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Management of high-risk acute pulmonary embolism: an emulated target trial analysis

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Abstract

Background: High-risk acute pulmonary embolism (PE) is a life-threatening condition necessitating hemodynamic stabilization and rapid restoration of pulmonary perfusion. In this context, evidence regarding the benefit of advanced circulatory support and pulmonary recanalization strategies is still limited.

Methods: In this observational study, we assessed data of 1060 patients treated for high-risk acute PE with 991 being included in a target trial emulation to investigate all-cause in-hospital mortality estimates with different advanced treatment strategies. The four treatment groups consisted of patients undergoing (I) veno-arterial extracorporeal membrane oxygenation (VA-ECMO) alone ($n = 126$), (II) intrahospital systemic thrombolysis (SYS) ($n = 643$), (III) surgical thrombectomy

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(ST) ($n = 49$), and (IV) percutaneous catheter-directed treatment (PCDT) ($n = 173$). VA-ECMO was allowed as bridging to pulmonary recanalization in groups II, III, and IV. Marginal causal contrasts were estimated using the g-formula with logistic regression models as the primary approach. Sensitivity analyses included targeted maximum likelihood estimation (TMLE) with machine learning, inverse probability of treatment weighting (IPTW), as well as variations of estimands, handling of missing values, and a complete target trial emulation excluding the VA-ECMO alone group.

Results: In the overall target trial population, the median age was 62.0 years, and 53.3% of patients were male. The estimated probability of in-hospital mortality from the primary target trial intention-to-treat analysis for VA-ECMO alone was 57% (95% confidence interval [CI] 47%; 67%), compared to 48% (95% CI 44%; 53%) for intrahospital SYS, 34% (95%CI 18%; 50%) for ST, and 43% (95% CI 35%; 51%) for PCDT. The mortality risk ratios were largely in favor of any advanced recanalization strategy over VA-ECMO alone. The robustness of these findings was supported by all sensitivity analyses. In the crude outcome analysis, patients surviving to discharge had a high probability of favorable neurologic outcome in all treatment groups.

Conclusion: Advanced recanalization by means of SYS, ST, and several promising catheter-directed systems may have a positive impact on short-term survival of patients presenting with high-risk PE compared to the use of VA-ECMO alone as a bridge to recovery.

Keywords: High-risk pulmonary embolism, Systemic thrombolysis, Surgical thrombectomy, Percutaneous catheter-directed treatment, Mechanical circulatory support

Introduction

Pulmonary embolism (PE) constitutes a major cardiovascular disease entity affecting more than 35 per 100,000 persons annually [1–5]. Approximately 5% of all PE patients present with persistent hypotension, cardiogenic shock, or cardiac arrest as a result of acute right ventricular (RV) failure [6–9]. The presence of hemodynamic instability defines high-risk PE which is associated with an exceptionally high mortality rate [6, 8–13]. In severe cases, progressive RV distension and loss of contractility may lead to obstruction of left ventricular (LV) diastolic filling and systemic hypoperfusion, aggravated by hypoxemia. Thus, the principal objectives of emergency care in patients experiencing high-risk PE are hemodynamic stabilization, restoration of adequate gas exchange, and alleviation of pulmonary vascular obstruction.

In patients with PE and refractory circulatory failure or cardiac arrest, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) represents the current first-line mechanical circulatory support device in clinical practice [5, 9, 13]. VA-ECMO is capable of restoring systemic perfusion and oxygenation, but also of decreasing RV preload, thereby reducing wall stress and myocardial oxygen consumption [14]. In conjunction with advanced circulatory support, novel catheter-based systems have diversified the therapeutic armamentarium for pulmonary recanalization, complementing established treatment options, such as systemic thrombolysis (SYS) and surgical thrombectomy (ST) [5, 10, 13, 15–19]. However, evidence regarding the efficacy of VA-ECMO as a bridge to recovery or reperfusion, as well as the optimal selection of an advanced recanalization strategy, is sparse, and data from randomized controlled trials in high-risk populations are not available at present and difficult to obtain.

In order to address the remaining uncertainties regarding emergency management of high-risk acute PE, we emulated a target trial from one of the largest retrospective datasets compiled to date. The purpose of this study was to estimate the treatment effect of VA-ECMO alone, SYS, ST, and percutaneous catheter-directed treatment (PCDT) on in-hospital mortality. Results of the primary target trial analysis along with a series of sensitivity analyses aim to further develop treatment algorithms for this life-threatening condition.

Take-home message

Advanced recanalization may have a positive impact on short-term survival of patients presenting with high-risk pulmonary embolism compared to the use of VA-ECMO alone as a bridge to recovery.

The role of surgical thrombectomy in managing high-risk PE may be underestimated in current clinical practice and this approach, but also the use of novel promising catheter-directed systems, could have a positive impact on outcomes.

Further prospective investigation of risk prediction models and efficacy of specific treatment approaches are urgently needed to improve multidisciplinary management and outcomes of patients experiencing high-risk pulmonary embolism.

Methods

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee at Ludwig-Maximilians-Universität (LMU) Munich (IRB 22-0193).

Study design, patient population, and data management

The present study features a target trial emulation that was designed to investigate in-hospital all-cause mortality with different advanced treatment strategies for patients with high-risk acute PE. Retrospective data was collected from 34 European clinical centers (Appendix A.2). Adult patients experiencing high-risk acute PE, defined as the presence of cardiogenic shock, cardiac arrest, or persistent hypotension, between January 2012 and August 2022 were included in the study (Fig. 1). Patients who had undergone prehospital SYS before admission were excluded from the analysis. PE diagnosis and risk stratification were in accordance with the European Society of Cardiology (ESC) guidelines on management of PE [9]. Standardized definitions of all parameters of interest as well as a data dictionary were provided to each clinical site. Study data were collected by a senior physician at each site following strict anonymization. Validity and integrity of the dataset was controlled by one senior member of the lead study team and by the independent statistical team at the Institute for Medical Information Processing, Biometry, and Epidemiology (IBE) at LMU Munich. The statistical analysis plan was pre-registered at IBE before the data were received by the statistical team.

Study outcomes

All-cause in-hospital mortality was selected as the primary outcome variable. Secondary outcomes included all-cause 3-month and 1-year mortality, cerebral performance category (CPC) score at hospital discharge among survivors, total length of intensive care unit (ICU) stay, total length of hospital stay, and major and non-major bleeding complications according to the International Society on Thrombosis and Haemostasis (ISTH) definition.

Target trial emulation

We emulated a target trial [20, 21] using observational data with the following patient population being included: adult patients diagnosed with high-risk acute PE who were eligible to undergo intrahospital SYS, ST, PCDT, or VA-ECMO. The target trial protocol is presented in the electronic supplementary material (Appendix A.3).

We considered four treatment arms: (I) VA-ECMO alone, (II) intrahospital SYS, (III) ST, and (IV) PCDT. Notably, patients were assigned to groups II-IV regardless of prior VA-ECMO use, as VA-ECMO was considered a method for hemodynamic stabilization when followed by one of these advanced recanalization strategies. We considered the time of treatment assignment as time zero. All arms received heparin as basic treatment for PE. Individuals were not randomly allocated, so we assumed no unmeasured confounding at baseline conditional on the following measured confounders: severity of disease as measured through pH at admission (due to high correlation between pH and lactate, only pH was considered), presence of cardiogenic and/or obstructive shock, cardiac arrest, and duration of cardiopulmonary resuscitation (CPR); morbidity at admission: chronic heart failure, previous myocardial infarction, diabetes mellitus, chronic renal failure, history of stroke or cancer as well as age and sex. These potential confounders were selected a priori based on clinical knowledge and information from the literature which factors may have (I) influenced the treating physicians' decision for choosing one of the four treatment options and (II) also potentially affected the respective outcomes [21]. Similarly, two analysis definitions, i.e., intention-to-treat (ITT) and non-naïve per-protocol (PP) (see below), were pre-registered. Aim of this analysis was to obtain results for the most detailed definition, contrasting the above-mentioned treatment regimens, as the reference group consisted of patients who only received VA-ECMO without further treatments.

The causal contrasts of interests were both the mortality risk differences and risk ratios between the four treatment arms, quantified through both pre-registered ITT and (non-naïve, adjusted) PP analyses [22]. That is, for ITT, we were interested in the mortality risk under any of the four assigned strategies, i.e., intrahospital SYS, ST, PCDT, and VA-ECMO, independent of whether the treating physician decided to continue with additional treatments thereafter. An exception to this was the VA-ECMO group, to which only patients who were treated exclusively with VA-ECMO without further treatments were assigned. Note that if VA-ECMO as first treatment was followed by either intrahospital SYS, PCDT, or ST, it was considered that this initial use of VA-ECMO aimed to stabilize patients towards one of the other treatments. Consequently, these patients were analyzed as belonging to one of the three aforementioned treatment arms. In cases where this applies, SYS, PCDT, or ST are typically used minutes or hours after the initial stabilizing use of VA-ECMO. In the non-naïve PP, we estimate the effect of intrahospital SYS, ST, PCDT, and VA-ECMO if none of the patients had received additional treatments thereafter. We assumed that the above listed confounders are appropriate to adjust for "treatment switch" (i.e., second or third additional treatments). We followed patients from treatment assignment (time zero) until either death occurred or for a maximum of one year. More details are

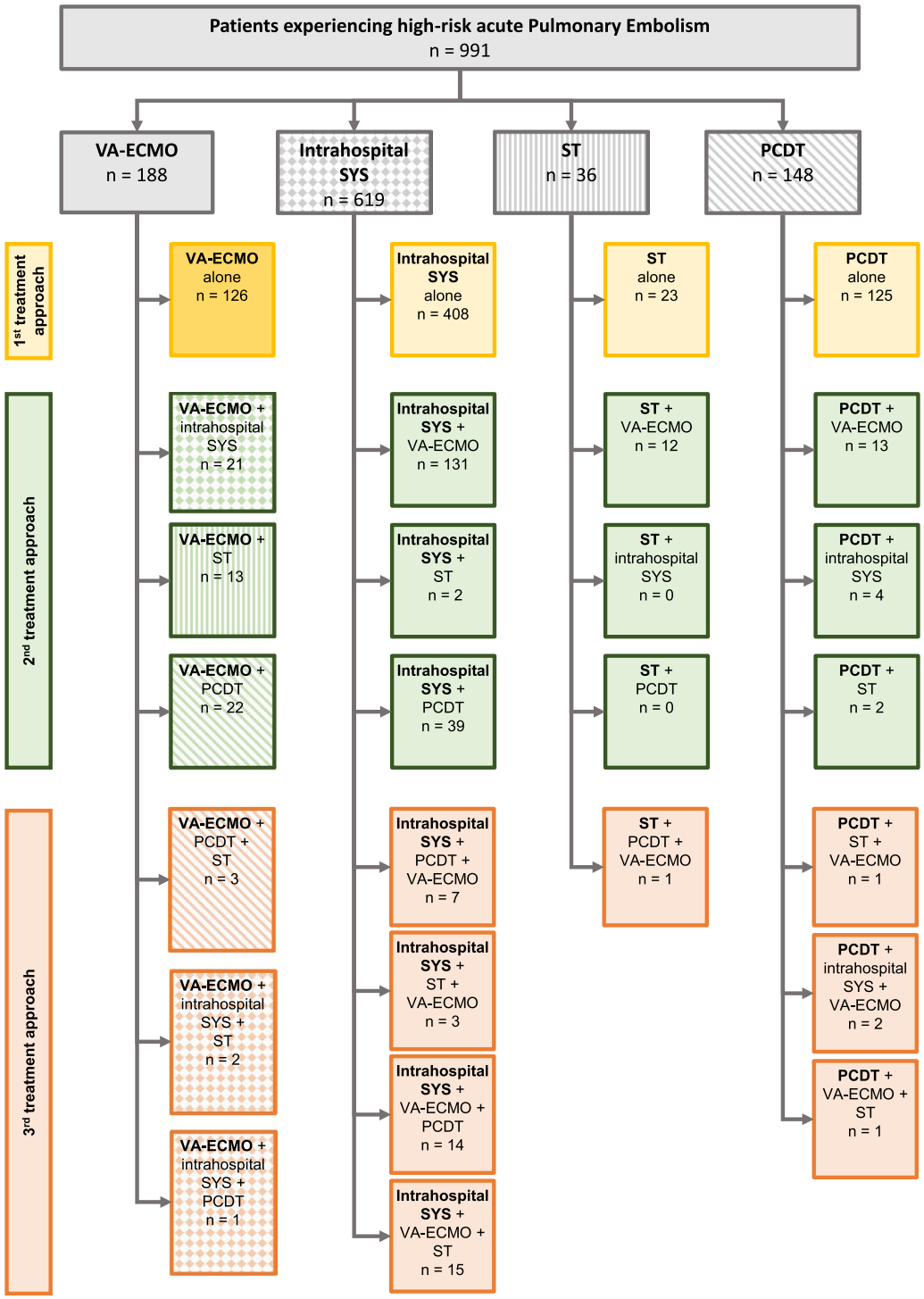

Fig. 1 Overview of treatment approaches. Each column includes all patients, who first received the respective treatment approach (VA-ECMO, intrahospital SYS, ST, or PCDT). Number of patients receiving only one treatment approach shown in yellow boxes. Second- and third-line treatment approaches shown in green, and orange, respectively. Group I in the intention-to-treat analysis corresponds to the "VA-ECMO alone" group (dark yellow box). Group II includes patients who received intrahospital SYS, regardless of prior stabilization with VA-ECMO (checkered boxes). Group III consists of patients undergoing ST, regardless of prior VA-ECMO stabilization (boxes with straight lines). Group IV includes patients treated with PCDT, regardless of prior VA-ECMO stabilization (boxes with oblique lines). *PCDT* percutaneous catheter-directed treatment, *ST* surgical thrombectomy, *SYS* systemic thrombolysis, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation

given in the electronic supplementary material (Appendix A.3).

Statistical analysis: (I) Estimation of causal contrasts

We used standardization, by means of the g-formula, generalized marginal effects and adjusted predictions, as the primary approach to estimate our causal contrasts of interest—under the assumption of no unmeasured confounding [21, 23]. This means, we modeled in-hospital mortality with logistic regression, and then predicted the marginal probability of death for every patient under each of the four different intervention strategies. The g-formula thus standardizes the analysis with respect to the confounder distribution, ensuring a fair comparison between patients with different confounder (i.e., disease severity) levels. Marginal effects plots and adjusted prediction plots display the expectation function for in-hospital mortality, averaged over all non-modifiable risk factors according to their joint empirical distribution after marginalizing out the categorical treatment variable. By following this approach, the adjusted prediction plots and marginal effects plots can be interpreted as the expected in-hospital mortality had all patients received a given treatment (under the no unmeasured confounders assumption discussed above and below). Additionally, they can also be interpreted as the change in predicted in-hospital mortality if the treatment was changed from the reference (i.e., VA-ECMO alone) to a given treatment, meanwhile adjusting for the measured confounders, respectively. Missing data (<5%) were multiply imputed using the expectation-maximization bootstrap algorithm [24]. For the results using the g-formula, compatibility intervals, which are numerically identical to what has been traditionally called confidence intervals [25], were obtained with bootstrapping [26]. E-values referring to a bias adjustment that would account for any direct effects between a specific unmeasured confounder and the outcome variable have been calculated for the ITT and adjusted PP analyses. The statistical analysis was performed using R® (version 4.3.2).

(II) Sensitivity analyses

For the sensitivity analyses, statistical approaches were varied. First, with respect to missing data, we categorized variables with missing values and added a "missing data category". Second, we used targeted maximum likelihood estimation (TMLE) as a secondary statistical analysis approach [27, 28]. Briefly, TMLE models both the outcome and treatment mechanisms, and allows the incorporation of machine learning algorithms—while still retaining valid inference. TMLE thereby reduces the chances of model-misspecification. However, for our estimand, the comparisons are not made between all four treatment groups separately but always for one group compared to the other three. TMLE first standardizes the analysis with respect to the confounder distribution, ensuring a fair comparison between patients with different confounder (i.e., disease severity) levels. In the second step, initial estimates are corrected—if needed—using a "clever covariate" that uses the propensity scores. More details are given in the electronic supplementary material (Appendix A.4). Third, we added an "as-treated" analysis definition. The as-treated treatment variable is based on the last given treatment of up to three recanalization approaches (i.e., SYS, ST, and PCDT). Fourth, we used inverse probability of treatment weighting (IPTW). This is another valid estimation approach in which only the treatment assignment mechanisms need to be modeled [21]. Propensity scores were estimated using logistic regression, and the derived weights were applied to the analysis to adjust for confounding. Love plots were used to visualize the mean differences for categorical baseline covariates and standardized mean differences (SMD) for continuous baseline covariates before and after weighting.

In addition, a complete target trial emulation was also performed excluding the VA-ECMO alone group to assess the robustness of the main findings with respect to the inclusion of this group of patients, since they may present with more severe disease condition than the other three groups. To assess the possibility of immortal time bias, treatment switching times were assessed in patients who were bridged to advanced recanalization with VA-ECMO, and a final sensitivity analysis was conducted excluding VA-ECMO patients who died within the first five hours after hospital admission.

Results

Study population

Between January 2012 and August 2022, 1060 patients were treated for high-risk acute PE at 34 participating study centers, of whom 188 patients received circulatory support with VA-ECMO as a primary treatment approach, and a total of 803 patients initially underwent advanced recanalization by means of intrahospital SYS ($n=619$), ST ($n=36$), or PCDT ($n=148$). The remaining 69 patients received prehospital SYS and were excluded from the analysis. Further information regarding subsequent second- and third-line treatment strategies are presented in Fig. 1.

Baseline characteristics

Table 1 and Table S1 contain baseline characteristics of patients who received VA-ECMO alone (group I, $n = 126$), and patients who underwent at least one advanced in-hospital recanalization approach, regardless of whether or not VA-ECMO was used for initial hemodynamic stabilization (intrahospital SYS [group II, $n = 643$], ST [group III, $n = 49$], and PCDT [group IV, $n = 173$]). In the overall population, the median age was 62.0 years, and 53.3% of patients were male. Several baseline variables appeared to differ between groups I to IV, including median age, pH at admission, the number of patients experiencing cardiac arrest or presenting with cardiogenic shock, and the Simplified Acute Physiology Score (SAPS) II at admission.

Diagnosis and management of pulmonary embolism

The diagnosis of PE was established by computed tomography pulmonary angiography in most cases (Table 2). The usage rate of mechanical ventilation, vasoactive/inotropic medication, and renal replacement therapy was lowest in group IV, and highest in groups I and III. The percentage of patients receiving mechanical circulatory support with VA-ECMO before or after intrahospital SYS, ST, or PCDT was 30.2%, 53.1%, and 24.3% in group II, III, and IV, respectively. The least frequently used approach for recanalization was ST (78/991 [7.9%]). By contrast, a total of 235/991 (23.7%) patients underwent PCDT. The most commonly utilized techniques for PCDT, in descending order, were mechanical suction thrombectomy, ultrasound-assisted thrombolysis, and catheter-directed local thrombolysis.

Outcomes

Unadjusted in-hospital mortality, 3-month and 1-year mortality rates are presented in Table 3. Notably, the majority of survivors to hospital discharge in each subgroup reported favorable neurologic outcome (CPC 1 or 2), with the highest percentage of survivors classified as CPC 1 in group IV (111 of 122 [91%]). Both the median length of ICU stay and length of hospital stay were longest in group III.

The estimated probability of in-hospital mortality from the primary target trial ITT analysis for VA-ECMO alone was 57% (95% CI 47%; 67%), compared to 48% (95% CI 44%; 53%) for intrahospital SYS, 34% (95% CI 18%; 50%) for ST, and 43% (95% CI 35%; 51%) for PCDT (Table 4). The robustness of these findings was proven by the secondary TMLE and IPTW analysis approaches and the adjusted prediction plots shown in Fig. 2. Accordingly, the mortality risk ratios between intrahospital SYS vs. VA-ECMO alone, ST vs. VA-ECMO alone, and PCDT vs. VA-ECMO alone were largely in favor of any advanced recanalization strategy over VA-ECMO alone, supported also by a mortality risk ratio of 1.34 (95% CI 1.07; 1.67) between VA-ECMO alone vs. any other treatment approach in the TMLE analysis. The risk differences resulting from the g-formula- and TMLE-based statistical approaches similarly suggest, that each advanced recanalization technique translates to a lower in-hospital mortality compared to VA-ECMO alone, with the greatest risk reduction associated with ST (Table S2). The generalized marginal effects plots presented in Fig. S1 provide estimates for the reduction of in-hospital mortality associated with a hypothetical change of treatment strategy from VA-ECMO alone to one of the three advanced reperfusion techniques, also indicating the greatest benefit with ST.

The results from the corresponding adjusted PP and as-treated analyses are presented in Table S2, Fig. 2, and figure S1. In summary, both under the PP and as-treated assumptions, the in-hospital mortality estimates, risk ratios, and risk differences with respect to the four treatment strategies and the abovementioned group comparisons were similar to the results from the ITT analysis. The results of the sensitivity analyses which did not use multiple imputation to address missing data, led to very similar estimates, both for the ITT and PP analyses (Table S3). Another sensitivity analysis was conducted with the intrahospital SYS, ST, and PCDT treatment approaches only, which demonstrated an estimated in-hospital mortality of 46%, 30%, and 40%, respectively, for these strategies in the ITT analysis (Table S4). The Kaplan–Meier curve for treatment switch probability among patients bridged with VA-ECMO to advanced recanalization shows that the decision for subsequent intrahospital SYS, ST, or PCDT was made within the first 5 h in over 85% of cases (Figs. S2, S3). Finally, the Love plots for the IPTW analysis (Fig. S4) and the diagnostics for TMLE (Table S5) demonstrate very good covariate balance between the treatment groups. Of note, the associations (reported as Odds Ratios (OR) with 95%CI) between in-hospital mortality and the selected confounders established by multivariable logistic regression models (results not to be interpreted as causal contrasts) are presented in Table S6.

Adverse events

The overall rate of major bleeding complications was 28.8% (Table 5). Notably, major bleeding occurred in 15.0% of patients undergoing PCDT, compared to 47.6% in the VA-ECMO alone group, and 28.5% and 32.7% in the intrahospital SYS and ST group, respectively. Moreover, patients in group IV less frequently experienced

Table 1 Baseline characteristics according to treatment regimen

Characteristics	Overall (*n* = 991)	VA-ECMO alone (*n* = 126) (group I)	Intrahospital SYS (*n* = 643) (group II)	ST (*n* = 49) (group III)	PCDT (*n* = 173) (group IV)
Demographics					
Age at admission [years], median [IQR]	62.00 [52.00, 73.00]	56.35 [47.00, 64.72]	63.00 [52.15, 73.00]	61.00 [52.00, 71.00]	66.00 [56.00, 78.00]
Sex at birth [male], *n* (%)	528 (53.3)	69 (54.8)	339 (52.7)	26 (53.1)	94 (54.3)
Body mass index [kg/m^2], median [IQR]	28.11 [25.02, 32.55]	28.10 [25.50, 33.00]	28.05 [25.00, 32.14]	27.80 [24.72, 31.17]	28.70 [26.00, 32.70]
Cardiovascular risk factors					
Smoking, *n* (%)	212 (21.4)	25 (19.8)	141 (21.9)	5 (10.2)	41 (23.7)
Arterial hypertension, *n* (%)	475 (47.9)	56 (44.4)	294 (45.7)	27 (55.1)	98 (56.6)
Dyslipidemia, *n* (%)	213 (21.5)	17 (13.5)	136 (21.2)	11 (22.4)	49 (28.3)
Diabetes mellitus, *n* (%)	211 (21.3)	26 (20.6)	135 (21.0)	9 (18.4)	41 (23.7)
Medical history					
History of stroke, *n* (%)	62 (6.3)	3 (2.4)	34 (5.3)	4 (8.2)	21 (12.1)
History of cancer, *n* (%)	154 (15.5)	20 (15.9)	94 (14.6)	10 (20.4)	30 (17.3)
Chronic obstructive pulmonary disease, *n* (%)	76 (7.7)	3 (2.4)	50 (7.8)	3 (6.1)	20 (11.6)
Chronic heart failure, *n* (%)	82 (8.3)	12 (9.5)	53 (8.2)	3 (6.1)	14 (8.1)
Coronary artery disease, *n* (%)	102 (10.3)	14 (11.1)	72 (11.2)	4 (8.2)	12 (6.9)
Previous myocardial infarction, *n* (%)	70 (7.1)	10 (7.9)	49 (7.6)	2 (4.1)	9 (5.2)
Previous percutaneous coronary intervention, *n* (%)	58 (5.9)	9 (7.1)	40 (6.2)	2 (4.1)	7 (4.0)
Previous coronary artery bypass grafting, *n* (%)	16 (1.6)	3 (2.4)	10 (1.6)	2 (4.1)	1 (0.6)
Peripheral artery disease, *n* (%)	46 (4.6)	7 (5.6)	20 (3.1)	3 (6.1)	16 (9.2)
Chronic renal disease, *n* (%)	152 (15.3)	9 (7.1)	95 (14.8)	4 (8.2)	44 (25.4)
Deep vein thrombosis, *n* (%)	369 (37.2)	27 (21.4)	241 (37.5)	18 (36.7)	83 (48.0)
Morbidity at hospital admission					
Cardiac arrest, *n* (%)	544 (54.9)	109 (86.5)	362 (56.3)	23 (46.9)	50 (28.9)
Cardiopulmonary resuscitation, *n* (%)	537 (54.2)	108 (85.7)	357 (55.5)	23 (46.9)	49 (28.3)
CPR duration [min], median [IQR]	30.00 [12.00, 55.00]	45.00 [20.00, 60.00]	30.00 [10.00, 50.00]	31.00 [18.75, 56.25]	24.00 [10.00, 45.00]
VA-ECMO initiation during cardiac arrest, *n* (%)	216 (21.8)	81 (64.3)	98 (15.2)	12 (24.5)	25 (14.5)
Cardiogenic shock, *n* (%)	696 (70.2)	121 (96.0)	471 (73.3)	34 (69.4)	70 (40.5)
Arterial lactate [mmol/L], median [IQR]*	4.70 [1.89, 11.52]	12.95 [5.30, 16.00]	5.00 [2.10, 11.50]	4.35 [1.53, 10.05]	1.85 [1.30, 4.12]
pH, median [IQR]*	7.30 [7.07, 7.41]	7.10 [6.91, 7.27]	7.29 [7.07, 7.40]	7.30 [7.16, 7.40]	7.40 [7.30, 7.44]
PaO_2 [mmHg], median [IQR]*	80.00 [61.05, 113.00]	82.00 [64.00, 114.00]	77.00 [59.00, 110.00]	89.30 [65.20, 132.00]	88.35 [66.10, 116.00]
$PaCO_2$ [mmHg], median [IQR]*	42.70 [33.05, 59.00]	53.50 [41.60, 68.25]	42.00 [32.00, 59.80]	40.00 [32.50, 48.00]	42.00 [35.00, 52.00]
SAPS II at admission, median [IQR]	48.00 [32.00, 68.00]	55.00 [41.75, 72.25]	51.00 [34.00, 71.00]	38.50 [26.75, 60.00]	33.00 [26.00, 50.00]
SOFA score at admission, median [IQR]	10.00 [5.00, 14.00]	12.00 [8.50, 15.00]	10.00 [6.00, 13.00]	12.00 [6.00, 14.00]	5.00 [2.00, 10.00]

Group I includes all patients treated with VA-ECMO alone. Group II includes patients who received intrahospital SYS, regardless of prior stabilization with VA-ECMO. Group III consists of patients undergoing ST, regardless of prior VA-ECMO stabilization. Group IV includes patients treated with PCDT, regardless of prior VA-ECMO stabilization. Groups I–IV correspond to the subgroups analyzed in the intention-to-treat target trial emulation. *CPR* cardiopulmonary resuscitation, *IQR* interquartile range, *PaCO2* arterial partial pressure of carbon dioxide, *PaO2* arterial partial pressure of oxygen, *PCDT* percutaneous catheter-directed treatment, *SAPS II* simplified acute physiology score II, *SOFA score* sequential organ failure assessment score, *ST* surgical thrombectomy, *SYS* systemic thrombolysis, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation. *First value measured at hospital admission

Table 2 Diagnosis and management of high-risk acute pulmonary embolism

Characteristics	Overall (*n* = 991)	VA-ECMO alone (*n* = 126) (group I)	Intrahospital SYS (*n* = 643) (group II)	ST (*n* = 49) (group III)	PCDT (*n* = 173) (group IV)
Diagnosis modality					
PE diagnosis made on CT scan, *n* (%)	813 (82.0)	99 (78.6)	519 (80.7)	38 (77.6)	157 (90.8)
PE diagnosis made on pulmonary angiography, *n* (%)	30 (3.0)	5 (4.0)	13 (2.0)	1 (2.0)	11 (6.4)
PE diagnosis based on high clinical probability, acute RV dysfunction, and the absence of other plausible causes, in accordance with the ESC guidelines, *n* (%)	149 (15.0)	22 (17.5)	111 (17.3)	11 (22.4)	5 (2.9)
Systemic Anticoagulation					
Heparin, *n* (%)	915 (92.3)	114 (90.5)	589 (91.6)	42 (85.7)	170 (98.3)
Argatroban, *n* (%)	32 (3.2)	5 (4.0)	19 (3.0)	2 (4.1)	6 (3.5)
Management of organ dysfunction					
Mechanical ventilation, *n* (%)	696 (70.2)	125 (99.2)	451 (70.1)	41 (83.7)	79 (45.7)
PaO2/FiO2 ratio, median [IQR]*	184.29 [92.00, 280.00]	105.00 [70.00, 265.00]	193.00 [97.00, 280.00]	217.00 [116.00, 347.00]	203.00 [101.25, 271.75]
Vasopressors/Inotropes					
Epinephrine, *n* (%)	362 (36.5)	64 (50.8)	241 (37.5)	29 (59.2)	28 (16.2)
Norepinephrine, *n* (%)	728 (73.5)	107 (84.9)	493 (76.7)	43 (87.8)	85 (49.1)
Dobutamine, *n* (%)	195 (19.7)	22 (17.5)	141 (21.9)	8 (16.3)	24 (13.9)
Vasopressin, *n* (%)	85 (8.6)	10 (7.9)	62 (9.6)	5 (10.2)	8 (4.6)
Any vasoactive/inotropic medication, *n* (%)	766 (77.3)	110 (87.3)	521 (81.0)	44 (89.9)	91 (52.6)
Renal replacement therapy, *n* (%)	211 (21.3)	50 (39.7)	130 (20.2)	19 (38.8)	12 (6.9)
Mechanical circulatory support					
Venoarterial extracorporeal membrane oxygenation, *n* (%)	388 (39.2)	126 (100.0)	194 (30.2)	26 (53.1)	42 (24.3)
Peripheral cannulation, *n* (%)	375 (37.8)	123 (97.6)	189 (29.4)	21 (42.9)	42 (24.3)
Combined with Intra-aortic balloon pump, *n* (%)	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.6)
Combined with Impella, *n* (%)	11 (1.1)	9 (7.1)	1 (0.2)	1 (2.0)	0 (0.0)
Total duration of VA-ECMO treatment [h], median [IQR]	70.00 [24.00, 139.75]	57.00 [24.00, 133.50]	58.00 [24.00, 120.00]	81.00 [47.75, 144.00]	93.00 [48.00, 151.50]
Systemic thrombolysis					
Treated with systemic thrombolysis, *n* (%)	649 (65.5)	0 (0.0)	643 (100.0)	0 (0.0)	6 (3.5)
Systemic thrombolytic agent					
Alteplase, *n* (%)	621 (62.7)	0 (0.0)	615 (95.6)	0 (0.0)	6 (3.5)
Tenecteplase, *n* (%)	26 (2.6)	0 (0.0)	26 (4.0)	0 (0.0)	6 (3.5)
Urokinase, *n* (%)	2 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
Intrahospital thrombolysis, *n* (%)	649 (65.5)	0 (0.0)	643 (100.0)	0 (0.0)	6 (3.5)
Surgical thrombectomy					

Table 2 (continued)

Characteristics	Overall (*n* = 991)	VA-ECMO alone (*n* = 126) (group I)	Intrahospital SYS (*n* = 643) (group II)	ST (*n* = 49) (group III)	PCDT (*n* = 173) (group IV)
Treated with surgical thrombectomy, *n* (%)	78 (7.9)	0 (0.0)	22 (3.4)	49 (100.0)	7 (4.0)
Percutaneous catheter-directed treatment					
Treated with percutaneous catheter-directed treatment, *n* (%)	235 (23.7)	0 (0.0)	61 (9.5)	1 (2.0)	173 (100.0)
Ultrasound-assisted thrombolysis					
EKOS	93 (9.4)	0 (0.0)	16 (2.5)	0 (0.0)	77 (44.5)
Mechanical suction thrombectomy					
AngioJet	20 (2.0)	0 (0.0)	8 (1.2)	0 (0.0)	12 (6.9)
Inari	50 (5.0)	0 (0.0)	12 (1.9)	0 (0.0)	38 (22.0)
Indigo	33 (3.3)	0 (0.0)	6 (0.9)	0 (0.0)	27 (15.6)
AngioVac	18 (1.8)	0 (0.0)	7 (1.1)	1 (2.0)	10 (5.8)
Aspirex	4 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	3 (1.7)
Catheter-directed local thrombolysis					
Pigtail catheter	12 (1.2)	0 (0.0)	8 (1.2)	0 (0.0)	4 (2.3)
Multipurpose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swan-Ganz catheter	2 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.6)

Group I includes all patients treated with VA-ECMO alone. Group II includes patients who received intrahospital SYS, regardless of prior stabilization with VA-ECMO. Group III consists of patients undergoing ST, regardless of prior VA-ECMO stabilization. Group IV includes patients treated with PCDT, regardless of prior VA-ECMO stabilization. Groups I–IV correspond to the subgroups analyzed in the intention-to-treat target trial emulation. *CT* computed tomography, *ESC* European Society of Cardiology, *ICU* intensive care unit, *IQR* interquartile range, *PaO2/FiO2* arterial partial pressure of oxygen to fractional inspired oxygen, *PCDT* percutaneous catheter-directed treatment, *PE* pulmonary embolism, *RV* right ventricle, *ST* surgical thrombectomy, *SYS* systemic thrombolysis, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation. *First value measured at ICU admission

Table 3 Clinical outcomes according to treatment regimen

Characteristics	Overall (*n* = 991)	VA-ECMO alone (*n* = 126) (group I)	Intrahospital SYS (*n* = 643) (group II)	ST (*n* = 49) (group III)	PCDT (*n* = 173) (group IV)
In-hospital all-cause mortality, *n* (%)	475 (47.9)	92 (73.0)	317 (49.3)	15 (30.6)	51 (29.5)
1-Month all-cause mortality, *n* (%)	450 (45.4)	84 (66.7)	305 (47.4)	14 (28.6)	47 (27.2)
3-Month all-cause mortality, *n* (%)	482 (48.6)	94 (74.6)	322 (50.1)	15 (30.6)	51 (29.5)
1-Year all-cause mortality, *n* (%)	489 (49.3)	94 (74.6)	328 (51.0)	15 (30.6)	52 (30.1)
CPC 1 at hospital discharge	402 (40.6)	14 (11.1)	254 (39.5)	23 (46.9)	111 (64.2)
CPC 2 at hospital discharge	71 (7.2)	12 (9.5)	42 (6.5)	8 (16.3)	9 (5.2)
CPC 3 at hospital discharge	24 (2.4)	3 (2.4)	17 (2.6)	2 (4.1)	2 (1.2)
CPC 4 at hospital discharge	9 (0.9)	2 (1.6)	6 (0.9)	1 (2.0)	0 (0.0)
Total length of ICU stay [d], median [IQR]	4.00 [1.77, 11.00]	5.50 [2.00, 14.00]	4.00 [2.00, 10.00]	9.00 [4.00, 24.00]	3.00 [1.18, 7.00]
Total length of hospital stay [d], median [IQR]	11.00 [3.00, 21.00]	8.00 [2.00, 22.00]	10.00 [3.00, 20.00]	19.00 [15.00, 45.00]	10.85 [6.00, 18.00]

Group I includes all patients treated with VA-ECMO alone. Group II includes patients who received intrahospital SYS, regardless of prior stabilization with VA-ECMO. Group III consists of patients undergoing ST, regardless of prior VA-ECMO stabilization. Group IV includes patients treated with PCDT, regardless of prior VA-ECMO stabilization. Groups I–IV correspond to the subgroups analyzed in the intention-to-treat target trial emulation. *CPC* cerebral performance category, *d* days, *IQR* interquartile range, *PCDT* percutaneous catheter-directed treatment, *ST* surgical thrombectomy, *SYS* systemic thrombolysis, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation

Table 4 Target trial emulation with multiple imputation for missing data (intention-to-treat analysis): in-hospital mortality

	In-hospital mortality (G-formula)	In-hospital mortality (TMLE)	In-hospital mortality (IPTW)
VA-ECMO alone	0.57 (0.47; 0.67)	0.63 (0.49; 0.76)	0.67 (0.55; 0.79)
Intrahospital systemic thrombolysis	0.48 (0.44; 0.53)	0.48 (0.45; 0.52)	0.49 (0.45; 0.52)
Surgical thrombectomy	0.34 (0.18; 0.50)	0.36 (0.23; 0.48)	0.31 (0.18; 0.44)
Catheter-directed treatment	0.43 (0.35; 0.51)	0.53 (0.45; 0.61)	0.49 (0.41; 0.58)
	Risk ratio (G-formula)	Risk ratio (TMLE)	Risk ratio (IPTW)
Intrahospital systemic thrombolysis vs. VA-ECMO alone	0.85 (0.70; 1.03)		
Intrahospital systemic thrombolysis vs. surgical thrombectomy	1.42 (0.87; 2.32)		
Intrahospital systemic thrombolysis vs. any other treatment		1.02 (0.90; 1.16)	1.05 (0.90; 1.22)
Catheter-directed treatment vs. VA-ECMO alone	0.75 (0.58; 0.97)		
Catheter-directed treatment vs. Intrahospital systemic thrombolysis	0.89 (0.73; 1.08)		
Catheter-directed treatment vs. surgical thrombectomy	1.26 (0.75; 2.12)		
Catheter-directed treatment vs. any other treatment		1.08 (0.92; 1.27)	1.00 (0.83; 1.20)
Surgical thrombectomy vs. VA-ECMO alone	0.60 (0.36; 0.99)		
Surgical thrombectomy vs. any other treatment		0.73 (0.51; 1.05)	0.63 (0.42; 0.96)
VA-ECMO alone vs. any other treatment		1.34 (1.07; 1.67)	1.42 (1.17; 1.73)

IPTW inverse probability of treatment weighting, *TMLE* targeted maximum likelihood estimation, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation

multiorgan failure, acute kidney injury, or lower limb ischemia, and less often required transfusion of blood products compared to groups I-III, although these differences are subject to various biases considering, e.g., the usage rate of VA-ECMO.

Discussion

In the present retrospective analysis of one of the largest cohorts including patients suffering high-risk acute PE, potential causal relation between a VA-ECMO-only approach and three advanced recanalization strategies, i.e., intrahospital SYS, ST, and PCDT, and all-cause in-hospital mortality was investigated in an emulated target trial. The primary analysis suggests that managing high-risk PE with VA-ECMO alone, without subsequent recanalization, results in the highest estimated in-hospital mortality. Our data also indicates that the greatest survival benefit may be achievable with ST, while the advantage of intrahospital SYS and PCDT over VA-ECMO alone was less pronounced. Despite all methodological efforts to minimize sources of bias and confounding, our findings are hypothesis generating and will ultimately have to be confirmed in adequately powered randomized controlled trials (RCT). However, it has to be noted that the interpretation of the results from RCTs in such high-risk settings involves similar challenges with respect to treatment switches and combined strategies given that from an ethical perspective the trial design may have to allow for bail-out options if the initially assigned treatment approach proves ineffective for example.

The 2019 ESC guidelines for the diagnosis and management of acute PE recommend the use of VA-ECMO in combination with surgical thrombectomy or percutaneous catheter-based treatment options for high-risk patients presenting with refractory circulatory collapse or cardiac arrest (Class IIb, Level of evidence C) [9, 29–32]. In one of the largest case series informing this recommendation, Meneveau and colleagues reported an unadjusted 30-day all-cause mortality rate of 77.7% in patients receiving VA-ECMO alone ($n=18$), compared to 76.5% among those who underwent VA-ECMO and systemic thrombolysis ($n=17$), and 29.4% among those treated

(See figure on next page.)

Fig. 2 In-hospital mortality prediction plots adjusted for all non-modifiable risk factors according to treatment strategy. Adjusted prediction plots providing the expected probability of in-hospital death for a given treatment strategy adjusted for non-modifiable risk factors with point estimates as points and 66.66% and 95% confidence intervals given through thick and thin bars, respectively. **A** intention-to-treat analysis, **B** adjusted per-protocol analysis and **C** as-treated analysis

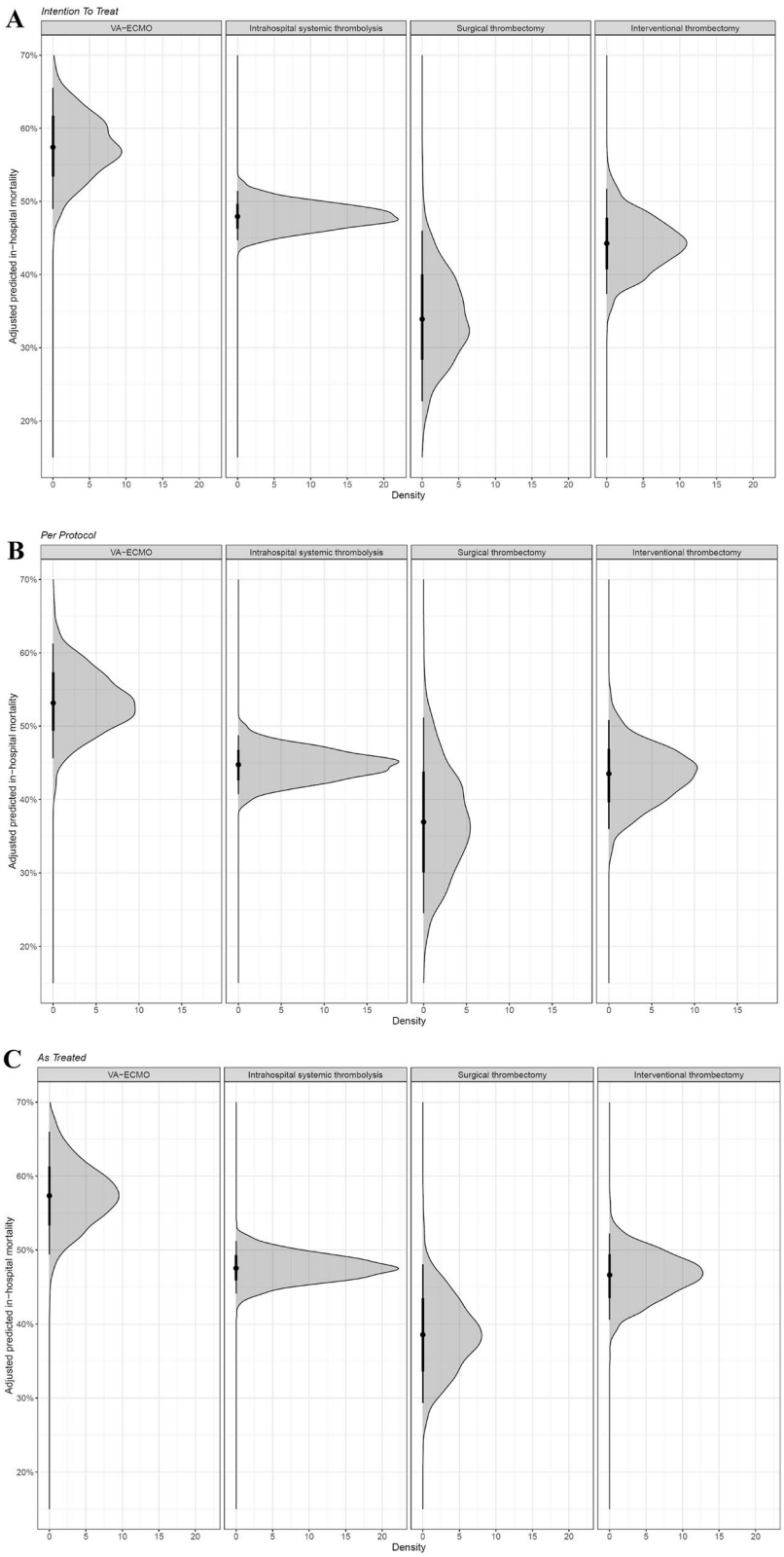

Fig. 2 (See legend on previous page.)

Table 5 Adverse events according to treatment regimen

Characteristics	Overall (*n* = 991)	VA-ECMO alone (*n* = 126 (group I)	Intrahospital SYS (*n* = 643) (group II)	ST (*n* = 49) (group III)	PCDT (*n* = 173) (group IV)
ISTH major bleeding, *n* (%)	285 (28.8)	60 (47.6)	183 (28.5)	16 (32.7)	26 (15.0)
ISTH non-major bleeding, *n* (%)	149 (15.0)	20 (15.9)	90 (14.0)	7 (14.3)	32 (18.5)
Stroke, *n* (%)	51 (5.1)	4 (3.2)	36 (5.6)	3 (6.1)	8 (4.6)
Recurrent PE, *n* (%)	45 (4.5)	6 (4.8)	26 (4.0)	2 (4.1)	11 (6.4)
Ventilator-associated pneumonia, *n* (%)	186 (18.8)	30 (23.8)	123 (19.1)	15 (30.6)	18 (10.4)
Multi-organ failure, *n* (%)	276 (27.9)	55 (43.7)	179 (27.8)	15 (30.6)	27 (15.6)
Septicemia, *n* (%)	198 (20.0)	30 (23.8)	109 (17.0)	10 (20.4)	49 (28.3)
Acute kidney injury, *n* (%)	429 (43.3)	73 (57.9)	278 (43.2)	27 (55.1)	51 (29.5)
Wound infection, *n* (%)	27 (2.7)	8 (6.3)	15 (2.3)	0 (0.0)	4 (2.3)
Lower limb ischemia, *n* (%)	55 (5.5)	17 (13.5)	29 (4.5)	3 (6.1)	6 (3.5)
Red blood cell transfusion, *n* (%)	487 (49.1)	104 (82.5)	292 (45.4)	38 (77.6)	53 (30.6)
Red blood cell transfusion [units], median [IQR]	6.00 [2.00, 12.00]	7.50 [2.00, 15.00]	6.00 [2.50, 12.00]	8.50 [3.25, 22.25]	4.00 [2.00, 8.00]
Platelet transfusions, *n* (%)	202 (20.4)	49 (38.9)	109 (17.0)	25 (51.0)	19 (11.0)
Platelet transfusions [units], median [IQR]	3.00 [2.00, 5.00]	3.00 [2.00, 5.00]	2.50 [2.00, 5.00]	3.00 [2.00, 6.00]	2.00 [2.00, 4.00]
Plasma transfusions, *n* (%)	258 (26.0)	59 (46.8)	153 (23.8)	24 (49.0)	22 (12.7)
Plasma transfusions [units], median [IQR]	5.00 [2.00, 10.00]	6.00 [4.00, 15.00]	4.00 [2.00, 9.00]	6.50 [4.00, 11.25]	4.00 [2.00, 6.00]

IQR interquartile range, *ISTH* International Society of Thombosis and Haemostasis, *PCDT* percutaneous catheter-directed treatment, *PE* pulmonary embolism, *ST* surgical thrombectomy, *SYS* systemic thrombolysis, *VA-ECMO* veno-arterial extracorporeal membrane oxygenation

with VA-ECMO and surgical thrombectomy (*n* = 17) [31]. In the present study, baseline variables including SAPS II, cardiogenic shock, and resuscitated cardiac arrest at admission suggest that VA-ECMO alone is used for the sickest patients within this high-risk population. Keeping in mind the risk of undetected confounding, the estimated in-hospital mortality after adjustment for several markers of disease severity and patient-related variables in the target trial analysis was highest in the VA-ECMO alone group compared to all other primary treatment approaches including combined strategies with VA-ECMO as a bridge to reperfusion. While the sequence, timing, and optimal complication management with such combined treatment approaches should be investigated further, our data suggests, that VA-ECMO as a bridge to recovery without subsequent recanalization may not be the most beneficial treatment strategy, unless advanced reperfusion is unavailable, contraindicated, or unsuccessful.

Systemic thrombolysis was by far the most frequently utilized first-line recanalization modality in our study population in accordance with the 2019 guideline recommendations [9]. The current class I recommendation in favor of systemic thrombolysis is mainly derived from studies that excluded high-risk patients and used heparin only for control groups [9, 17, 33, 34]. Our results suggest that intrahospital SYS regardless of other advanced therapies may translate to a reduction of in-hospital mortality in patients with high-risk PE, compared to VA-ECMO support without recanalization. The rationale for choosing this strategy over surgical or interventional recanalization was not assessed directly but could at least partially be explained by the relatively poor clinical state at baseline compared to patients managed primarily with ST or PCDT. Also, there is limited information on outcomes with respect to the combination of systemic thrombolysis with VA-ECMO, ST, or PCDT [18, 31, 35–38]. In a recent retrospective analysis of 72 high-risk PE patients supported by VA-ECMO (excluding patients who underwent prior ST or PCDT), systemic thrombolysis before VA-ECMO initiation was not associated with higher moderate-to-severe bleeding rates or mortality [38]. In the present high-risk cohort, approximately 30% of patients receiving intrahospital SYS were stabilized with VA-ECMO, and 9.5% and 3.4% underwent PCDT and ST, respectively. Although more evidence is needed to optimize such complex treatment pathways, this reflection of current clinical practice emphasizes the importance of multidisciplinary teams and tertiary centers to provide the full spectrum of advanced hemodynamic support for recanalization.

Basic prerequisites for surgical thrombectomy in the context of high-risk acute PE include availability of experienced surgical teams, general operability, absence of specific contraindications (e.g., to cardiopulmonary bypass), and hemodynamic stability [39–41]. Although surgical embolectomy was, in principle, an option at all clinical sites participating in this study, less than 5% underwent surgery as a first-line treatment strategy. This finding contrasts with the estimated survival benefit of ST over VA-ECMO alone, intrahospital SYS, and PCDT, which was one of the most consistent findings of our analyses. Patient-related factors likely influenced the infrequent decision for ST in favor of a non-invasive or a minimal-invasive primary treatment strategy. However, baseline indicators of disease severity were largely comparable between those undergoing PCDT and ST as a first-line approach. Compared to the estimated in-hospital mortality of 34% in our primary analysis, multiple previous studies focusing on ST in high-risk PE reported much lower mortality rates, although comparability between these studies is limited by differences in inclusion criteria and methodology [18, 42–44]. Nonetheless, our analysis in accordance with the 2023 AHA scientific statement on surgical management in high-risk PE suggests, that the role of ST in the management of high-risk PE is possibly underestimated in current clinical practice, and that this approach could contribute to improved survival [18, 40–43, 45].

Various percutaneous catheter-directed systems achieved market approval for PE and have been proposed for management of high-risk PE, primarily relying on data from low-risk/intermediate-risk/submassive PE populations and limited evidence in patients with hemodynamic compromise [8–10, 15, 16, 46–52]. A survival advantage attributed to minimal-invasive recanalization compared to treatment with VA-ECMO alone seems plausible, but the reasons for a potential mortality difference between a primary surgical and catheter-directed strategy remain unclear. Possible influencing factors may be the lack of experience, but also the differences in efficacy of this heterogenous group of devices. On the other hand, there are a number of potential advantages associated with catheter-directed recanalization: (I) An interventional approach offers the unique advantage of combining the diagnosis (i.e., pulmonary angiography) and treatment of PE within a single procedure. (II) Potential mobility of both PCDT devices and cardiac interventionalists may allow for rapid treatment of hemodynamically unstable patients admitted to centers without on-site availability of surgical or catheter-directed recanalization options. (III) PCDT may be associated with a lower risk of major bleeding complications, multi-organ failure, requirement of blood transfusions, and higher probability of excellent neurological outcome, although various biases may have contributed to these differences in our study [51].

Investigating these aspects further is essential to integrate catheter-directed systems together with established options of circulatory support and recanalization into adaptable treatment algorithms for high-risk patients. Given the vulnerability of this patient population and diversity of recanalization options, selecting the most promising treatment concept remains a challenging task. In fact, on-site multidisciplinary PE response teams have already been formed in many centers in the United States and Europe, with the central goal of streamlining emergency care and advanced management in these complex cases [53–55]. Further prospective investigation regarding the efficacy of specific treatment approaches and risk prediction models are urgently needed to optimize management and improve long-term outcomes of patients experiencing high-risk PE.

Limitations

Important limitations of this retrospective study are related to possible unmeasured confounding and violations of assumptions made in the statistical analyses, all of which may have influenced the results of the main target trial and secondary analyses. Uncertainty related to relatively large differences in group sizes remains, and preferences for certain treatments related to personal skills or institutional factors could have introduced additional biases. In addition, indication bias may have persisted despite adjustment for confounders by the best statistical models available and baseline variables may have been influenced by early therapeutic interventions. In order to address potential violations of statistical assumptions, we applied multiple approaches to account for missing data and varied model specifications. Overall, only few data points were missing and there were no obvious reasons as to why specific data were not captured by the centers. Therefore, we believe that the missing at random assumption required for a multiple imputation analysis was likely met. Furthermore, given the 10-year study period, it is not possible to retrospectively ensure that all treatment options were accessible without restriction for each patient at each center at all times. This is an inherent limitation of such a retrospective study. Finally, the lack of precise treatment protocols may limit the generalizability of our results, although the multicenter setup of this study should have limited center-specific biases.

Conclusion

The key findings from the presented target trial emulation suggest that advanced recanalization may improve short-term survival in patients presenting with high-risk PE compared to the use of VA-ECMO alone as a bridge

to recovery. While our findings should be interpreted as hypothesis generating, the data indicate that the role of ST in managing high-risk PE may be underestimated in current clinical practice and that this approach but also the use of novel promising catheter-directed systems could have a positive impact on outcomes.

Supplementary Information
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Declarations

Conflicts of interest
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References

1. Lehnert P, Lange T, Møller C et al (2018) Acute pulmonary embolism in a national Danish cohort: increasing incidence and decreasing mortality. Thromb Haemost 118:539–546. https://doi.org/10.1160/TH17-08-0531
2. Wendelboe AM, Raskob GE (2016) Global burden of thrombosis. Circ Res 118:1340–1347. https://doi.org/10.1161/CIRCRESAHA.115.306841
3. Centers for Disease Control and Prevention (CDC) (2012) Venous thromboembolism in adult hospitalizations - United States, 2007–2009. MMWR Morb Mortal Wkly Rep 61:401–404
4. Keller K, Hobohm L, Ebner M et al (2020) Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J 41:522–529. https://doi.org/10.1093/eurheartj/ehz236
5. Millington SJ, Aissaoui N, Bowcock E et al (2024) High and intermediate risk pulmonary embolism in the ICU. Intens Care Med 50:195–208. https://doi.org/10.1007/s00134-023-07275-6
6. Kahn SR, de Wit K (2022) Pulmonary embolism. N Engl J Med 387:45–57. https://doi.org/10.1056/NEJMcp2116489
7. Kucher N, Rossi E, De Rosa M, Goldhaber SZ (2006) Massive pulmonary embolism. Circulation 113:577–582. https://doi.org/10.1161/CIRCULATIONAHA.105.592592
8. Piazza G (2020) Advanced management of intermediate- and high-risk pulmonary embolism: JACC focus seminar. J Am Coll Cardiol 76:2117–2127. https://doi.org/10.1016/j.jacc.2020.05.028
9. Konstantinides SV, Meyer G, Becattini C et al (2019) 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. https://doi.org/10.1183/13993003.01647-2019
10. Giri J, Sista AK, Weinberg I et al (2019) 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 140:e774–e801. https://doi.org/10.1161/CIR.0000000000000707
11. Assouline B, Assouline-Reinmann M, Giraud R et al (2022) Management of high-risk pulmonary embolism: What is the place of extracorporeal membrane oxygenation? J Clin Med. https://doi.org/10.3390/jcm11164734
12. Silver MJ, Giri J, Duffy Á et al (2023) Incidence of mortality and complications in high-risk pulmonary embolism: a systematic review and meta-analysis. J Soc Cardiovasc Angiograp Intervent 2:100548. https://doi.org/10.1016/j.jscai.2022.100548
13. Helms J, Carrier M, Klok FA (2023) High-risk pulmonary embolism in the intensive care unit. Intens Care Med 49:579–582. https://doi.org/10.1007/s00134-023-07011-0
14. Lüsebrink E, Binzenhöfer L, Hering D et al (2024) Scrutinizing the role of venoarterial extracorporeal membrane oxygenation: has clinical practice outpaced the evidence? Circulation 149:1033–1052. https://doi.org/10.1161/CIRCULATIONAHA.123.067087
15. Avgerinos ED, Jaber W, Lacomis J et al (2021) Randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism: The SUNSET sPE trial. JACC Cardiovasc Interv 14:1364–1373. https://doi.org/10.1016/j.jcin.2021.04.049
16. Bashir R, Foster M, Iskander A et al (2022) Pharmacomechanical catheter-directed thrombolysis with the Bashir endovascular catheter for acute pulmonary embolism: The RESCUE study. JACC Cardiovasc Interv 15:2427–2436. https://doi.org/10.1016/j.jcin.2022.09.011
17. Marti C, John G, Konstantinides S et al (2015) Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. Eur Heart J 36:605–614. https://doi.org/10.1093/eurheartj/ehu218
18. Goldberg JB, Giri J, Kobayashi T et al (2023) Surgical management and mechanical circulatory support in high-risk pulmonary embolisms: historical context, current status, and future directions: a scientific statement from the American Heart Association. Circulation. https://doi.org/10.1161/CIR.0000000000001117
19. Capanegro J, Quinn E, Arndt M, Sherard D (2021) Successful removal of a Life-threatening PE using the INARI flow Triever device. Radiol Case Rep 16:1878–1881. https://doi.org/10.1016/j.radcr.2021.04.045
20. Lodi S, Phillips A, Lundgren J et al (2019) Effect estimates in randomized trials and observational studies: comparing apples with apples. Am J Epidemiol 188:1569–1577. https://doi.org/10.1093/aje/kwz100
21. Hernan M, Robins J (2024) Causal Inference: What If. Chapman & Hall/CRC, Boca Raton
22. Hernán MA, Robins JM (2017) Per-protocol analyses of pragmatic trials. N Engl J Med 377:1391–1398. https://doi.org/10.1056/NEJMsm1605385
23. Kümpel H, Hoffmann S A formal framework for generalized reporting methods in parametric settings
24. Honaker J, King G, Blackwell M (2011) Amelia II: a program for missing data. J Stat Softw https://doi.org/10.18637/jss.v045.i07
25. Rafi Z, Greenland S (2020) Semantic and cognitive tools to aid statistical science: replace confidence and significance by compatibility and surprise. BMC Med Res Methodol 20:244. https://doi.org/10.1186/s12874-020-01105-9
26. Schomaker M, Heumann C (2018) Bootstrap inference when using multiple imputation. Stat Med 37:2252–2266. https://doi.org/10.1002/sim.7654
27. Luque-Fernandez MA, Schomaker M, Rachet B, Schnitzer ME (2018) Targeted maximum likelihood estimation for a binary treatment: a tutorial. Stat Med 37:2530–2546. https://doi.org/10.1002/sim.7628

28. Mark J. van der Laan, Sherri Rose (2011) Targeted learning: causal inference for observational and experimental data
29. Stadlbauer A, Philipp A, Blecha S et al (2021) Long-term follow-up and quality of life in patients receiving extracorporeal membrane oxygenation for pulmonary embolism and cardiogenic shock. Ann Intens Care 11:181. https://doi.org/10.1186/s13613-021-00975-6
30. Corsi F, Lebreton G, Bréchot N et al (2017) Life-threatening massive pulmonary embolism rescued by venoarterial-extracorporeal membrane oxygenation. Crit Care 21:76. https://doi.org/10.1186/s13054-017-1655-8
31. Meneveau N, Guillon B, Planquette B et al (2018) Outcomes after extracorporeal membrane oxygenation for the treatment of high-risk pulmonary embolism: a multicentre series of 52 cases. Eur Heart J 39:4196–4204. https://doi.org/10.1093/eurheartj/ehy464
32. Swol J, Buchwald D, Strauch J, Schildhauer TA (2016) Extracorporeal life support (ECLS) for cardiopulmonary resuscitation (CPR) with pulmonary embolism in surgical patients - a case series. Perfusion 31:54–59. https://doi.org/10.1177/0267659115583682
33. Konstantinides S, Geibel A, Heusel G et al (2002) Heparin plus Alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 347:1143–1150. https://doi.org/10.1056/NEJMoa021274
34. Meyer G, Vicaut E, Danays T et al (2014) Fibrinolysis for patients with intermediate-risk pulmonary embolism. N Engl J Med 370:1402–1411. https://doi.org/10.1056/NEJMoa1302097
35. Giraud R, Laurencet M, Assouline B et al (2021) Can VA-ECMO be used as an adequate treatment in massive pulmonary embolism? J Clin Med 10:3376. https://doi.org/10.3390/jcm10153376
36. Boey JJE, Dhundi U, Ling RR et al (2023) Extracorporeal membrane oxygenation for pulmonary embolism: a systematic review and meta-analysis. J Clin Med 13:64. https://doi.org/10.3390/jcm13010064
37. Lin T-W, Tsai M-T, Hu Y-N et al (2021) Simultaneous thrombolysis and extracorporeal membrane oxygenation for acute massive pulmonary emboli. Ann Thorac Surg 111:923–929. https://doi.org/10.1016/j.athoracsur.2020.05.155
38. Levy D, Saura O, Passarelli MT et al (2024) Thrombolysis before venoarterial ECMO for high-risk pulmonary embolism: a retrospective cohort study. Intensive Care Med 50:1287–1297. https://doi.org/10.1007/s00134-024-07501-9
39. Kolkailah AA, Hirji S, Piazza G et al (2018) Surgical pulmonary embolectomy and catheter-directed thrombolysis for treatment of submassive pulmonary embolism. J Card Surg 33:252–259. https://doi.org/10.1111/jocs.13576
40. Neely RC, Byrne JG, Gosev I, et al (2015) Surgical embolectomy for acute massive and submassive pulmonary embolism in a series of 115 patients. Ann Thorac Surg 100:1245–51; discussion 1251–2. https://doi.org/10.1016/j.athoracsur.2015.03.111
41. Ius F, Hoeper MM, Fegbeutel C et al (2019) Extracorporeal membrane oxygenation and surgical embolectomy for high-risk pulmonary embolism. Eur Respir J. https://doi.org/10.1183/13993003.01773-2018
42. Goldberg JB, Spevack DM, Ahsan S et al (2020) Survival and right ventricular function after surgical management of acute pulmonary embolism. J Am Coll Cardiol 76:903–911. https://doi.org/10.1016/j.jacc.2020.06.065
43. Keeling WB, Sundt T, Leacche M et al (2016) Outcomes after surgical pulmonary embolectomy for acute pulmonary embolus: a multi-institutional study. Ann Thorac Surg 102:1498–1502. https://doi.org/10.1016/j.athoracsur.2016.05.004
44. Pasrija C, Shah A, George P et al (2018) Triage and optimization: a new paradigm in the treatment of massive pulmonary embolism. J Thorac Cardiovasc Surg 156:672–681. https://doi.org/10.1016/j.jtcvs.2018.02.107
45. QiMin W, LiangWan C, DaoZhong C et al (2020) Clinical outcomes of acute pulmonary embolectomy as the first-line treatment for massive and submassive pulmonary embolism: a single-centre study in China. J Cardiothorac Surg 15:321. https://doi.org/10.1186/s13019-020-01364-z
46. Piazza G, Hohlfelder B, Jaff MR et al (2015) 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 8:1382–1392. https://doi.org/10.1016/j.jcin.2015.04.020
47. Kucher N, Boekstegers P, Müller OJ et al (2014) Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 129:479–486. https://doi.org/10.1161/CIRCULATIONAHA.113.005544
48. Tu T, Toma C, Tapson VF et al (2019) A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism. JACC Cardiovasc Interv 12:859–869. https://doi.org/10.1016/j.jcin.2018.12.022
49. Stępniewski J, Kopeć G, Musiałek P et al (2021) 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 141:133–139. https://doi.org/10.1016/j.amjcard.2020.11.004
50. Kucher N, Ouda A, Voci D et al (2023) Percutaneous large-bore aspiration embolectomy with veno-arterial extracorporal membrane oxygenation support or standby in patients with high-risk pulmonary embolism and contraindications to thrombolysis: a preliminary single centre experience. Eur Heart J Acute Cardiovasc Care 12:232–236. https://doi.org/10.1093/ehjacc/zuad014
51. Silver MJ, Gibson CM, Giri J et al (2023) Outcomes in high-risk pulmonary embolism patients undergoing flow Triever mechanical thrombectomy or other contemporary therapies: results from the FLAME Study. Circ Cardiovasc Interv 16:e013406. https://doi.org/10.1161/CIRCINTERVENTIONS.123.013406
52. Luedemann WM, Zickler D, Kruse J et al (2023) Percutaneous large-bore pulmonary thrombectomy with the flow Triever device: initial experience in intermediate-high and high-risk patients. Cardiovasc Intervent Radiol 46:35–42. https://doi.org/10.1007/s00270-022-03266-0
53. Dudzinski DM, Piazza G (2016) Multidisciplinary pulmonary embolism response teams. Circulation 133:98–103. https://doi.org/10.1161/CIRCULATIONAHA.115.015086
54. Sagoschen I, Scibior B, Farmakis IT et al (2024) A multidisciplinary pulmonary embolism response team (PERT): first experience from a single center in Germany. Clin Res Cardiol 113:581–590. https://doi.org/10.1007/s00392-023-02364-4
55. Lüsebrink E, Binzenhöfer L, Adamo M et al (2024) Cardiogenic shock. Lancet 404:2006–2020. https://doi.org/10.1016/S0140-6736(24)01818-X