Journal of the Society for Cardiovascular Angiography & Interventions 3 (2024) 101124

JSCAI

The official journal of the Society for Cardiovascular Angiography & Interventions

Original Research

Mechanical Thrombectomy for High-Risk Pulmonary Embolism: Insights From the US Cohort of the FLASH Registry

James M. Horowitz, MD [a,*], Wissam A. Jaber, MD [b], Brian Stegman, MD [c], Michael Rosenberg, MD [d], Christina Fanola, MD, MSc [e], Ambarish P. Bhat, MD [f], Sreedevi Gondi, MD [g], Jordan Castle, MD [h], Mustafa Ahmed, MD [i], Michael A. Brown, MD [j], Rohit Amin, MD [k], Mohannad Bisharat, MD [l], Paul Butros, MD [m,n], Aaron DuCoffe, MD [m], Michael Savin, MD [o], Jeffrey S. Pollak, MD [p], Mitchell D. Weinberg, MD, MBA [q], Daniel Brancheau, DO [r], Catalin Toma, MD [s]; for the FLASH Investigators

[a] *Division of Cardiology, Department of Medicine, NYU Grossman School of Medicine, New York, New York;* [b] *Emory University Hospital, Atlanta, Georgia;* [c] *CentraCare Heart and Vascular Center, St. Cloud, Minnesota;* [d] *Department of Radiology, University of Minnesota, Minneapolis, Minnesota;* [e] *Department of Cardiology, University of Minnesota, Minneapolis, Minnesota;* [f] *Section of Vascular and Interventional Radiology, Department of Radiology, University of Missouri, Columbia, Missouri;* [g] *Baptist Health, Louisville, Kentucky;* [h] *Inland Imaging, Providence Sacred Heart, Spokane, Washington;* [i] *UAB Division of Cardiovascular Disease, Birmingham, Alabama;* [j] *Missouri Cardiovascular Specialists, Columbia, Missouri;* [k] *Ascension Sacred Heart Hospital Pensacola, Pensacola, Florida;* [l] *HCA Florida Memorial Hospital Jacksonville, Jacksonville, Florida;* [m] *Inova Health System, Fairfax, Virginia;* [n] *Southpark Vascular Center, Colonial Heights, Virginia;* [o] *Section of Interventional Radiology, Department of Radiology, Corewell Health William Beaumont University Hospital, Royal Oak, Michigan;* [p] *Department of Radiology and Biomedical Imaging, Yale University, New Haven, Connecticut;* [q] *Department of Cardiology, Northwell Health, Zucker School of Medicine at Hofstra/Northwell, Staten Island University Hospital, Staten Island, New York;* [r] *Ascension Genesys Hospital, Grand Blanc, Michigan;* [s] *University of Pittsburgh Medical Center Heart and Vascular Institute, Pittsburgh, Pennsylvania*

ABSTRACT

Background: Acute mortality for high-risk, or massive, pulmonary embolism (PE) is almost 30% even when treated using advanced therapies. This analysis assessed the safety and effectiveness of mechanical thrombectomy (MT) for high-risk PE.

Methods: The prospective, multicenter FlowTriever All-comer Registry for Patient Safety and Hemodynamics (FLASH) study is designed to evaluate real-world PE patient outcomes after MT with the FlowTriever System (Inari Medical). In this study, acute outcomes through 30 days were evaluated for the subset of patients with high-risk PE as determined by the sites and following European Society of Cardiology guidelines. An independent medical monitor adjudicated adverse events (AEs), including major AEs: device-related mortality, major bleeding, or intraprocedural device-related or procedure-related AEs.

Results: Of the 799 patients in the US cohort, 63 (7.9%) were diagnosed with high-risk PE; 30 (47.6%) patients showed a systolic blood pressure <90 mm Hg, 29 (46.0%) required vasopressors, and 4 (6.3%) experienced cardiac arrest. The mean age of patients with high-risk PE was 59.4 ± 15.6 years, and 34 (54.0%) were women. At baseline, 45 (72.6%) patients were tachycardic, 18 (54.5%) showed elevated lactate levels of ≥2.5 mM, and 21 (42.9%) demonstrated depressed cardiac index of <2 L/min/m^2. Immediately after MT, heart rate improved to 93.5 ± 17.9 bpm. Twenty-five (42.4%) patients did not require an overnight stay in the intensive care unit, and no mortalities or major AEs occurred through 48 hours. Moreover, no mortalities occurred in 61 (96.8%) patients followed up through the 30-day visit.

Conclusions: In this cohort of 63 patients with high-risk PE, MT was safe and effective, with no acute mortalities reported. Further prospective data are needed in this population.

Abbreviations: CDT, catheter-directed thrombolysis; CI, cardiac index; MAE, major adverse event; mMRC, Modified Medical Research Council; mPAP, mean pulmonary artery pressure; MT, mechanical thrombectomy; PE, pulmonary embolism; SAE, serious adverse event.

Keywords: aspiration thrombectomy; embolectomy; mechanical thrombectomy; percutaneous aspiration thrombectomy; pulmonary embolism.

* Corresponding author: jameshorowitz@gmail.com (J.M. Horowitz).

https://doi.org/10.1016/j.jscai.2023.101124
Received 12 May 2023; Received in revised form 26 July 2023; Accepted 2 August 2023
Available online 31 October 2023

Introduction

The defining feature of high-risk, or massive, pulmonary embolism (PE) is hemodynamic instability, which warrants rapid reperfusion therapy. When treated solely using anticoagulation (AC), hemodynamic collapse and death occur in ~50% of patients with high-risk PE.[1–3] In a meta-analysis of PE literature, which included 4 studies enrolling high-risk patients, systemic fibrinolytics were associated with a significant reduction in early mortality compared with AC alone (pooled odds ratio, 0.59; 95% CI, 0.36-0.96; $P = .03$), and systemic lysis in conjunction with AC is the current guideline-recommended treatment for high-risk disease.[4–6] Nevertheless, the rates of major bleeding and intracranial hemorrhage in that meta-analysis were approximately 10% and 2%, respectively, and patients may demonstrate contraindications, or fail to respond, to systemic fibrinolytics. In addition, even after systemic lysis or other interventional therapies, contemporary early mortality for patients with high-risk PE remains ~30%.[1,3,7] Consequently, catheter-directed approaches, such as lower-dose catheter-directed thrombolysis (CDT) and mechanical thrombectomy (MT), are playing expanding roles in the treatment of patients with high-risk PE.

Several clinical trials of CDT and MT in the context of PE have been performed in recent years. However, patients with high-risk PE have been excluded from many of the largest studies of catheter-directed reperfusion treatments. For example, the EXTRACT-PE and FLARE investigational device exemption trials and the OPTALYSE and SUNSET sPE randomized trials enrolled patients with intermediate-risk PE only.[8–11] Furthermore, high-risk disease will not be investigated in many of the currently active interventional PE randomized controlled trials, such as HI-PEITHO, PEERLESS, STORM-PE, and PE-TRACT. Thus, limited data exist regarding interventional catheter-directed therapies for high-risk PE, with little forthcoming evidence expected. One notable exception is the FlowTriever for Acute Massive PE (FLAME) study, which is designed to evaluate high-risk PE treatments.

Unlike the aforementioned studies, the FlowTriever All-comer Registry for Patient Safety and Hemodynamics (FLASH) is enrolling patients with either intermediate-risk or high-risk PE. Previous publications of FLASH registry data, including the most recent encompassing acute outcomes for 799 patients in the fully enrolled US cohort, reported results without stratification by disease severity.[12,13] To help address the present evidence gap for MT outcomes specific to high-risk disease, the objective of this analysis was to describe the characteristics and acute outcomes of patients with high-risk PE only in the full US cohort of FLASH.

Materials and methods

Study design

The prospective, multicenter, all-comer FLASH registry (ClinicalTrials.gov identifier: NCT03761173) is designed to assess the outcomes of real-world PE patients treated with MT using the FlowTriever System (Inari Medical). The FLASH registry design has been published previously.[12] Before patient enrollment, investigators at each site obtained approval from their institutional review board, and all patients provided written informed consent before the procedure or shortly after the procedure.

Key inclusion criteria consist of age ≥18 years and acute intermediate-risk or high-risk PE based on current European Society of Cardiology (ESC) guidelines.[5] Diagnosis of high-risk PE was made by each participating site and was based on clinician determination of hemodynamic instability according to ESC guideline definitions included in the study protocol, which requires 1 of the following presentations: cardiac arrest with cardiopulmonary resuscitation, obstructive shock with systolic blood pressure (SBP) <90 mm Hg or vasopressors required to achieve SBP of ≥90 mm Hg and evidence of end-organ hypoperfusion, or persistent hypotension with SBP <90 mm Hg or SBP drop ≥40 mm Hg lasting longer than 15 minutes not caused by new-onset arrhythmia, hypovolemia, or sepsis.[5] Although all patients were diagnosed with high-risk PE at the site level per these protocolized criteria, the study database did not elicit or capture which specific criterion was used to arrive at this diagnosis for each patient. Key exclusion criteria include life expectancy <30 days and inability to receive AC. Patients were not excluded for fibrinolytic contraindications as defined in current American College of Chest Physicians guidelines.[14] The treating physician or local PE response team determined patient eligibility for enrollment and treatment using MT. This report aimed to present acute effectiveness and safety outcomes, including results from 48-hour and 30-day follow-up evaluations, for all high-risk patients in the full US cohort of the FLASH registry.

Primary end point

The primary end point is a composite of major adverse events (MAEs) within 48 hours of MT, consisting of device-related mortality, major bleeding, and intraprocedural device-related or procedure-related adverse events (AEs). An independent, third-party medical monitor adjudicated components of the composite primary end point and relatedness to the study device, procedure, or both. Device-related or procedure-related AEs were defined as device-related pulmonary vascular injury, device-related cardiac injury, and hemodynamic or respiratory worsening meeting specific thresholds. The major bleed definition was similar to Bleeding Academic Research Consortium (BARC) type 3b bleeding or higher: symptomatic bleeding in a critical organ or area or bleeding that led to a hemoglobin decrease of ≥5 g/dL, transfusion of ≥2 units of blood products, or fatality.[15]

Secondary end points and additional data collected

The secondary safety end points are the individual elements of the composite primary end point; major access site complications requiring open surgical repair, endovascular intervention, or blood transfusion; and device-related serious adverse events (SAEs) per ISO 14155.

The secondary effectiveness end points include vital sign and hemodynamic improvements during the procedure and echocardiographically assessed changes in the right ventricle/left ventricle (RV/LV) ratio at the 30-day follow-up. Echocardiography was also performed at the 48-hour follow-up in some patients. Either computed tomography pulmonary angiography (CTPA) or echocardiography could be used to assess RV/LV ratio at baseline, but follow-up assessments were most often performed using echocardiography to minimize radiation and contrast exposure. Therefore, baseline RV/LV ratio is presented as a composite of CTPA and echocardiography, prioritizing CTPA if data using both techniques were available. Analysis of RV/LV ratio change over time was performed using only paired echocardiographic results to preclude bias from differences in imaging methods. Echocardiographic measurements of RV function and systolic pressure were also collected at baseline and follow-ups using the standard practice at each site.

Further in-hospital data were collected, such as thrombectomy time from Triever catheter vasculature entry until final removal, estimated blood loss, length of postprocedural hospital and intensive care unit (ICU) stay, and patient-reported dyspnea and quality-of-life measurements. Dyspnea was assessed at baseline and at 48-hour and 30-day follow-ups using the Modified Medical Research Council (mMRC) dyspnea scale that ranges from 0 to 4, with scores ≥3 indicating severe dyspnea. Pulmonary Embolism Quality-of-Life questionnaires were used to quantify patient-reported quality of life and were collected only at 48-hour and 30-day follow-up visits owing to the emergent nature of high-risk PE.

Hemodynamic calculations

Per protocol, right heart catheterization was used for invasive hemodynamic assessment before Triever catheter insertion and ≥5 minutes after Triever catheter removal. Hemodynamic assessments were performed before and after thrombectomy and include direct measurement of mean right atrial pressure, mean pulmonary artery pressure (mPAP), and systolic pulmonary artery pressure (sPAP). Derived measurements of total pulmonary vascular resistance (TPVR) and cardiac index (CI) were also collected. Cardiac output (CO) was estimated using the indirect Fick method and divided by body surface area to calculate CI. To calculate TPVR, mPAP was divided by CO.

Data analysis

Categorical data are presented as counts with percentages, and continuous data are reported as mean with standard deviation or median with interquartile range (IQR). Box plots present median values bounded by the IQR. Upper whiskers extend to the value closest to but not greater than the third quartile plus 1.5 × IQR, and lower whiskers extend to the value closest to but not less than the first quartile minus 1.5 × IQR. Values beyond this range are considered outliers and indicated as points. Wilcoxon signed-rank tests and McNemar tests, or McNemar-Bowker tests, were used to analyze changes from baseline using available paired values for continuous and categorical variables, respectively. A 2-sided *P* value of .05 was used to determine statistical significance. Analyses were performed using SAS 9.4 (SAS Institute) and R version 4.1.2.[16]

Results

Demographic characteristics and clinical presentation

The FLASH registry enrolled 800 patients at 50 sites in the United States from December 2018 to December 2021. In the analysis population of 799 patients, 63 (7.9%) were diagnosed with high-risk PE. This high-risk PE cohort is the basis for the current analysis. Owing to the acuity of high-risk PE, 37 (58.7%) patients consented to participate in the registry on a day after the procedure, with a median consent latency of 1.0 (1.0-2.0) days. Baseline characteristics are summarized in Table 1. The mean age was 59.4 ± 15.6 years, 34 (54.0%) patients were women, 34 (54.8%) were diagnosed with concomitant deep vein thrombosis, and 16 (25.4%) demonstrated contraindications for fibrinolytics. Eight (12.9%) patients had failed previous therapy for the index PE, including 3 who received systemic fibrinolytics and 1 who underwent MT with another device.

Multiple physiologic metrics were indicative of high-risk disease, including markers of hemodynamic instability: 4 (6.3%) patients experienced cardiac arrest requiring cardiopulmonary resuscitation; 29 (46.0%) were on vasopressors before the procedure, including 21 (33.3%) who were on vasopressors at arrival; and 30 (47.6%) showed SBP of <90 mm Hg. The lowest SBP at any point before MT was 90.8 ± 17.8 mm Hg, which was likely affected by one-third of the patients having received vasopressors before presenting to the study hospital.

Additional indicators of severe disease were demonstrated. The in-hospital average heart rate before MT was 106.6 ± 17.0 bpm, with 45 (72.6%) patients being tachycardic (≥100 bpm) at presentation and the highest prethrombectomy heart rate being 120.5 ± 20.8 bpm. Moreover, 18 (54.5%) patients demonstrated elevated lactate concentration of ≥2.5 mM. During prethrombectomy invasive hemodynamic assessment, 21 (42.9%) patients exhibited reduced CI of <2 L/min/m^2, an indicator of possible cardiogenic shock. Furthermore, 6 (10.0%) patients were intubated before MT.

Table 1. Demographic characteristics and clinical presentation.

	Values	N
Demographics and medical history		
Age, y	59.4 ± 15.6	63
Women	34 (54.0)	63
Body mass index, kg/m^2	33.9 ± 9.9	63
Race		
Black or African American	15 (25.0)	60
White	44 (73.3)	60
Other	1 (1.7)	60
Hispanic or Latino ethnicity	4 (7.4)	54
History of DVT	7 (11.1)	63
History of PE	7 (11.1)	63
History of PHTN	4 (6.3)	63
History of cancer	14 (22.2)	63
Active cancer	7 (11.1)	63
Clinical presentation		
Cardiac arrest with cardiopulmonary resuscitation	4 (6.3)	63
Vasopressor use before presentation or before procedure	29 (46.0)	63
Systolic blood pressure <90 mm Hg	30 (47.6)	63
Lowest systolic blood pressure, mm Hg[a]	90.8 ± 17.8	63
Tachycardic (heart rate ≥100 bpm)	45 (72.6)	62
Highest heart rate, bpm	120.5 ± 20.8	63
In-hospital average heart rate, bpm	106.6 ± 17.0	63
Elevated lactate (≥2.5 mM)	18 (54.5)	33
Depressed cardiac index (<2.0 L/min/m^2)	21 (42.9)	49
Vasopressor use before presentation at study hospital	21 (33.3)	63
Severe PHTN (sPAP ≥70 mm Hg)	7 (11.5)	61
Intubated before thrombectomy	6 (10.0)	60
RV/LV ratio (CTPA or echocardiographic composite)[b]	1.7 ± 0.5	58
RV/LV ratio (CTPA)	1.7 ± 0.5	46
RV/LV ratio (echocardiography)	1.5 ± 0.7	43
Duration of current PE symptoms, d	1.0 (0.0-1.0)	63
Failed previous therapy for current PE[c]	8 (12.9)	62
Anticoagulation	6 (75.0)	8
Fibrinolytics, systemic	3 (37.5)	8
Fibrinolytics, catheter-directed	0 (0.0)	8
Other mechanical thrombectomy	1 (12.5)	8
Fibrinolytics contraindication	16 (25.4)	63
Absolute	4 (25.0)	16
Relative	12 (75.0)	16
PE location at screening[d]		
Central	59 (93.7)	63
Saddle	25 (39.7)	63
Lobar	4 (6.3)	63
Concomitant DVT	34 (54.8)	62
Proximal only	9 (27.3)	33
Distal only	18 (54.5)	33
Both	6 (18.2)	33

Values are mean ± SD, median (IQR), or n (%).
CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; IQR, interquartile range; LV, left ventricle; PE, pulmonary embolism; PHTN, pulmonary hypertension; RV, right ventricle; sPAP, systolic pulmonary artery pressure.
[a] Value likely affected by prearrival vasopressor use in 21 (33.3%) patients. [b] Composite RV/LV ratios used CTPA or echocardiographic measurements, prioritizing CTPA when both were available. [c] More than 1 previous therapy was attempted in some patients. [d] As assessed by the treating physician. Central is defined as main, left, or right pulmonary artery, or a combination of all 3, and lobar is defined as left lobar, right lobar, or both.

Procedural characteristics

Most (93.7%) patients did not receive general anesthesia and were treated using only local anesthesia, with or without sedation. The preprocedural SBP, measured after vasopressors were administered to some patients, was 116.8 ± 17.7 mm Hg. The access site for almost all (98.4%) patients was a femoral or common femoral vein, and there were no major access site complications. The median thrombectomy and procedure times were 47.0 (27.5-64.0) and 64.0 (53.0-91.0) minutes, respectively. The estimated blood loss was 200.0 (100.0-395.0) mL, whereas the 8 (12.7%) patients whose treatment included use of the FlowSaver Blood

Table 2. Procedural characteristics and length of stay.

Characteristic	Values	N
Anesthesia[a]		
General anesthesia	4 (6.3)	63
Local anesthesia	10 (15.9)	63
Local anesthesia with sedation	50 (79.4)	63
Femoral or common femoral vein access site[b]	61 (98.4)	62
Major access site complications	0 (0.0)	63
Location of treated PE[c]		
Central only	21 (33.3)	63
Lobar only	4 (6.3)	63
Both	38 (60.3)	63
Thrombectomy time, min	47.0 (27.5-64.0)	60
Total procedure time, min	64.0 (53.0-91.0)	58
Estimated blood loss, mL	200.0 (100.0-395.0)	61
With FlowSaver blood return	157.5 (25.0-200.0)	8
Preprocedural ECMO use	1 (1.6)	63
Postprocedural ECMO use	1 (1.6)	63
Preprocedural vasopressor use	22 (34.9)	63
Postprocedural vasopressor use	16 (25.4)	63
Adjunctive PE therapy[d]	3 (4.8)	63
Catheter-directed thrombolysis	3 (4.8)	63
Other mechanical thrombectomy	0 (0.0)	63
Postprocedural hospital overnights	4.0 (2.0-7.0)	60
Postprocedural ICU overnights	1.0 (0.0-2.0)	59
No postprocedural overnight ICU stay	25 (42.4)	59
One postprocedural overnight ICU stay	12 (35.3)	34
Site-reported reason for ICU stay		
Standard-of-care practice only	14 (41.2)	34
Need for additional care	20 (58.8)	34

Values are n (%) or median (IQR).
ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; PE, pulmonary embolism.
[a] Patients might have received more than 1 type of anesthesia. [b] More than 1 access site may have been used during the procedure. Access site sample size is the total number of access sites. [c] As assessed by the treating physician. Central is defined as main, left, or right pulmonary artery, or a combination of all 3, and lobar is defined as left lobar, right lobar, or both. [d] Patients may have received more than 1 type of adjunctive PE therapy.

Return System demonstrated a lower estimated blood loss of 157.5 (25.0-200.0) mL.

Postprocedural extracorporeal membrane oxygenation was used for only 1 (1.6%) patient. Three (4.8%) patients received an adjuvant PE therapy, all of which were CDT without open surgical thrombectomy or other mechanical device treatment. After thrombectomy, the length of ICU stay was 1.0 (0.0-2.0) nights, and 25 (42.4%) patients did not stay in the ICU overnight. Of the 34 (57.6%) patients who spent ≥1 overnight in the ICU, 12 (35.3%) stayed only 1 night, and 14 (41.2%) received intensive care owing to standard-of-care practice only. These data and additional procedural characteristics are included in Table 2.

Safety and mortality outcomes

No deaths occurred during the procedure, and all 63 patients survived to 48 hours (Table 3). At the 30-day visit, mortality status was known for 61 (96.8%) patients; 2 (3.2%) patients survived the procedure but had withdrawn from the study. There were 0 (0%) all-cause mortalities in the 61 (96.8%) patients followed up through the 30-day visit.

No patients met the composite primary end point of MAEs; there were no device-related deaths, major bleeds, or intraprocedural device-related or procedure-related AEs at 48 hours (Table 3). There were 4 (6.3%) SAEs through 48 hours, none of which were adjudicated to be related to the FlowTriever System. The SAEs included 2 patients who developed a subsequent PE, 1 with additional right atrial embolus-in-transit and the other with concomitant deep vein thrombosis and inferior vena cava filter placement. Another patient developed a pelvic retroperitoneal hematoma contralateral to the access site limb and demonstrated a hemoglobin decrease from 10.7 g/dL before the procedure to 7.5 g/dL (−3.2 g/dL) after, not meeting the BARC 3b criteria for major bleeding of a 5-g/dL reduction; the patient remained stable and recovered without sequelae. The final SAE was in a patient who presented with a 1-cm right groin hematoma 5 days after the procedure, which also did not meet the BARC 3b criteria for major bleeding. This patient underwent computed tomography imaging with no significant findings and was discharged home 6 days post SAE.

Table 3. Safety and mortality outcomes.

	Value	N
Safety outcome (48 h)		
Major adverse event composite	0 (0.0)	63
Device-related death	0 (0.0)	63
Major bleeding	0 (0.0)	63
Intraprocedural device-related or procedure-related adverse event	0 (0.0)	63
Serious adverse event	4 (6.3)	63
Device-related serious adverse event	0 (0.0)	63
All-cause mortality		
48-h visit	0 (0.0)	63
30-d visit	0 (0.0)	61

Values are n (%).

Immediate hemodynamic and vital sign improvements

Acute changes in hemodynamics and vital signs are presented in Table 4. Immediately after thrombectomy, mPAP decreased from 31.5 ± 9.7 to 24.3 ± 9.6 mm Hg (mean change, −7.2 mm Hg [−22.6%]; $P < .0001$), and sPAP decreased from 50.7 ± 15.3 to 38.3 ± 15.1 mm Hg (mean change, −12.3 mm Hg [−24.3%], $P < .0001$). Although not statistically significant, intraprocedural SBP increased from 116.8 ± 17.7 to 121.3 ± 18.8 mm Hg (mean change, 4.5 mm Hg [5.3%]; $P = .1302$). Heart rate also improved from 98.4 ± 19.9 to 93.5 ± 17.9 bpm (mean change, −4.8 bpm [−3.7%]; $P = .0091$). Among the 42.9% of patients with depressed baseline CI <2 L/min/m^2, CI increased from 1.54 ± 0.21 to 1.91 ± 0.56 L/min/m^2 (mean change, 0.41 L/min/m^2 [26.5%], $P < .0001$). The TPVR also decreased from 7.3 ± 3.8 to 5.3 ± 2.7 mm Hg·min/L (mean change, −2.1 mm Hg·min/L [−21.6%]; $P < .0001$) immediately after thrombectomy.

Right ventricular echocardiographic assessments

Improvements were also observed for RV assessments by echocardiography, with the RV/LV ratio decreasing from 1.5 ± 0.7 at baseline (n = 43) to 1.1 ± 0.4 at 48 hours (n = 22; $P < .0001$) and 0.9 ± 0.2 at 30 days (n = 24; $P < .0001$) (Figure 1A). In addition, RV systolic pressure decreased from 51.0 ± 16.8 mm Hg before the procedure (n = 34) to 38.4 ± 15.1 mm Hg at 48 hours (n = 18; $P = .0076$) and 30.5 ± 14.1 mm Hg at 30 days (n = 13; $P = .0017$) (Figure 1B). The proportion of patients with normal or mildly reduced RV function increased from 15.9% at baseline (n = 44) to 56.5% at 48 hours (n = 23; $P = .0296$) and 92.3% at 30 days (n = 26; $P = .0008$) (Figure 1C).

Dyspnea and quality-of-life measures

Decreases in mMRC scores from 2.9 ± 1.5 at baseline (n = 40) to 1.8 ± 1.5 at 48 hours (n = 34; $P = .0003$) and 1.1 ± 1.1 at 30 days (n = 33; $P < .0001$) indicated significant improvement of dyspnea after thrombectomy. Similarly, the proportion of patients with severe dyspnea decreased from 72.5% at baseline to 38.2% at 48 hours ($P = .0010$) and 15.1% at 30 days ($P < .0001$). Distributions for all dyspnea scores are

Table 4. Immediate intraprocedural hemodynamic and vital sign improvements.

Variable	Preprocedure	Postprocedure	Mean change	*P*
mPAP, mm Hg	31.5 ± 9.7 (60)	24.3 ± 9.6 (60)	−7.2 (−22.6), 60	<.0001
sPAP, mm Hg	50.7 ± 15.3 (61)	38.3 ± 15.1 (61)	−12.3 (−24.3), 61	<.0001
Mean right atrial pressure, mm Hg	12.8 ± 5.1 (58)	10.6 ± 5.7 (48)	−2.3 (−15.4), 48	<.0001
Systolic blood pressure, mm Hg[a]	116.8 ± 17.7 (60)	121.3 ± 18.8 (60)	4.5 (5.3), 60	.1302
Heart rate, bpm	98.4 ± 19.9 (62)	93.5 ± 17.9 (61)	−4.8 (−3.7), 61	.0091
CI, L/min/m^2[b]	1.54 ± 0.21 (21)	1.91 ± 0.56 (18)	0.41 (26.5), 18	<.0001
TPVR, mm Hg·min/L	7.3 ± 3.8 (48)	5.3 ± 2.7 (42)	−2.1 (−21.6), 42	<.0001

Values are mean ± SD (n) or mean change (%), n.
CI, cardiac index; mPAP, mean pulmonary artery pressure; sPAP, systolic pulmonary artery pressure; TPVR, total pulmonary vascular resistance.
[a] Values likely affected by vasopressor use before presentation or before procedure in 29 (46.0%) patients. [b] For patients with baseline CI <2.0 L/min/m^2. *P* values were calculated using available paired assessments and Wilcoxon signed-rank tests.

presented in Figure 2A. In agreement, 49 (83.1%) patients demonstrated lower postprocedural supplemental oxygen requirements. The number of patients on room air increased from 8 (13.8%) before thrombectomy to 33 (57.9%) at 48 hours ($P < .0001$) and 52 (98.1%) at 30 days ($P < .0001$).

Patient quality of life also increased, with Pulmonary Embolism Quality of Life Frequency of Complaints scores improving from 15.6 (6.3-31.3) when first assessed at 48 hours (n = 21) to 0.0 (0.0–6.3) at 30 days (n = 15; $P = .0010$) (Figure 2B).

Readmissions

At 30 days, there were 5 (8.5%) all-cause readmissions. One (1.7%) readmission was related to the PE treatment, with the patient admitted to the emergency department 5 days post procedure for a 1-cm groin hematoma and discharged the following day.

Discussion

To date, this cohort analysis of the FLASH registry represents the largest reported interventional experience to evaluate MT outcomes in patients with high-risk PE. The 63 patients in this study presented with severe disease and hemodynamic compromise: 72.6% were tachycardic, 42.9% of patients presented with depressed CI, 46.0% were on vasopressors before thrombectomy, 10.0% were intubated before the procedure, and 6.3% required cardiopulmonary resuscitation on arrival.

Despite the elevated disease severity, this large cohort of patients with high-risk PE exhibited considerably favorable outcomes. All patients survived to 48 hours, and there were no all-cause mortalities in the 61 (96.8%) patients followed up through the 30-day visit. There were also no MAEs or device-related SAEs through 48 hours, indicating that MT can offer a safe treatment option for this patient population. Moreover, patients showed immediate hemodynamic and vital sign improvements, including a significant on-table reduction of mPAP and a resolution of tachycardia for the average patient, and 42.4% of patients avoided a postprocedural overnight ICU stay. These results demonstrate that patients can rapidly respond to this reperfusion treatment (Central Illustration).

Patients presenting with high-risk PE are at substantial risk of early mortality. A recent meta-analysis reporting outcomes for high-risk PE found the aggregate in-hospital all-cause mortality rate to be 28.3% among a subset of 15 studies involving treatments ranging from AC alone to extracorporeal membrane oxygenation.[7] Current guidelines recommend systemic fibrinolytics for these patients in the absence of contraindication, but the guidelines are based on an earlier meta-analysis that was highly sensitive to a study of only 8 randomized patients with high-risk PE.[4–6,17]

In one study, patients with high-risk PE who received intravenous fibrinolytics still demonstrated an in-hospital mortality of 28.6%.[3] Moreover, only 11.3% to 30.4% of patients with high-risk disease were administered systemic fibrinolytics in recent reports, potentially owing to high rates of contraindications in these medically complex patients and hesitancy due to concern for bleeding-related complications.[1,3,18] In patients analyzed without risk stratification, the rates of major

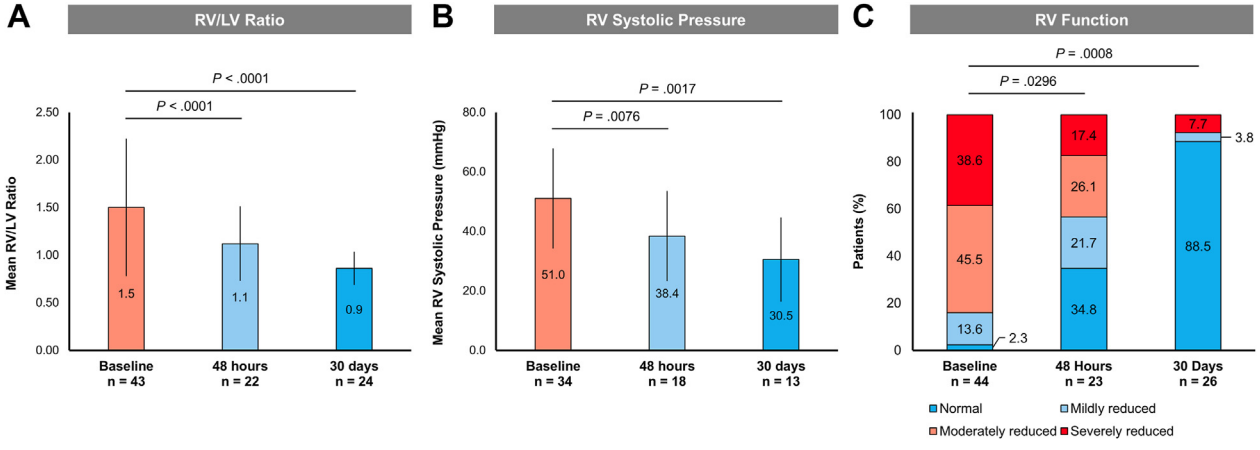


Figure 1.
Right ventricle echocardiographic assessments. (**A**) RV/LV ratio (mean ± SD), (**B**) RV systolic pressure (mean ± SD), and (**C**) RV function profile were evaluated from echocardiograms collected at baseline and 48-hour and 30-day follow-up visits. From available paired measurements, *P* values for RV/LV ratio and RV systolic pressure were calculated using Wilcoxon signed-rank tests, and *P* values for RV function category distributions were calculated using McNemar-Bowker tests. LV, left ventricle; RV, right ventricle; SD, standard deviation.

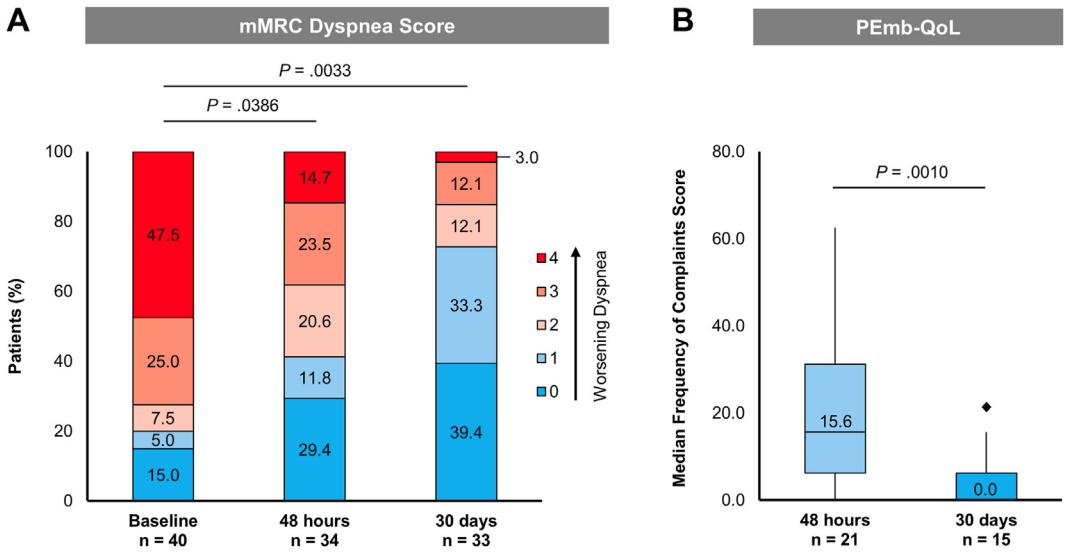
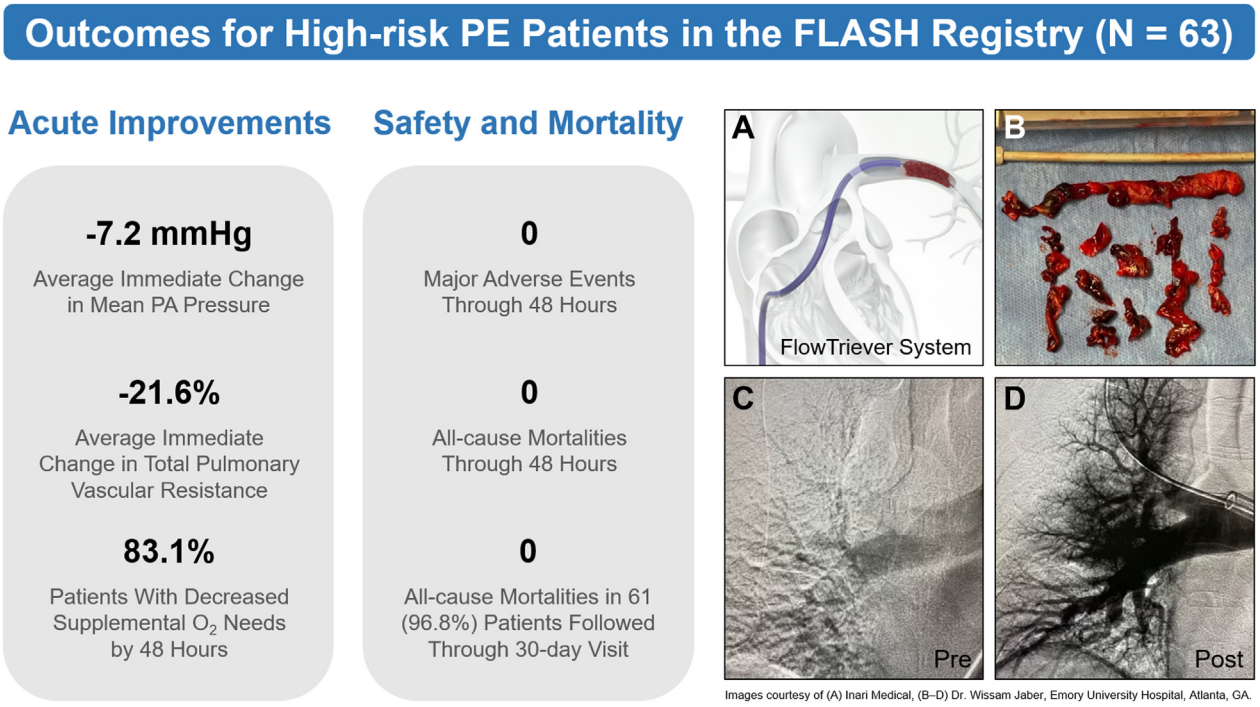


Figure 2.

Dyspnea and quality-of-life measures. (**A**) Dyspnea was evaluated at baseline and 48-hour and 30-day follow-up visits using mMRC assessments in which a higher score is equivalent to more severe dyspnea. (**B**) Quality of life was evaluated using PEmb-QoL questionnaires collected at 48-hour and 30-day follow-ups. An outlier PEmb-QoL score at 30 days is indicated. From available paired measurements, *P* values for dyspnea were calculated using McNemar-Bowker tests, and the *P* value for quality of life was calculated using a Wilcoxon signed-rank test. mMRC, Modified Medical Research Council; PEmb-QoL, pulmonary embolism quality of life.

bleeding and intracranial hemorrhage after systemic fibrinolytics for PE were 9.2% to 9.9% and 1.5%, respectively, and recent evidence suggests that the frequencies are greater in high-risk patients.[1,4,7,19] By contrast, there were no major bleeds, intracranial hemorrhages, or all-cause mortalities by the 30-day visit after MT in this study.

Given the historical in-hospital mortality rate of nearly 30%, it is highly clinically relevant that there were no acute mortalities in any of the 63 patients with high-risk PE in this multicenter registry. It is possible that selection bias contributed to the low in-hospital and 30-day mortality rates because patients with life expectancy <30 days were excluded from the study, and patients with high-risk PE often have complex comorbid conditions or sequelae of cardiogenic shock that can lead to mortality even when the PE is effectively treated. Nonetheless, all patients in this cohort were hemodynamically unstable, and a low mortality rate after large-bore MT for high-risk PE is not unprecedented. The FLAME study (ClinicalTrials.gov identifier: NCT04795167)



Central Illustration.

Acute outcomes after mechanical thrombectomy for high-risk PE. (**A**) Diagram of a Triever catheter from the FlowTriever System crossing the right heart for thrombectomy in a pulmonary artery. (**B**) Thromboemboli removed from pulmonary arteries in a case example, with (**C**) preprocedural and (**D**) postprocedural pulmonary angiograms presented. PA, pulmonary artery; PE, pulmonary embolism.

is a prospective, multicenter, and all-comer study designed to evaluate outcomes for patients with high-risk PE after treatment with either the FlowTriever System or alternative therapies. Fifty-three patients were enrolled in the FlowTriever Arm of FLAME, and in close agreement with the lack of all-cause mortalities in the current FLASH analysis, the in-hospital mortality rate for these patients was low at 1.9%.[20]

Other studies have also demonstrated positive outcomes for patients with high-risk PE who were treated with the FlowTriever System. A retrospective analysis of 34 patients with either high-risk or borderline high-risk PE reported no clinical AEs attributable to large-bore MT despite 18 (52.9%) patients presenting with high-risk disease and 16 (47.1%) being normotensive but with either depressed CI or respiratory failure requiring intubation.[21] There was only 1 (2.9%) mortality event in that analysis, with all other patients surviving to a mean follow-up of 205 days. The investigators observed immediate improvements in vital signs and hemodynamics. Altogether, these data support the conclusion that the subset of high-risk patients who are deemed appropriate candidates for thrombectomy based on the decision of the treating physician or local PE response team, and who can be transported to the catheterization laboratory for treatment with large-bore MT, experience excellent mortality outcomes and low procedural complications.

The immediate hemodynamic improvement offered by this treatment is likely key to the low mortality rate observed. Removal of emboli using large-bore MT allows for rapid unloading of RV strain, resulting in swift increases in CO and SBP. This reverses hemodynamic deterioration, leading to decreased RV oxygen demands, wall tension, and dilatation. Patients correspondingly demonstrate rapid improvement of hemodynamic parameters and dyspnea symptoms, as reported in this analysis. Large-bore MT is a fast-acting intervention that is effective for patients who can be stabilized for transportation to a catheterization laboratory.[20,21]

Intravenous fibrinolytics also act quickly, and some high-risk patients present with extreme urgency requiring immediate reperfusion therapy. Systemic lysis may still be the optimal or only available approach in such instances. However, systemic therapy is most effective for PE resulting from thromboembolus formed within a few weeks of symptom onset.[22] A postmortem histologic analysis of thromboemboli specimens from the pulmonary arteries or deep veins of 140 subjects who experienced fatal PE events found that only 34.3% of examined thromboemboli were <1 week old, and 15.7% formed >2 months before patient death.[23]

Owing to a mechanism of action that does not rely on fibrinolytic processes, the effectiveness of MT is less likely to be affected by embolus chronicity. Combined with the obviation of significant major bleeding risks associated with the administration of fibrinolytics, a mechanical approach to treating patients with high-risk PE may be a safer and more effective therapeutic option in many cases. The current research and other recent data indicate that treatment with large-bore MT leads to objectively low rates of acute mortality in high-risk PE for candidate patients who can be successfully transported to a catheterization laboratory.

Limitations

The FLASH registry is limited by the lack of a comparator arm and assessment relative to other PE therapies. Although all patients were rigorously diagnosed with high-risk PE at the site level according to ESC criteria for hemodynamic instability, the study database did not elicit or capture the specific criterion used to arrive at the diagnosis. This limitation in the database design precluded independent corroboration of the reason for high-risk PE diagnosis in some patients. Screen failures were not routinely collected; therefore, it cannot be confirmed that patients were not excluded for life expectancy <30 days owing to effects from the index PE alone, introducing a source of potential selection bias. In addition, owing to the high disease severity and urgent presentation and the effects of the COVID-19 pandemic on clinical investigations, >50% of patients consented to participate in the registry after procedural completion. Although this allowed study sites to maximize the inclusion of patients treated using the FlowTriever System, the consent window design and high rate of postprocedural consenting introduces the possibility of selection bias. Furthermore, and similar to most other registries, a detailed treatment protocol was not specified, increasing the potential for variability in procedures and outcome measurements. Aside from AEs and their device or procedural relatedness, which were centrally adjudicated by a third party, outcome measurements were individually assessed by each site, presenting an additional source of possible bias. Measurements collected after patient discharge may be influenced by follow-up bias. In addition, 48-hour echocardiograms were not required during some of the enrollment period owing to the COVID-19 pandemic, leaving echocardiographic data available for only a subset of patients.

Conclusions

In this analysis of all 63 patients with high-risk PE from the full US cohort of the FLASH registry, there were no MAEs within 48 hours of MT. The treatment resulted in immediate improvements in invasively measured hemodynamics. All patients survived to 48 hours, and there were no mortalities in the 96.8% of patients followed up through the 30-day visit despite significant risk of deterioration and death due to hemodynamic instability. These findings indicate that MT has a highly favorable safety profile and is rapidly effective in the context of patients who can be stabilized for catheterization. Thus, MT using the FlowTriever System could be considered as a viable frontline approach to treating patients with high-risk PE.

Acknowledgments

The authors acknowledge medical writing and editorial support from Kyle Hoban, PhD, Jessica Parsons, PhD, and Craig Markovitz, PhD, and biostatistical support from Milan Bimali, PhD.

Declaration of competing interests

James Horowitz is a consultant for Inari Medical and Penumbra. Ambarish Bhat and Mohannad Bisharat are consultants for Inari Medical. Michael Savin owns stock in Inari Medical. Mitchell Weinberg is a consultant for Magneto Thrombectomy Solutions and Boston Scientific. The other authors reported no financial interests.

Funding sources

The FLASH registry was funded by Inari Medical.

Ethics statement and patient consent

This research was approved by the institutional review board at each site before patient enrollment. All patients provided written informed consent.

References

1. Secemsky E, Chang Y, Jain CC, et al. Contemporary management and outcomes of patients with massive and submassive pulmonary embolism. *Am J Med*. 2018; 131(12):1506–1514.e0. https://doi.org/10.1016/j.amjmed.2018.07.035
2. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Massive pulmonary embolism. *Circulation*. 2006;113(4):577–582. https://doi.org/10.1161/CIRCULATIONAHA.105.592592
3. Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. *Eur Heart J*. 2020;41(4):522–529. https://doi.org/10.1093/eurheartj/ehz236

4. Marti C, John G, Konstantinides S, et al. Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J*. 2015; 36(10):605–614. https://doi.org/10.1093/eurheartj/ehu218
5. Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020; 41(4):543–603. https://doi.org/10.1093/eurheartj/ehz405
6. Stevens SM, Woller SC, Baumann Kreuziger L, et al. Executive summary: antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. *Chest*. 2021;160(6):2247–2259. https://doi.org/10.1016/j.chest.2021.07.056
7. Silver MJ, Giri J, Duffy A, et al. Incidence of mortality and complications in high-risk pulmonary embolism: a systematic review and meta-analysis. *J Soc Cardiovasc Angiogr Interv*. 2023;2(1):100548. https://doi.org/10.1016/j.jscai.2022.100548
8. Sista AK, Horowitz JM, Tapson VF, et al. Indigo aspiration system for treatment of pulmonary embolism: results of the EXTRACT-PE trial. *J Am Coll Cardiol Intv*. 2021;14(3):319–329. https://doi.org/10.1016/j.jcin.2020.09.053
9. Tu T, Toma C, Tapson VF, et al. A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: the FLARE study. *J Am Coll Cardiol Intv*. 2019;12(9): 859–869. https://doi.org/10.1016/j.jcin.2018.12.022
10. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE trial. *J Am Coll Cardiol Intv*. 2018;11(14): 1401–1410. https://doi.org/10.1016/j.jcin.2018.04.008
11. Avgerinos ED, Jaber W, Lacomis J, et al. Randomized trial comparing standard versus ultrasound-assisted thrombolysis for submassive pulmonary embolism: The SUNSET sPE Trial. *J Am Coll Cardiol Intv*. 2021;14(12):1364–1373. https://doi.org/10.1016/j.jcin.2021.04.049
12. Toma C, Bunte MC, Cho KH, et al. Percutaneous mechanical thrombectomy in a real-world pulmonary embolism population: interim results of the FLASH registry. *Catheter Cardiovasc Interv*. 2022;99(4):1345–1355. https://doi.org/10.1002/ccd.30091
13. Toma C, Jaber WA, Weinberg MD, et al. Acute outcomes for the full US cohort of the FLASH mechanical thrombectomy registry in pulmonary embolism. *EuroIntervention*. 2023;18(14):1201–1212. https://doi.org/10.4244/EIJ-D-22-00732
14. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(2 Suppl):e419S–e496S. https://doi.org/10.1378/chest.11-2301
15. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123(23):2736–2747. https://doi.org/10.1161/CIRCULATIONAHA.110.009449
16. R Core Team R: A language and environment for statistical computing. R Foundation for Statistical Computing. https://www.R-project.org/
17. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis*. 1995;2(3):227–229. https://doi.org/10.1007/BF01062714
18. Sedhom R, Megaly M, Elbadawi A, et al. Contemporary national trends and outcomes of pulmonary embolism in the United States. *Am J Cardiol*. 2022;176: 132–138. https://doi.org/10.1016/j.amjcard.2022.03.060
19. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA*. 2014;311(23):2414–2421. https://doi.org/10.1001/jama.2014.5990
20. Silve MMJ, Gibson CM, Giri J, et al. Outcomes in high-risk pulmonary embolism patients undergoing FlowTriever mechanical thrombectomy or other contemporary therapies: results from the FLAME study. Circ Cardiovasc Interv. In press. https:/doi.org/10.1161/CIRCINTERVENTIONS.123.013406
21. Toma C, Khandhar S, Zalewski AM, D'Auria SJ, Tu TM, Jaber WA. Percutaneous thrombectomy in patients with massive and very high-risk submassive acute pulmonary embolism. *Catheter Cardiovasc Interv*. 2020;96(7):1465–1470. https://doi.org/10.1002/ccd.29246
22. Czaplicki C, Albadawi H, Partovi S, et al. Can thrombus age guide thrombolytic therapy? *Cardiovasc Diagn Ther*. 2017;7(Suppl 3):S186–S196. https://doi.org/10.21037/cdt.2017.11.05
23. Fineschi V, Turillazzi E, Neri M, Pomara C, Riezzo I. Histological age determination of venous thrombosis: a neglected forensic task in fatal pulmonary thrombo-embolism. *Forensic Sci Int*. 2009;186(1-3):22–28. https://doi.org/10.1016/j.forsciint.2009.01.006