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Editorial

Endovascular Therapies for Pulmonary Embolism: A Landscape of Uncertainties and Opportunities

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Acute pulmonary embolism (PE) is a leading preventable cause of in-hospital death and the third most common cause of vascular death in the United States.[1] PE events range from incidental defects found on imaging studies for other purposes to severe illness with circulatory collapse. Among those with hemodynamic stability, patients who present with imaging evidence of right ventricular dysfunction and/or elevated cardiac biomarkers (ie, intermediate-risk PE) have a higher risk for decompensation or death compared with those without.[2] Although systemic fibrinolysis is effective, it is not the standard treatment for intermediate-risk PE since the benefits are small and offset by major and intracranial hemorrhage (ICH) risk.[2] Among patients with hemodynamic instability (ie, high-risk PE), systemic fibrinolysis is the standard of care in many patients; however, it may be compounded by contraindications or other complexities in care.[1] Data from routine practice indicates underutilization of reperfusion in many patients with high-risk PE.[3] In this context, alternative therapies that can offer safe and effective reperfusion are needed.

Endovascular therapies for PE arose as promising technologies for this specific group of patients.[4] These therapies include catheter-directed thrombolysis, ultrasound-assisted catheter-directed thrombolysis (USCDT), and various percutaneous thrombectomy tools. Although showing promising results in reducing right ventricular dysfunction and hemodynamic compromise improvement in small randomized controlled trials (RCT) and registries, these therapies have not been compared with either standard anticoagulation or systemic fibrinolysis in adequately powered clinical outcomes trials. Professional societies do not recommend these therapies as an upfront treatment for patients with intermediate-risk PE.[2,5]

In this issue of *JSCAI*, the REAL-PE investigators report the short-term clinical outcomes of patients with PE treated with USCDT or mechanical thrombectomy (MT).[6] The authors analyzed data from an electronic health record-based platform, encompassing 83 million patients to identify those treated with USCDT or MT for PE. Baseline characteristics, laboratory test results, and in-hospital mortality were extracted through specific codes from standard ontologies. The authors modeled 2 bleeding definitions: the International Society on Thrombosis and Haemostasis (ISTH) and the Bleeding Academic Research Consortium (BARC) 3b, which required codes for major bleeding, plus a decrease in hemoglobin concentration of $\geq$2 g/dL,[7] or $\geq$5 g/dL decrease in hemoglobin regardless if they required blood transfusion.[8] They also explored ICH by using codes. The authors analyzed outcomes in 2 cohorts depending on the date in which the index procedure was performed: primary analysis (January 2009 to May 2023) and contemporary analysis (January 2018 to May 2023).

Among the 83,612,413 patients with available data, 535,567 (0.6%) had a diagnosis of PE. In the primary analysis, 2259 (0.4%) patients (n = 1577 USCDT, n = 682 MT) met the selection criteria, and 1798 (0.3%) (n = 1137 USCDT, n = 661 MT) met the selection criteria for the contemporary analysis. In the primary analysis, a larger proportion of patients were female, aged $\geq$60 y, or had a cancer diagnosis in MT-treated compared with the USCDT cohort. In both primary and contemporary analyses, there were no differences in in-hospital mortality between the USCDT-treated and MT-treated cohorts (primary: 2.6% vs. 3.7%; $P = .167$ and contemporary: 2.9% vs. 3.5%; $P = .497$), or in 30-d all-cause readmission rates. In both analyses, the MT-treated cohort had a higher rate of blood transfusion at 7 d, ISTH-modeled, as well as BARC 3b-modeled major bleeding (primary: 11.8% vs. 15.4%; $P < .001$ and contemporary: 10.6% vs. 15.4%; $P < .001$). The authors conducted a multivariable analysis of variables associated with major bleeding. In both analyses, the use of MT was associated with a higher risk of ISTH-modeled (primary: odds ratio [OR], 1.37; 95% CI, 1.10-1.74; and contemporary: OR, 1.61; 95% CI, 1.23-2.10) and BARC 3b-modeled major bleeding (primary: OR, 1.23; 95% CI, 0.96-1.58; and contemporary: OR, 1.76; 95% CI, 1.40-2.22). Although there was no difference in the rate of ischemic stroke between the MT-treated and USCDT-treated cohorts, the study reported a higher rate of ICH in the MT-treated cohort compared with the USCDT cohort (primary: 0.3% vs. 1.3%; $P = .005$ and contemporary: 0.4% vs. 1.4%; $P < .015$).

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The REAL-PE investigators should be commended for this investigation, which provides insight into a clinically relevant topic. Strengths of the study include the large sample size and the comparison of 2 devices frequently used in clinical practice, with anticipation for results from an ongoing randomized trial, but no current high-quality data on head-to-head comparison.[9] The comparative mortality and readmission rates are helpful additions to the literature. Blood loss with MT is also known in the literature, and these data provide additional evidence from a large-scale study. Observational data are also helpful in providing routine practice insights that may complement findings from clinical trials. That said, this analysis warrants further insights. Patients in the MT-treated cohort were older, had a higher frequency of cancer-associated PE, and had lower use of prior direct oral anticoagulants. Indeed, prior studies have reported that patients with cancer-associated PE exhibit worse clinical outcomes than those with noncancer-associated PE.[10] Notably, age and cancer are important predictors of bleeding and cerebrovascular events. Moreover, to our knowledge, no major prior study, including prospective registries or those based on chart review, has reported a potential safety signal for ICH with MT.[11,12] The mechanism proposed by the authors for such a large between-group difference in ICH, while not implausible, is also improbable. Research using administrative claims codes (such as International Classification of Diseases codes) would benefit from validation of the approach not only for the intended disease condition (PE)[13] but also for that of outcomes (such as ICH in this case) against adjudication of patient-level records by independent physicians. Moreover, it should be highlighted that the use of MT in clinical practice before 2018 was marginal.

Table 1[14-23] summarizes selected clinical outcomes of recent studies assessing the outcomes of different endovascular therapies, including USCDT and MT. Although the all-cause death rate of the REAL-PE study appears similar to prior studies, the rates of bleeding and transfusions are remarkably higher than in prior studies using the devices. Notably, the methodology used for outcome ascertainment (through codes) in the REAL-PE study differs substantially from the prior studies that used clinical data, in some cases with clinical event committees for event adjudication. A prior study has suggested that claims data has a good agreement compared to event adjudication committees for identifying deaths but poor agreement with high specificity for bleeding and stroke.[24]

Blood loss volume is a concern in thrombectomy procedures with a large-bore device; however, the levels of estimated hemoglobin decrease found in REAL-PE are inconsistent with previous reports with the same device.[17,22] The estimated average blood loss in a few recent studies ranged between 220 to 300 mL.[11,12] Recently, a blood return system was introduced, which might be associated with lower estimated blood loss. In addition, in assessing the association between therapies and bleeding, or with ICH, the authors did not assess (or report in the main text) the findings for USCDT. Finally, adjusting for clustering of observations, which may correlate with center-level expertise or clustering of other risk factors or unmeasured confounders, would be helpful in multicenter observational comparative effectiveness studies.

Future observational comparative effectiveness studies can also include a cohort of patients with PE who are treated with anticoagulation monotherapy as a point of reference. Such analyses can complement the findings from completed and ongoing RCT.

The landscape of endovascular therapies for PE remains full of uncertainties, as their role compared to systemic thrombolysis has yet to be adequately tested, representing the pivotal clinical question that needs to be urgently answered. To date, differences between the performance of these devices represent a very interesting but secondary topic of discussion; however, whenever there is a challenge, there is also an opportunity to face it. Currently, there are several ongoing RCT (NCT04790370, NCT05591118, NCT05111613, NCT06055920, and NCT04088292) assessing the role of endovascular therapies for PE treatment. Finally, we need to do better at risk stratification for patients,

Table 1. Outcomes in prior prospective studies of endovascular therapies for pulmonary embolism.

Study	Methodology	All-cause death	Intracranial bleeding	Major bleeding	Blood transfusions	Length of stay (d)
ULTIMA,[14] intermediate-risk, 2013 (n = 59)	RCT comparing USCDT vs. heparin. Primary outcome: RV/LV ratio at 24 h. Clinical outcomes at 90 d	USCDT: 0	USCDT: 0	USCDT: 0	NA	NA
SEATTLE II,[15] intermediate and high-risk, 2015 (n = 150)	Single-arm, multicenter study describing safety and efficacy of USCDT	In-hospital: 2% 30 d: 2.7%	In-hospital: 0	30 d: 10%	NA	8.8 ± 5
OPTALYSE,[16] intermediate-risk, 2018 (n = 100)	RCT comparing 4 USCDT regimens. Primary outcome: RV/LV ratio at 48 h	30 d: 1% 1 y: 2%	72 h: 1%	72 h: 4%	NA	NA
FLARE,[17] intermediate-risk, 2019 (n = 106)	Single-arm, multicenter study describing safety and efficacy of large-bore MT	48 h: 0%	48 h: 0	48 h: 0.9%	NA	4.1 ± 3.5
EXTRACT-PE,[18] intermediate-risk, 2021 (n = 119)	Single-arm, multicenter study describing the outcomes of aspiration thrombectomy	30 d: 2.5%	48 h: 0	48 h: 1.7%	48 h: 2.5%	NA
SUNSET sPE,[19] intermediate-risk, 2021 (n = 81)	RCT comparing USCDT vs. CDT. Primary outcome: clearance of pulmonary thrombus at 48 h	48 h USCDT: 2.5% CDT: 0	48 h USCDT: 2.5% CDT: 0	48 h USCDT: 5% CDT: 0	48 h USCDT: 2.5% CDT: 0	USCDT: 7.7 ± 8.7 CDT: 4.6 ± 1.8
Kroupa et al,[20] intermediate-risk, 2022 (n = 81)	RCT comparing CDT vs. heparin. Primary endpoint: improvement in RV function	24 h CDT: 0 Heparin: 0	24 h CDT: 0 Heparin: 0	24 h CDT: 0 Heparin: 0	NA	CDT: 7.9 ± 2.7 Heparin: 9.7 ± 4.1
CANARY,[21] intermediate-risk, 2022 (n = 94)	RCT comparing CDT vs. heparin. Primary endpoint: echocardiographic RV/LV ratio >0.9 at 90 d	90 d CDT: 0 Heparin: 6.5%	90 d CDT: 0 Heparin: 0	90 d CDT: 2.1% Heparin: 0	NA	CDT: 6 (5-8) Heparin: 6 (5-8)
FLASH,[22] intermediate and high-risk, 2023 (n = 800)	Single-arm, multicenter study describing the outcomes with large-bore MT	48 h: 0.3% 30 d: 0.8%	48 h: 0	48 h: 1.4%	48 h: 0.25%	3
FLAME,[23] high-risk, 2023 (n = 115)	Parallel-arm, multicenter nonrandomized study describing the outcomes with large-bore MT vs. other therapies (the study was nonrandomized and unadjusted)	MT in-hospital: 1.9%	MT in-hospital: 0	MT in-hospital: 11.3%	NA	7 (3-12)

Numbers expressed as %, mean ± SD, or median (IQR).
CDT, catheter-directed thrombolysis; LV, left ventricle; MT, mechanical thrombectomy; NA, not available; RCT, randomized controlled trial; RV, right ventricle; USCDT, ultrasound-assisted catheter-directed thrombolysis.

likely beyond the few traditional risk factors or the current prognostication scheme. Once the results of the ongoing RCT accrue, better phenotyping may help assign patients to therapies from which they may derive the most net benefit.[25] Overall, these high-quality pieces of evidence will move the field forward and improve patient care.

Declaration of competing interest

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