – which was previously reserved for high-risk population – has been more commonly used for intermediate-risk patients in the last decade who may exhibit features of sudden decompensation.^[3,4,6,16] Catheter-directed thrombolysis (CDT) seemed a reasonable option at this setting based on the hypothesis of increased efficacy due to local administration of thrombolytics which might also be potentiated by adjunctive modalities such as suction or ultrasound-assisted fragmentation. Moreover, a significant decline in bleeding events was expected by utilizing considerably reduced doses of these agents. In various publications, earlier improvement in RV function and less clinical deterioration were elicited by CDT use. However, a definite projection of this virtue to the clinical outcome was not observed.^[2,3,6,7,17]

Here, we sought to distinguish our intermediate-high-risk PE patients treated either with anticoagulation (AC) alone or CDT added to AC by clinical and laboratory features. We also aimed to discriminate individuals who had higher systolic pulmonary artery pressure (sPAP) measurements at discharge from others who had relatively lower values (<40 mmHg). Estimated sPAP \geq 40 mmHg at discharge was accepted as a cutoff

point which may represent a candidacy for progression to CTEPH.

Patients and Methods

Study qualification and patient selection

Retrospective data of 77 patients followed in the coronary care unit of a tertiary center between September 2015 and August 2019 were analyzed. After exclusion of 29 high-risk patients treated either with systemic thrombolysis (ST) or CDT and 4 intermediate-risk patients to whom ST was given, 44 patients were found to be eligible for inclusion. Among those, 11 cases could not be included because of lacking critical data. Finally, 3 patients whose initial creatinine levels were higher than 1.5 mg/dl were further excluded to eliminate the possibility of improper dose adjustment of anticoagulants. Eventually, 30 patients constituted the final sample population. Flow diagram is displayed in Figure 1.

All patients had a central occlusive thrombus accompanied by images compatible with increased RV afterload in CT angiography. Systolic blood pressure (SBP) was over 90 mmHg at the presentation in the entire population as required for assigning to the intermediate-risk group. As suggested, a minimal initial troponin I level of 0.4 ng/ml was sought for confirmation of intermediate-high-risk status before the assignment.^[8] This retrospective investigation was approved by the ethical committee of Istanbul Medipol University (Approval ID: 787, Date: 09.10.2019), hence met the global standards stated by the Declaration of Helsinki. Permission for using the data was granted by the same institution.

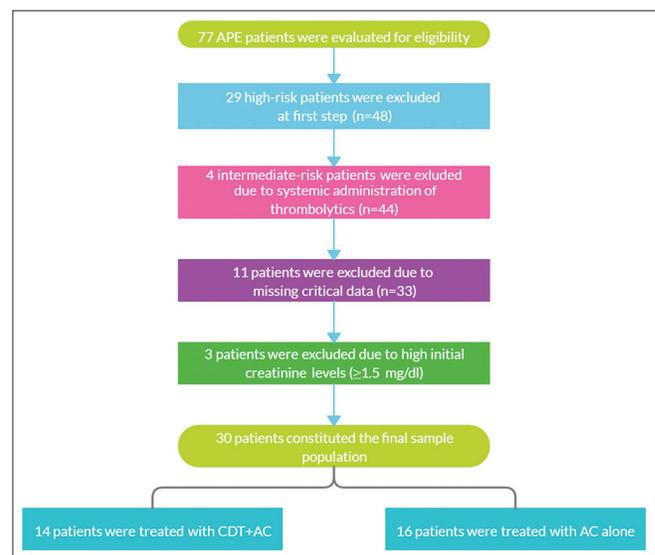


Figure 1: Flow diagram of the study. AC: Anticoagulation; APE: Acute pulmonary embolism, CDT: Catheter-directed thrombolysis

Demographic features, diagnostic tests, treatment algorithms, and clinical endpoints

Once eligibility for inclusion was confirmed demographic features including hypertension, diabetes mellitus, obesity (body mass index [BMI] ≥ 30 kg/m²), and presence of malignancy were noted. In addition to underlying malignant disease, orthopedic or other major surgeries, oral contraceptive use, and immobilization were accepted as provoking factors for a PE episode and specified if existed. HAS-BLED score was used for estimating bleeding risk during hospitalization.^[18]

Initial SBP, mean arterial pressure, heart rate, and oxygen saturation detected with pulse oximeter were recorded. D-dimer, troponin I, and creatinine levels at presentation were noted. Chronic Kidney Disease Epidemiology Collaboration creatinine formula (which was automatically generated by the information management system using the equation: $A \times [\text{Scr}/B]^C \times 0.993^{\text{age}}$) was used to calculate estimated glomerular filtration rate.^[19] Estimated sPAP values measured by echocardiographic examination at baseline and discharge were received from physician logs. A sPAP value equal to or higher than 40 mmHg was identified as a cutoff point in analogy to previous investigations.^[20,21] Patients with and without residual high sPAP levels were also compared apart from the choice of treatment.

According to the institutional algorithms, patients treated with AC alone received subcutaneous low-molecular-weight heparin (100 U/kg enoxaparin, b. i. d) injections. If warfarin was chosen for long-term AC, treatment had started the day before discharge. For non-Vitamin K oral anticoagulating agents, treatment shift was performed on the day of discharge with the recommended dosing scheme. In the CDT group, conventional technique or ultrasound-assisted thrombolysis (USAT) with EkoSonic Endovascular System (EKOS Corp.) was used. In conventional technique, alteplase was administered through a multi-side hole 5F or 6F infusion catheter which had been placed in the trunk or one of the major branches (in case of unilateral dominance of central thrombus burden). After administration of 5 mg alteplase bolus at cath lab, 1 mg/h infusion was continued for 24 h. Meanwhile, a subtherapeutic dose of unfractionated heparin (400–600 U/kg) was given via intravenous route to provide an activated partial thromboplastin time prolongation between 40 and 50 s. AC was sustained by twice-a-day subcutaneous enoxaparin injections at the succeeding days. Oral anticoagulating agent shift was carried out as described above. If USAT was utilized, one or two dedicated catheters were advanced to right and/or left pulmonary arteries. 5 mg bolus dose of alteplase was administered at cath lab followed by 1 mg/h infusion through the catheters for 24 h. Infusion dose was

reduced to 0.5 mg/h per catheter if two catheters were used. The AC regimen was identical to that used in the conventional method.

Mortality, clinical deterioration, and major and nonmajor bleeding events according to ISTH definitions were designated as in-hospital clinical endpoints.^[22] The length of hospital stay was additionally noted.

Statistical analysis

The normality of continuous variables was tested with the Shapiro–Wilk test. Variables with and without normal distribution were expressed as mean \pm standard deviation and median [range], respectively. Categorical variables were displayed as percentage (number of cases). Student's *t*-test was used to compare normally distributed continuous variables. Exact significance was considered in this test for distinguishing the groups, while Mann–Whitney U-test was utilized to compare the ones which were not normally distributed. Frequencies of categorical variables among groups were distinguished via Chi-square test. Pearson and Spearman tests were used to determine the correlation between continuous variables regarding the distribution pattern of relevant variables. A *P* value below 0.05 was deemed significant in all analyses. The Statistical Package for the Social Sciences (SPSS) (SPSS version 22.0, SPSS Inc., Chicago, IL, USA) was used for these assessments.

Results

Thirty patients (62.4 ± 16 years; 53.3% – female) were enrolled for the study. CDT was used in 14 (46.7%) cases. Four out of 14 cases were treated with USAT and two catheters were used in two patients. Patients in the CDT group tended to be relatively younger and had a higher BMI ($P = 0.09$ and $P = 0.08$, respectively). The patients in this group also had a lower bleeding tendency estimated by HAS-BLED scoring (2 [0–3] vs. 1 [0–3], $P = 0.03$). In the entire population, three patients had malignant disease as an underlying cause and all of them were in the AC group. The remaining demographic features, baseline hemodynamic variables, and laboratory tests were comparable among groups. These data are displayed in Table 1.

Although initial estimated sPAP values were comparable among treatment arms, sPAP at discharge was significantly lower in the CDT group. Besides, numerical and fractional reduction in sPAP at discharge was also significantly higher in this group [Table 2]. The comparison of sPAP at discharge and the degree of reduction were demonstrated with boxplots in Figure 2.

Table 1: Demographic features, initial vital parameters, and laboratory test results of the treatment arms

	Overall (n=30)	AC (n=16)	CDT (n=14)	P
Age (years); mean±SD ^a	62.4±16	67.1±14.4	57.1±16.5	0.09
Gender, female, n (%) ^c	16 (53.3)	10 (62.5)	6 (42.9)	0.28
BMI (kg/m ²); mean±SD ^a	26±3.6	24.9±3.8	27.2±3	0.08
Obesity, n (%) ^c	5 (16.7)	2 (12.5)	3 (21.4)	0.51
Hypertension, n (%) ^c	13 (43.3)	9 (56.3)	28.6 (4)	0.13
Diabetes mellitus, n (%) ^c	4 (13.3)	2 (12.5)	2 (14.3)	0.89
Malignancy, n (%) ^c	3 (10)	3 (18.8)	0	0.09
Provoked episode, n (%) ^c	10 (33.3)	5 (31.3)	5 (35.7)	0.80
HAS-BLED score; median (range) ^b	1 (0-3)	2 (0-3)	1 (0-3)	0.03
SBP, mmHg; mean±SD ^a	124.5±18.2	129.3±19	119.1±16.1	0.12
MBP, mmHg; mean±SD ^a	89.1±14	92±13.9	85.7±13.7	0.18
Heart rate, beats/min; mean±SD ^a	103.5±14.7	103.4±14.4	103.7±15.6	0.95
SaO ₂ , %; mean±SD ^a	91.8±3.6	90.7±4	93±2.5	0.07
D-Dimer, ng/ml; mean±SD ^a	5656.2±2987.7	5000.4±2933	6405±2975	0.20
Troponin I, ng/ml; median (range) ^b	0.4 (0.3-3)	0.4 (0.3-1.5)	0.4 (0.4-3)	0.31
Creatinine, mg/dl; mean±SD ^a	1±0.22	0.99±0.24	1.03±0.20	0.62
eGFR, ml/min; mean±SD ^a	81.1±21.7	79.5±20.7	82.8±23.5	0.69

^aStudent's *t*-test was used, ^bMann-Whitney *U*-test was used, ^cChi-square test was used. AC: Anticoagulation, BMI: Body mass index, CDT: Catheter-directed thrombolysis, eGFR: Estimated glomerular filtration rate, MBP: Mean blood pressure, SaO₂: Oxygen saturation, SBP: Systolic blood pressure

Table 2: Comparison of the echocardiographic systolic pulmonary artery pressure measurements and clinical endpoints of the study population

	Overall (n=30)	AC (n=16)	CDT (n=14)	P
Echocardiographic variables				
sPAP-baseline, mmHg; mean±SD ^a	61.3±13.3	57.4±14.2	65.7±11.1	0.08
sPAP-discharge, mmHg; mean±SD ^a	38.1±11.2	42±11.2	33.6±9.7	0.04
sPAP-reduction, mmHg; mean±SD ^a	23.2±12.7	15.4±10.5	32.1±8.6	<0.01
sPAP-percent reduction, mmHg; mean±SD ^a	36.8±16.1	26.1±12.2	49.1±10.1	<0.01
Clinical endpoints				
Length of stay (days); median (range) ^b	6 (3-14)	5 (3-12)	6.5 (3-14)	0.19
Major bleeding, n (%) ^c	10 (3)	0	21.4 (3)	0.06
Nonmajor bleeding, n (%) ^c	6.7 (2)	0	14.3 (2)	0.12

^aStudent's *t*-test was used, ^bMann-Whitney *U*-test was used, ^cChi-square test was used. AC: Anticoagulation, CDT: Catheter-directed thrombolysis, sPAP: Systolic pulmonary artery pressure

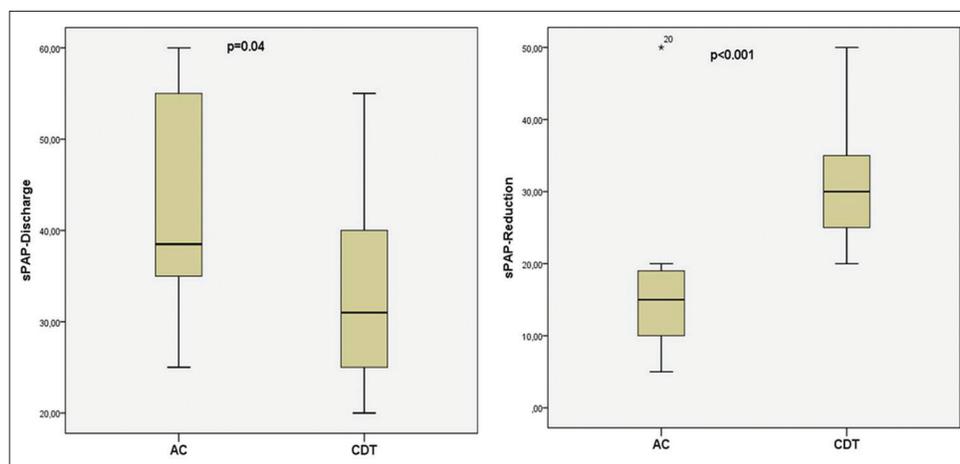


Figure 2: Box plots displaying comparison of discharge measurements and reduction amount of systolic pulmonary artery pressures between treatment arms. AC: Anticoagulation; CDT: Catheter-directed thrombolysis; sPAP: Systolic pulmonary artery pressure

The difference in length of hospitalization was statistically indistinctive between the groups (AC: 5 [3–12] vs. CDT: 6.5 [3–14], *P* = 0.19). Death and clinical deterioration

were not observed in our sample population. Three patients (21.4%) had nonfatal major bleeding according to ISTH classification. One of these events was

retroperitoneal bleeding (not required intervention) and the others were bleeding which required transfusion with 2 units of red blood cells. There were also two nonmajor bleeding events (14.3%), a hematuria case and access-site bleeding. All these events were observed in the CDT group [Table 2].

Cases were then regrouped according to the presence of an elevated sPAP (≥ 40 mmHg) at discharge. Of those treated with CDT, 5 patients (35.7%) had residually elevated sPAP at discharge while 8 patients (50%) in the AC group did so ($P = 0.43$). The mean HAS-BLED score was higher in the group with high sPAP (1 [0–3] vs. 2 [0–3], $P = 0.02$). The baseline sPAP level was also significantly higher in this group (56.6 ± 13.1 vs.

67.3 ± 11.3 , $P = 0.02$). The remaining parameters including the use of CDT were comparable among groups [Table 3].

The degree of reduction in sPAP at discharge was considerably correlated with baseline sPAP ($r: 63.2$, $P < 0.001$). This relationship is illustrated in Figure 3. There was also a reasonable negative correlation between sPAP reduction and age ($r: -42.7$, $P = 0.02$) and sPAP reduction and HAS-BLED score ($r: -45.4$, $P = 0.01$). Nevertheless, these correlations were presumably related to less frequent selection of CDT in older patients with an increased bleeding tendency. It should also be denoted that the correlation coefficients might not precisely interpret the relationship of these variables considering the small sample size.

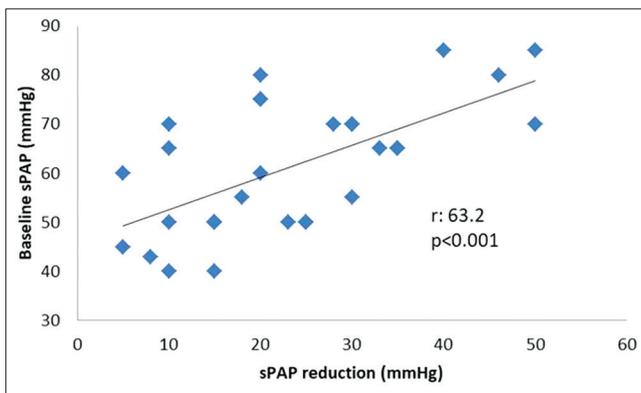


Figure 3: Scatter plot demonstrating the correlation between baseline values and reduction amount of systolic pulmonary artery pressure. sPAP: Systolic pulmonary artery pressure

Discussion

Despite having a lower mortality rate as compared to massive PE, submassive, or its correspondent intermediate risk, PE still poses a remarkable clinical significance through the likelihood of progression to shock in the acute phase and CTEPH at long term.^[6,7] Recognition of RV strain findings at ECG and imaging modalities in addition to centrally located thrombus was determined as the indicator of possible deterioration.^[4,23] However, only increased pulmonary artery systolic pressure was constantly found to be in a close relationship with the development of CTEPH.^[7,14,15,24] In this context, low-dose ST and catheter-directed techniques offer prevention of clinical worsening while providing

Table 3: Comparison of the demographic and clinical features of the patients with and without high systolic pulmonary artery pressure (≥ 40 mmHg) at discharge

	Low sPAP-d (n=17)	High sPAP-d (n=13)	P
Age, years; mean \pm SD ^a	58.7 \pm 16.5	67.3 \pm 14.4	0.14
Gender, female; n (%) ^c	10 (58.8)	6 (46.2)	0.49
BMI, kg/m ² ; mean \pm SD ^a	26 \pm 4	26 \pm 3.2	0.98
Obesity; n (%) ^c	4 (23.5)	1 (7.7)	0.25
Hypertension; n (%) ^c	8 (47.1)	5 (38.5)	0.64
Diabetes mellitus, n (%) ^c	3 (17.6)	1 (7.7)	0.43
Malignancy; n (%) ^c	2 (11.8)	1 (7.7)	0.71
Provoked episode; n (%) ^c	5 (29.4)	5 (38.5)	0.60
HAS-BLED score; median (range) ^b	1 (0-3)	2 (0-3)	0.02
SBP, mmHg; mean \pm SD ^a	123.2 \pm 17.8	126.2 \pm 19.3	0.68
MBP, mmHg; mean \pm SD ^a	87.4 \pm 12.2	91.2 \pm 16.3	0.49
Heart rate, beats/min; mean \pm SD ^a	103.4 \pm 15.7	103.8 \pm 13.8	0.94
SaO ₂ , %; mean \pm SD ^a	92.4 \pm 3.6	90.9 \pm 3.5	0.26
D-Dimer, ng/ml; mean \pm SD ^a	5725.7 \pm 2718.2	5565.4 \pm 3421.2	0.89
Troponin I, ng/ml; median (range) ^b	0.4 (0.3-3.0)	0.4 (0.4-3.0)	0.81
Creatinine, mg/dl; mean \pm SD ^a	1.03 \pm 0.23	0.98 \pm 0.21	0.52
eGFR, ml/min; mean \pm SD ^a	81.9 \pm 22.1	80 \pm 22	0.81
sPAP-Baseline, mmHg; mean \pm SD ^a	56.6 \pm 13.1	67.3 \pm 11.3	0.02
Length of stay, days; median (range) ^b	6 (3-10)	6 (3-14)	0.41
Treatment strategy, CDT; n (%) ^c	9 (52.9)	5 (38.5)	0.43

^aStudent's *t*-test was used, ^bMann-Whitney *U*-test was used, ^cChi-square test was used. BMI: Body mass index, CDT: Catheter-directed thrombolysis, eGFR: Estimated glomerular filtration rate, MBP: Mean blood pressure, SaO₂: Oxygen saturation, SBP: Systolic blood pressure, sPAP: Systolic pulmonary artery pressure

rapid improvement at exaggerated RV afterload and possibly leading to a more favorable clinical outcome at the expense of increased bleeding rates.^[1,6,7,16,25,26] However, the relatively low rate of adverse events leaves the advanced treatment modalities a little room for exhibiting these advantages.^[6,7,10] Hence, conflicting reports about outcome exist in the literature partly due to the high variability of study designs and the identification of endpoints. In our investigation, mortality was not observed and all bleeding events occurred in patients who were treated with CDT. This finding poses an additional significance considering the fact that common risk factors for bleeding events such as younger age, higher BMI, low HAS-BLED score, and absence of malignant disease were in favor of this group.

In a recent publication, advanced therapies (all treatment options apart from routine AC) were shown to decrease 30-day and 90-day mortality rates both in the massive and submassive groups. For submassive PE, advanced therapies were associated with a trend toward increased major bleeding events at 30 days, whereas this relationship lost significance at 90 days.^[27] Chen *et al.* denoted in their meta-analysis including 15 studies focused on moderate PE that thrombolytic treatment yielded a decline in rates of recurrent PE or death as against AC. They also reported a significant increase in nonmajor and a nonsignificant increase in major bleeding with thrombolytic therapy.^[11] Another meta-analysis performed by Chatterjee *et al.* also presented a similar output.^[28]

On the other hand, two large trials comparing ST with AC failed to confirm the mortality benefit.^[26,29] In TOPCOAT, a reduction solely in mortality was not stated, but a reduction in the composite endpoint including mortality was observed.^[29] In PEITHO, ST only decreased the probability of clinical worsening.^[26] Bleeding rates were remarkably high in both trials. Nakamura *et al.* verified these data in their meta-analysis.^[30] In line with these findings, reduced dose ST and CDT garnered interest as a first-line treatment option in intermediate-risk PE to avoid major bleeding.^[1,6]

In a retrospective registry, patients treated with low-dose ST had 2.2% inhospital mortality and 4.4% 30-day all-cause mortality. Although the mean HAS-BLED score of the patients was 0.8 in this investigation, ISTH major bleeding was observed in 11% of the cases.^[31] MOPETT trial which actually focused on pulmonary artery pressure changes also compared the efficacy of ST and AC for the treatment of intermediate-risk PE. Investigators identified acute bleeding, length of hospitalization, recurrent PE, death, and the combination of the last two as secondary endpoints. The comparison of combined secondary endpoint favored ST while no bleeding events were reported.^[20] Although a low dose of

alteplase was used in a group of patients with a median HAS-BLED score of 1, CDT was not a safe harbor for eliminating the risk of bleeding in our study. This finding was corroborating the former investigation.

Catheter-directed techniques were tested for replacing the conventional ST in patients without hemodynamic collapse.^[1,2,7] Simply inserting a multi-side hole catheter in the pulmonary artery to provide continuous infusion of the thrombolytic agent is the most commonly used method.^[5] Adjunctive modalities such as the ultrasound-assisted disruption of the thrombus and suction thrombectomy were also used to reduce the thrombolytic dose and enhance the efficacy.^[4,16,32-34] Suction thrombectomy was positioned as a bail-out treatment in the literature for patients at shock who had a contraindication for administration of thrombolytics.^[4] USAT seemed more appropriate for the treatment of intermediate-risk patients, particularly after the publication of first reports expressing high clinical success rates and lower major bleeding events.^[33,34] Thereafter, SEATTLE II raised again the questions about safety issues while revealing a major bleeding rate of 11%. It should be denoted that SEATTLE II used the most stringent criteria for the definition of major bleeding among its counterparts.^[25] On the other hand, investigators of these studies agreed on the rapid reversal of increased RV systolic pressure and strain pattern by utilization of CDT as compared to AC without an evident projection to clinical hard endpoints. Besides, none of these studies was powered sufficiently to establish the safety of the method.^[25,33-35] Graif *et al.* compared thrombolytic infusion through a simple pigtail catheter and a USAT system. In this retrospective analysis, mortality and complication rates were comparable between treatment arms with higher procedure and fluoroscopy times in the USAT group.^[36] Apart from these, Avgerinos and Chaer denoted that the length of hospitalization was lower in the AC group as compared to patients treated with CDT techniques in their sample population.^[35] The length of hospitalization was comparable among the AC and CDT groups in our population while the median day for stay was numerically higher in the latter (5 vs. 6.5). Patients in the CDT group tended to have higher baseline sPAP measurements. On the other hand, sPAP at discharge was significantly lower and the degree of reduction was more pronounced in this group (15.4 mmHg in AC vs. 32.1 mmHg in CDT).

Although precise evidence derived from head-to-head comparison of ST and CDT has been lacking in the literature, some registries and meta-analyses were published to fill the gap about this subject. Kaymaz *et al.* stated that when compared to randomized ST trials, CDT showed similar mortality but reduced major bleeding rates.^[37] Arora *et al.* compared 3107 patients treated

with ST and 1319 with CDT and reported that mortality, mortality combined with bleeding, and readmission rates were higher in the ST group.^[38] Similarly, Patel *et al.* found that CDT was associated with lower combined in-hospital mortality and intracranial bleeding.^[39] Nevertheless, the current data remain inconclusive to herald the use of CDT or ST as first-line therapy for intermediate-risk PE. The efficacy and safety of these modalities are yet to be supported with larger evidence. Particularly, qualifying the features of catheter-directed methods is more troublesome due to high diversities in certain issues such as the catheter selection, duration of administration, and type and dosing scheme of the thrombolytic agent.^[6] Thereby, recent European Society of Cardiology guidelines recommended CDT and ST (preferably low dose) for treatment of intermediate-risk PE only in case of rapid clinical deterioration with signs of persistent hypoxia and diminished cardiac output.^[9]

In our retrospective analysis, clinicians tended to reserve CDT for younger patients with higher body mass indices and lower HAS-BLED scores. Although statistical significance was not observed, bleeding events identified by strict ISTH criteria and length of hospital stay were relatively higher in the CDT group. However, we need hardly mention that our study was either focused on or empowered enough to interpret the clinical outcome. It should also be denoted that the data presented here refer to a period before publication of the most recent guidelines.

Vasoconstriction and acute inflammation overlapping the physical obstruction are the hallmarks of increased RV afterload in PE. In a certain fraction of these patients, pressure overload and vascular resistance augmentation persist which may contribute to the development of CTEPH.^[1] Aside from CTEPH, diminished functional capacity decreased quality of life, and recurrent PE might be observed as long-term complications of PE.^[1,7,11,12]

CTEPH has an estimated incidence of 3.2% in the 3rd year in intermediate-risk PE patients treated only with AC.^[12] Pengo *et al.* declared the 2-year frequency of CTEPH as 3.8% in a more heterogeneous PE population.^[13] Depending on the sample population, type of investigation, and definition of CTEPH, higher event rate up to 12.4% was reported.^[21] MOPETT trial identified pulmonary hypertension as the detection of a pulmonary artery systolic pressure over 40 mmHg at the echocardiographic examination. In this regard, pulmonary hypertension was observed at 16% and 57% of patients treated with ST or AC, respectively.^[20] Correlatively, Korkmaz *et al.* denoted that persistently elevated RV systolic pressure (>35 mmHg at echocardiography) was detected in 57% of their sample population. The incidence of symptomatic CTEPH was 4.6% after an episode of PE in this study which was diagnosed on an average of 9.4 months.^[14] Persistently

elevated sPAP at discharge was observed in 43.3% of our sample population with a relatively lower (statistically insignificant) frequency in the CDT group (35.7%).

Several factors were established as predictors of CTEPH development. High baseline sPAP values, age, and presence of intermediate-risk features were accused in this context.^[14,15,24,40] Klok *et al.* also suggested a prediction score that combined demographic features, CT findings, and treatment choices.^[40] Although the association of CTEPH incidence and high sPAP values at presentation had been iteratively demonstrated, rapid reduction of pulmonary arterial pressure via utilization of advanced treatments (including CDT) did not transform into a clinical achievement reflected by reduced event rates.^[7] In our population, HAS-BLED score and baseline sPAP measurements were higher in patients with elevated sPAP at discharge whereas the utilization of CDT was comparable among groups. In addition, the degree of reduction in sPAP was correlated with baseline measurements.

Regarding the retrospective nature of the study, estimated sPAP values at echocardiographic examination were used instead of invasive measurements. A value ≥ 40 mmHg at discharge was assumed to reflect a residually high sPAP level in our study. However, the clinical consequences of this incidence by means of CTEPH occurrence and long-term morbidity and mortality could not be specified due to lack of follow-up data. Another limitation of our analysis was utilization of both USAT and the conventional method in the CDT group.

Conclusion

In line with previous data, CDT was preferred as principal treatment when lower bleeding risk was anticipated for intermediate-high-risk PE patients in our sample population. Eventually, CDT provided lower discharge sPAP levels and a greater reduction in sPAP at the expense of more bleeding events. However, the factors associated with high sPAP at discharge were only high baseline sPAP measurement and HAS-BLED score. Ultimately, retrospective design, small sample size, absence of hard endpoints such as mortality and clinical deterioration, and utilization of two different catheters for CDT should be designated as major limitations of our study. Another consequence of the retrospective design is the heterogeneity of demographic features which may also confound the results about clinical event occurrence.

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Conflicts of interest

There are no conflicts of interest.

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