Prospective Multicenter International Registry of Ultrasound-Facilitated Catheter-Directed Thrombolysis in Intermediate-High and High-Risk Pulmonary Embolism (KNOCOUT PE)

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ORIGINAL ARTICLE

Prospective Multicenter International Registry of Ultrasound-Facilitated Catheter-Directed Thrombolysis in Intermediate-High and High-Risk Pulmonary Embolism (KNOCOUT PE)

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BACKGROUND: Prior clinical trials have demonstrated the efficacy of ultrasound-facilitated catheter-directed thrombolysis (USCDT) for the treatment of acute intermediate-risk pulmonary embolism (PE) using reduced thrombolytic doses and shorter infusion durations. However, utilization and safety of such strategies in broader PE populations remain unclear. The KNOCOUT PE (The EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With Pulmonary Embolism) registry is a multicenter international registry designed to study the treatment of acute PE with USCDT with focus on safety outcomes.

METHODS: The KNOCOUT PE prospective cohort included 489 patients (64 sites internationally) with acute intermediate-high or high-risk PE treated with USCDT between March 2018 and June 2020. Principal safety outcomes were independently adjudicated International Society on Thrombosis and Haemostasis major bleeding at 72 hours post-treatment and mortality within 12 months of treatment. Additional outcomes included change in right ventricular/left ventricular ratio and quality of life measures over 12 months.

RESULTS: Mean alteplase (r-tPA [recombinant tissue-type plasminogen activator]) infusion duration was 10.5 hours. Mean total r-tPA dose was 18.1 mg, with 31.0% of patients receiving ≤12 mg. Major bleeding events within 72 hours occurred in 1.6% (8/489) of patients. One patient experienced worsening of a preexisting subdural hematoma after USCDT and therapeutic anticoagulation, which ultimately required surgery. All-cause mortality at 30 days was 1.0% (5/489). Improvement in PE quality of life score was observed with a 41.1% (243/489, 49.7%) and 44.2% (153/489, 31.3%) mean relative reduction by 3 and 12 months, respectively.

CONCLUSIONS: In a prospective observational cohort study of patients with intermediate-high and high-risk PE undergoing USCDT, mean r-tPA dose was 18 mg, and the rates of major bleeding and mortality were low.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03426124.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: mortality ■ pulmonary embolism ■ quality of life ■ standard of care ■ ultrasound-facilitated catheter-directed thrombolysis

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WHAT IS KNOWN

- Patients with acute intermediate and high-risk pulmonary embolism (PE) may experience increased mortality, poor quality of life, and post-PE syndrome.
- Treatment of the patients with low-dose, short-infusion duration ultrasound-facilitated catheter-directed thrombolysis has been associated with reduction of right ventricular dysfunction similar to higher dose and longer duration trials. Incidence of major bleeding in the previously published OPTALYSE PE trial (Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk PE) was 4%.

WHAT THE STUDY ADDS

- The prospective observational KNOCOUT PE study (The EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With PE) describes the largest single prospective cohort study of r-tPA (recombinant tissue-type plasminogen activator) with ultrasound-facilitated catheter-directed thrombolysis in intermediate-high-risk and high-risk PE patients.
- KNOCOUT PE also observed a low major bleeding rate for ultrasound-facilitated catheter-directed thrombolysis in intermediate-high-risk and high-risk PE patients.

Nonstandard Abbreviations and Acronyms

CTA	computed tomography angiography
ICH	intracranial hemorrhage
ICU	intensive care unit
KNOCOUT PE	The EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With Pulmonary Embolism
LV	left ventricular
OPTALYSE PE	Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk Pulmonary Embolism trial
PE	pulmonary embolism
QoL	quality of life
r-tPA	recombinant tissue-type plasminogen activator
RV	right ventricular
SDH	subdural hematoma
SEATTLE II	A Prospective, Single-Arm, Multicenter Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism
sPESI	simplified pulmonary embolism severity index
TNK	tenecteplase
ULTIMA	ultrasound accelerated thrombolysis of pulmonary embolism
USCDT	ultrasound-facilitated catheter-directed thrombolysis

Selection of reperfusion therapy for intermediate-high and high-risk pulmonary embolism (PE) requires consideration of the individual patient's risk for adverse outcomes as well as major bleeding, in particular intracranial hemorrhage (ICH).[1] While systemic thrombolysis has been proven to be a lifesaving intervention in patients with intermediate and high-risk PE,[2,3] the clinical benefit may be at least partially offset by increased major bleeding (6.3% with peripherally administered thrombolytic therapy compared with 1.5% for anticoagulation alone).[4] The most feared complication of systemic thrombolysis is potentially life-threatening and disabling ICH with a frequency approaching 2% in a clinical trial population[4] and 5% in observational studies.[5] Concern for ICH has resulted in decreased utilization of systemic thrombolysis worldwide and has increased utilization of catheter-based techniques that employ reduced doses of thrombolytic drug or no thrombolytic agent.

Ultrasound-facilitated catheter-directed thrombolysis (USCDT) has been cleared for treatment of acute PE since May 21, 2014 and has been evaluated in several prospective clinical studies, including 3 randomized trials, over the past decade.[6–9] ULTIMA (Ultrasound Accelerated Thrombolysis of PE), a European prospective randomized controlled trial of 59 patients with intermediate PE, demonstrated that a surrogate outcome of PE mortality, right ventricular (RV)-to-left ventricular (LV) diameter ratio, improved to a greater extent at 24 hours with USCDT compared with anticoagulation alone.[6] The US-based SEATTLE II trial (A Prospective, Single-Arm, Multicenter Trial of EkoSonic Endovascular System and Activase for Treatment of Acute PE) showed an improvement in the RV-to-LV ratio at 48 hours after USCDT using 24 mg of alteplase (r-tPA [recombinant tissue-type plasminogen activator]) over 12 to 24 hours in patients with either intermediate- or high-risk PE with a major bleeding rate of 10% and no ICH.[7] The OPTALYSE PE trial (Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Intermediate-Risk PE) showed that the RV/LV ratio reduction from baseline computed tomography angiography (CTA) to 48 hours after USCDT with lower r-tPA doses was similar to that of previous studies with higher doses and had a major bleeding rate of 4%.[10] RV dysfunction by echocardiography, functional status, and quality of life improved over the course of the study observation, though it is unclear whether this improvement is attributable to USCDT because OPTALYSE did not include an anticoagulation-only control group.[8]

The multicenter, international KNOCOUT PE registry was launched to evaluate a larger cohort of patients receiving USCDT than was previously studied, with the goal of further assessing safety and dosing patterns.

METHODS

Study Design

The KNOCOUT PE study (EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With PE) was a prospective multi-center international registry across North America (ClinicalTrials.gov: NCT03426124) and Europe (EudraCT: 2018-001235-46). KNOCOUT PE was designed by the study steering committee in collaboration with the study sponsor (BTG/Boston Scientific Corporation, Marlborough, MA). The aim of the study was to evaluate a large cohort of patients with intermediate-high and high-risk PE treated with USCDT with regard to the dose and duration of r-tPA delivered and frequency of major bleeding.

Study Population

Enrollment for the Prospective arm of KNOCOUT PE took place from March 2018 through June 2020; each patient's participation in the registry was expected to last 12 months. A total of 489 patients were enrolled across 64 sites throughout North America (United States and Canada) and Europe (Austria, France, Germany, the Netherlands, Switzerland, and the United Kingdom). The protocol was approved by each site's institutional review board or ethics committee, and patients at each site were required to provide informed consent before enrollment in the registry. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients enrolled were risk-stratified and determined to have either intermediate-high risk or high-risk PE. Intermediate-high risk PE was defined by evidence of RV dysfunction (RV/LV >1.0) on either echocardiogram or computed tomography, and troponin elevation per the site's clinical laboratory protocol. High-risk PE was defined as having sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 minutes or requiring inotropic support). The study included patients who had already been selected for treatment with the EKOS device and were 18 to 80 years old, had RV/LV >1.0 measured by CTA or echocardiogram, PE symptom duration ≤14 days, troponin elevation ≥upper limit of normal per the institution's assay, and signed informed consent. Exclusion criteria were life expectancy <1 year and the clinician deeming the patient high-risk for catastrophic bleeding, per International Society on Thrombosis and Haemostasias criteria (defined as fatal or associated with any of the following: [1] a fall in Hb of 2 g/dL or more or transfusion of at least 2 units of red blood cells or [2b] involvement of a critical anatomic site).[11]

Of note, sites were allowed to complete inform consent in lieu of patients in KNOCOUT PE following USCDT if the patient had a severe presentation (such as high-risk PE) such that delay for obtaining consent was clinically inappropriate. Sites were encouraged to maintain screening logs but were not required to do so.

Intervention

USCDT was performed by a trained endovascular specialist in an angiographic suite or hybrid operating room with digital angiographic equipment using the EkoSonic (EKOS) Endovascular System (EKOS/BTG/Boston Scientific Corporation, Marlborough, MA) in conjunction with r-tPA (recombinant tissue-type plasminogen activator) administration. Treatment dose and duration were determined by the individual investigator's judgment. The EKOS catheter was inserted into the pulmonary artery using standard ultrasound and fluoroscopic-guidance techniques; the venous access site was selected by the treating physician. In the case of a unilateral filling defect in 1 main or proximal lobar pulmonary artery, only 1 device was placed. In the case of a bilateral filling defect in both main or proximal lobar pulmonary arteries, as determined by CTA, 2 devices were placed (one in each of the involved main or proximal pulmonary arteries).

Postintervention Follow-Up and Data Collection

Post-procedure, patients were followed per the investigator's usual clinical practice. At a minimum, health status checks were completed during the hospital stay, before discharge, and at 3 and 12 months post-treatment (Table 1). Safety data were to be collected and reported through 12 months post-treatment. An on-site visit with echocardiography was recommended at 3 months for patients with an abnormal echocardiogram post-treatment to allow for evaluation of chronic pulmonary hypertension, and at 12 months for all patients. Additionally, matched echocardiograms were required (ie, a patient could not have an echocardiogram at 1 visit and a CTA at the next). The availability of imaging-based assessment could vary across patients and centers due to differences in follow-up protocol employed at each center (Figure S1).

Data were collected via an electronic data capture system (DATATRAK International Inc, Mayfield Heights, OH) and were site-reported.

Outcome Measures

Safety outcome measures collected included frequency and severity of serious adverse events related to the device or procedure; recurrent venous thromboembolism, International Society on Thrombosis and Haemostasias–defined major bleeding, and mortality during index hospitalization and the first 12 months post-procedure. A third-party independent physician medical monitor, blinded to details of the dosing and duration protocol, adjudicated safety outcomes and reviewed all major bleeding events and serious adverse events.

An additional outcome measure of interest was a change in RV/LV ratio, as assessed by matched echocardiogram or CTA from baseline to between 24 and 48 hours after the start of the USCDT procedure. Additional outcomes are in Table S1.

Quality of life data were collected, as measured using the PE quality of life, the visual analog scale, and EuroQoL 5-dimension 5-level instruments at 3 and 12 months posthospitalization visits (Misery, Utility, and Composite scores; Table S2).[12–15]

Statistical Analyses

In this single-arm study, sample size was based on the expected enrollment per site, based on estimated cases per

Table 1. Post-USCDT Follow-Up

Assessment	Baseline	Procedure/ post-procedure	Follow-up	
	Day −1	Day 0 through discharge	3-mo (±14 d) post-USCDT (phone or visit)	12 mo (±14 d) post-USCDT (phone or visit)
Informed consent	X*			
Demographics	X*			
Medical history, risk factors	X*			
Vital signs†	X*	X		
Physical examination	X			
CTA	X*	X* (if collected)		
sPESI	X			
USCDT procedure		X		
Echocardiogram‡	X*	X§ (if collected)	X* (if collected)	X* (if collected)
Quality of life surveys‖		X*	X*	X*
Laboratory tests¶	X#	X		
Biomarkers**	X*	X		
Adverse/VTE/bleeding events		X*	X*	X*
Anticoagulation medications	X	X	X	X

Assessments performed per Investigator's practice and collected according to the schedule below. BNP indicates brain natriuretic peptide; CTA, computed tomography angiography; EQ-5D-5L, EuroQoL 5-Dimension 5-Level; eRSVP, estimated right ventricular systolic pressure; Hct, hematocrtit; Hgb, hemoglobin; INR, international normalized ratio; IVC, inferior vena cava; PEmb-QoL, pulmonary embolism quality of life; PT, partial thromboplastin time; RV/LV, right ventricular/left ventricular ratio; sPESI, simplified pulmonary embolism severity index; TAPSE, tricuspid annular plane systolic excursion; and USCDT, ultrasound-facilitated catheter-directed thrombolysis; and VTE, venous thromboembolic disease.

*Assessments pertain to an outcome measure or eligibility.

†Record heart rate, blood pressure, respiratory rate, oxygen saturation vital signs at admission, at start and end of treatment, and once at same time each day of hospitalization.

‡Includes RV/LV ratio, TAPSE, eRVSP, and collapse of the IVC with respiration.

§Collect 24 to 48 h after the start of the USCDT procedure.

‖PEmb-QoL and EQ-5D-5 L.

¶Hgb, Hct, platelet count, creatinine, activated partial thromboplastin time (USCDTT), PT, and INR.

#Record if collected within 48 h before the start of USCDT procedure.

**Troponin, BNP/NT-proBNP, lactate/lactic acid, and D-dimer.

physician across total number of study sites with no formal hypothesis testing. Up to 550 patients would be enrolled to collect data on current EKOS use at up to 100 sites. For baseline and procedure characteristics and safety outcomes, all patients who received the USCDT procedure were included. For the outcomes of RV/LV ratio, tricuspid annular plane systolic excursion, estimated RV systolic pressure and patient-reported outcomes, all patients who met eligibility criteria and received the USCDT procedure were included and changed from baseline was assessed using 2-sided *P* values from a *t* test. Sensitivity analyses were conducted post hoc to determine whether significant differences existed in major bleeding rate and mortality between patients who were consented before treatment versus after treatment by excluding the patients who consented after treatment; 2-sided *P* values were produced from Fisher exact test.

Continuous data were summarized with means, medians, SDs, minima and maxima, unless otherwise specified. Categorical data were summarized with observed counts and percentages for each category. Percentages were based on the total number of patients for all analysis. There was no imputation for missing values. Posthoc multivariable logistic regression models were performed to assess if the following fixed effects had an impact on mortality and major bleeding events: treatment center, body mass index, age, sex, whether the patient had active cancer and whether the patient was at a high or intermediate risk for PE. A $P<0.05$ would indicate the effect was impactful. In the event there were too few patients (<5) in a treatment center, the center's data was combined with other center(s) to achieve at least 5 patients. The combining of treatment centers was accomplished by ranking the sites that did not have at least 5 patients, with ties broken by treatment center number. The centers with the largest number of patients were combined with the smallest center as necessary until there were 5 patients. The process was repeated among the remaining centers. Centers were only combined within geographic region (United States versus outside the United States). A sensitivity analysis of the post hoc multivariable logistic regression models was also performed by excluding any centers with <5 patients.

RESULTS

Demographics and Baseline Disease Characteristics

A total of 489 patients were included in the prospective KNOCOUT PE cohort (Table 2; Table S3). Of the enrolled patients, 93.3% (456/489) were consented

Table 2. Demographics and Baseline Characteristics of the Patients With Intermediate-High and High-Risk Pulmonary Embolism Treated With Ultrasound-Facilitated Catheter-Directed Thrombolysis in the KNOCOUT PE Prospective Registry Study (N=489)

	Prospective cohort (N=489)
Median age, y (range)	63.0 (20–81)
Sex	
Men	259 (53.0%)
Women	230 (47.0%)
Race	
White patient	296 (60.5%)
Black patient	77 (15.7%)
Other	25 (5.1%)
Missing	91 (18.6%)
Ethnicity	
Hispanic	12 (2.5%)
Non-Hispanic	340 (69.5%)
No response	46 (9.4%)
Missing	91 (18.6%)
Medical history	
BMI ≥30 kg/m^2	319 (65.2%)
Family history of VTE	71 (14.5%)
Active cancer	20 (4.1%)
History of cancer remission	60 (12.3%)
Congestive heart failure	13 (2.7%)

BMI indicates body mass index; KNOCOUT PE, The EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With Pulmonary Embolism; and VTE, venous thromboembolic disease.

before enrollment; 6.7% (33/489) were consented post-procedure. Eleven sites had received the waiver to consent patients post-procedure in an effort to include more high-risk PE patients. Of the 33 patients consented post-procedure, 24 of the 33 were from 2 sites (1 United States and 1 non-United States).

Of the 489 patients, 463 (94.7%) were classified as intermediate-high risk and 26 (5.3%) were classified as high-risk (Table 3). Simplified PE severity index (sPESI) and Bova scores were calculated for patients based upon information in the database. Within the study population, 55.6% had an sPESI score greater than or equal to 1 (median=1.0; interquartile range, 0.0–1.0). For patients with systolic blood pressure ≥90 mm Hg (N=477), the mean Bova score was 4.4 (SD=0.61).

Procedure Characteristics

Procedural success, defined as having all catheters successfully placed and treatment administered, was 99.8% (488/489 patients; Table 4). Median length of hospital stay was 4.0 days (interquartile range, 3.0–6.0; Table 4). Of the 393 patients treated in the United States, 90.8% had a stay in the intensive care unit (ICU); of the 90 patients treated outside of the United States, 45.6% had an ICU stay as part of their treatment. For the entire patient population, the mean time in the ICU was 48.9 hours (SD=47.4). Decisions regarding triage post-procedure (ICU, step-down unit, general floor) were made according to each site's policies and procedures along with the clinical team.

The mean r-tPA dose was 18.1 mg (SD=7.4). Three patients outside of the United States received tenecteplase with doses between 19.8 and 20 mg; these patients were not included in r-tPA dose calculations. Of those who received r-tPA for whom complete dosing data were available, 69.5% received 20 mg or less; 31.0% of patients received 12 mg or less (Table 4; Figure S1). Mean duration of thrombolytic therapy overall was 10.5 hours (SD=5.4). In the United States, mean duration of thrombolytic therapy was 9.8 hours (SD=4.9); outside of the United States, it was 13.4 hours (SD=6.4).

Safety

Bleeding

Among the 489 patients, there were 8 major bleeding events within the first 72 hours post-treatment (1.6%; Table 5). One patient with bilateral subdural hematomas underwent bilateral craniotomies and developed postoperative PE. However, the patient had residual subdural hematomas; s/he was treated with both USCDT and therapeutic anticoagulation and developed worsening of the left-sided subdural hematomas, which ultimately required repeat surgical decompression. Other than this event, no other ICH events were reported. A sensitivity analysis showed no significant difference in major bleeding rates within the first 72 hours post-treatment when patients who were consented after intervention were removed from the population (1.5% [7/456] versus 1.6% [8/489] for the total study population (2-sided *P*=1.0).

Table 3. Clinical Presentation of Patients With Intermediate-High and High-Risk Pulmonary Embolism Treated With Ultrasound-Facilitated Catheter-Directed Thrombolysis in the KNOCOUT PE Prospective Registry Study (N=489)

	Prospective cohort (N=489)
Dyspnea	443 (90.6%)
Tachycardia	241 (49.3%)
Chest pain	195 (39.9%)
Hypoxemia	138 (28.2%)
Dizziness/lightheadedness	132 (27.0%)
Syncope (fainting)	93 (19.0%)
Tachypnea	80 (16.4%)
Leg Pain	65 (13.3%)

KNOCOUT PE indicates The EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With Pulmonary Embolism.

Table 4. Procedural Characteristics From Patients With Intermediate-High and High-Risk Pulmonary Embolism Treated With Ultrasound-Facilitated Catheter-Directed Thrombolysis in the KNOCOUT PE Prospective Registry Study (N=489)

	Prospective cohort (N=489)
Catheter placement time, h, mean (SD)	0.67 (0.37)
Duration of thrombolytic therapy, h, mean (SD)	10.5 (5.37)
Total r-tPA dose, mg, mean (SD)	18.1 (7.4)
Total r-tPA dose, mg*	
≥24	60 (12.6%)
20.01–24	86 (18.0%)
12.01–20	184 (38.5%)
4–12	147 (30.8%)
<4	1 (0.2%)
Location of USCDT catheter device, n (%)†	
Main pulmonary artery	74 (15.1%)
Right pulmonary artery	382 (78.1%)
Right upper lobar artery	10 (2.0%)
Right middle lobar artery	37 (7.6%)
Right lower lobar artery	94 (19.2%)
Left pulmonary artery	379 (77.5%)
Left upper lobar artery	9 (1.8%)
Left middle lobar artery	22 (4.5%)
Left lower lobar artery	108 (22.1%)
Catheter successfully placed and used for treatment? n (%)‡	
Yes	488 (99.8%)
No	1 (0.2%)
Ultrasound imaging used to locate target vein, n (%)	
Yes	366 (74.8%)
No	113 (23.1%)
Missing	10 (2.0%)
Interventional procedures attempted before USCDT, n (%)	1 (0.2%)
Peripherally administered systemic fibrinolytic therapy	1 (0.2%)
Adjunctive therapy after USCDT procedure, n (%)	4 (0.8%)
Surgical pulmonary embolectomy	1 (0.2%)
ECMO	1 (0.2%)

ECMO indicates extracorporeal membrane oxygenation; KNOCOUT PE, The EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With Pulmonary Embolism; r-tPA, recombinant tissue-type plasminogen activator (alteplase); and USCDT, ultrasound-facilitated catheter-directed thrombolysis.

*Percentages based on patients with complete r-tPA dose and treatment duration information.

†Patients could have more than 1 location; therefore, percentages add up to >100%.

‡Five patients with missing procedural success data were reviewed and determined to have had the device successfully placed and used for treatment.

Additionally, there were no meaningful differences in major bleeding in United States and outside of US patients. A post hoc regression analysis and a sensitivity analysis showed that none of the collected risk factors impacted the number of major bleeding events (Tables S4 and S5).

Recurrent Venous Thromboembolism

Two of the 489 patients suffered recurrent PE (0.4%; Table 5). Both occurred within the first 30 days following treatment; one of the patients was noted to be subtherapeutic on anticoagulation while transitioning from unfractionated heparin to oral anticoagulation; the other patient with a preexisting iliofemoral deep vein thrombosis experienced recurrence 3 days after completion of USCDT.

Mortality

Five patients died during the initial 30 days post-treatment (1.0%); all were intermediate-high risk patients (Table 5). Of the 26 patients with high-risk PE who were enrolled in KNOCOUT PE, there were no deaths. A sensitivity analysis showed no significant difference in mortality rates within the first 30 days post-treatment, when patients who consented after intervention were removed from the population (0.9% [4/456] versus 1.0% [5/489] for the whole population; 2-sided P=1.0). Additionally, there were no meaningful differences in mortality in United States and outside of US patients. A post hoc regression analysis and a sensitivity analysis showed that none of the collected risk factors impacted the mortality rate (Tables S4 and S5).

Imaging Assessments

Of the patients included in the prospective KNOCOUT PE registry, 176 (36%) had postprocedure-matched echocardiograms before discharge (Figure; Table 6). Mean baseline RV/LV ratio was 1.35 (SD=0.32). Of the 176 patients, 77 had a matched echocardiogram between 24 hours and up to 48 hours post-procedure, with a mean RV/LV ratio of 0.98 (SD=0.27); the mean relative reduction from this postprocedure time point as compared with baseline was 24.57% (2-sided P<0.0001; Table 6).

Another exploratory parameter was tricuspid annular plane systolic excursion. At baseline, mean tricuspid annular plane systolic excursion was 16.50 (SD=17.91) among the 67 patients evaluated (Table 6). The mean tricuspid annular plane systolic excursion among 36 patients assessed 24 to 48 hours post-procedure was 18.74 (SD=6.4); mean relative change was 82.58% (SD=232.95, 2-sided P=0.04; Table 6).

We also assessed the mean change in estimated right ventricular systolic pressure (mm Hg) on ECHO. At baseline, the mean estimated RV systolic pressure in the 62 patients evaluated was 50.35 mm Hg (SD=15.34). Mean estimated RV systolic pressure between 24 and 48 hours post-procedure in the 31 patients evaluated was 35.77 mm Hg (SD=16.73); mean relative reduction was 28.55% (SD=31.37; 2-sided P<0.0001; Table 6).

Patient-Reported Assessments

Patient-reported data were available for 243 (49.7%) patients at 3 months post-treatment and for 153

Table 5. Major Bleeding Events in Patients With Intermediate-High and High-Risk Pulmonary Embolism Treated With Ultrasound-Facilitated Catheter-Directed Thrombolysis in the KNOCOUT PE Prospective Registry Study (N=489)

Prospective cohort (N=489)		
	N (%)	Additional details from patient narratives
Bleeding events within 30 d	8 (1.6%)	
Gastrointestinal hemorrhage	2 (0.4%)	
Head laceration	1 (0.2%)	
Vascular access site hematoma	4 (0.8%)	
SDH (preexisting)	1 (0.2%)	•There was 1 patient with preexisting SDH that increased in size during the admission. He had a history of progressive headaches for 2 mo and was diagnosed with acute on chronic bilateral subdural hematomas and underwent craniotomies with evacuation of hematomas. The patient had residual SDHs and 4 d postoperatively, he developed acute PE and was treated with USCDT and therapeutic anticoagulation and was enrolled into KNOCOUT PE. He developed progression of his bilateral SDH requiring repeat left craniotomy with evacuation. Three days following reevacuation of hematoma, anticoagulation with warfarin was restarted. The patient was more alert and followed commands however there was no change in his SDHs on follow-up CT. His drain was ultimately removed. An MRI of the brain demonstrated multifocal nonhemorrhagic cerebral infarctions. Four days later, the patient subsequently developed a fever and became progressively obtunded with respiratory depression. He was transitioned to hospice care with the decision to not pursue additional treatment. He ultimately expired on day 10 post-USCDT.
Recurrent VTE within 30 d	2 (0.4%)	
Pulmonary embolism	2 (0.4%)	
Mortality	5 (1.0%)	
Cardiac tamponade	1 (0.2%)	•Patient with a history of CTEPH and pericardial effusion. This patient underwent successful USCDT. On day 6 post-procedure, the patient experienced cardiopulmonary arrest and attempted resuscitation, which included a pericardiocentesis without evidence of hemorrhage. Resuscitation was unsuccessful, and the patient expired.
Multiorgan system failure	2 (0.4%)	•One of the patients who expired from multisystem organ failure had severe baseline cardiomyopathy, pneumonia, exacerbation of COPD, and acute renal failure superimposed on chronic kidney disease in addition to his acute PE and expired 11 d post-USCDT. •The other patient who had multisystem organ failure underwent USCDT with progression of right heart failure and shock that was treated with mechanical ventilation, initiation of ECMO, high doses of catecholamines and vasopressors, and subsequent open pulmonary thromboembolectomy. The patient remained in shock and expired post-operatively.
Cardiorespiratory arrest	2 (0.4%)	•One patient had a history of CHF, acute on chronic PE who was noncompliant with anticoagulation. The patient was readmitted to the hospital with worsening respiratory failure, however, did not have recurrent PE but expired from worsening right heart failure 30 d following USCDT. •Second patient had progression of previously existing SDHs, developed multifocal ischemic strokes, became progressively obtund, and expired 10-d post-USCDT.

CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; ECMO, extracorporeal membrane oxygenation; KNOCOUT PE, The EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With Pulmonary Embolism; MRI, magnetic resonance imaging; PE, pulmonary embolism; SDH, subdural hematoma; and USCDT, ultrasound-facilitated catheter-directed thrombolysis.

(31.3%) patients at 12 months post-treatment (Table 7). The mean PEmb-Quality of life score 3 months post-procedure in 243 patients evaluated was 16.0 (SD=17.7), compared with 38.5 (SD=22.1) at baseline (41.1% change; 2-sided $P<0.0001$; Table 7; Table S2). Similarly, mean visual analog scale score improved from 63.1 (SD=23.0) to 75.5 (SD=19.8) from post-procedure to the 3-month time point in 242 patients evaluated (56.0% change; 2-sided $P=0.0008$; Table 7). The composite EuroQoL 5-dimension 5-level Misery score was reduced from a mean of 10.2 (SD=4.2) immediately post-procedure to 7.4 (SD=3.5) at 3 months (17.8% change, 2-sided $P<0.0001$) in 243 patients (Table 7). The composite EuroQoL 5-dimension 5-level Utility score also showed improvement, from a mean of 0.64 (SD=0.31) immediately post-procedure to 0.83 (SD=0.24) at 3 months (0.2, 2-sided $P<0.0001$) across the 243 patients assessed (Table 7). Improvement across all instruments was maintained through the 12-month follow-up period (Table 7).

DISCUSSION

The prospective multicenter, international KNOCOUT PE registry was designed to study a larger cohort of patients treated with USCDT following the OPTALYSE PE trial, with an emphasis on safety and dosing patterns. Across all patients enrolled in KNOCOUT PE, the mean total r-tPA dose administered was 18.1 mg, with a mean infusion duration of 10.5 hours. Both major bleeding within 72 hours post-procedure and all-cause mortality within 30 days of intervention were low (1.6% and 1.0%, respectively). Aside from the worsening of a preexisting subdural hematoma in 1 patient after initiation of

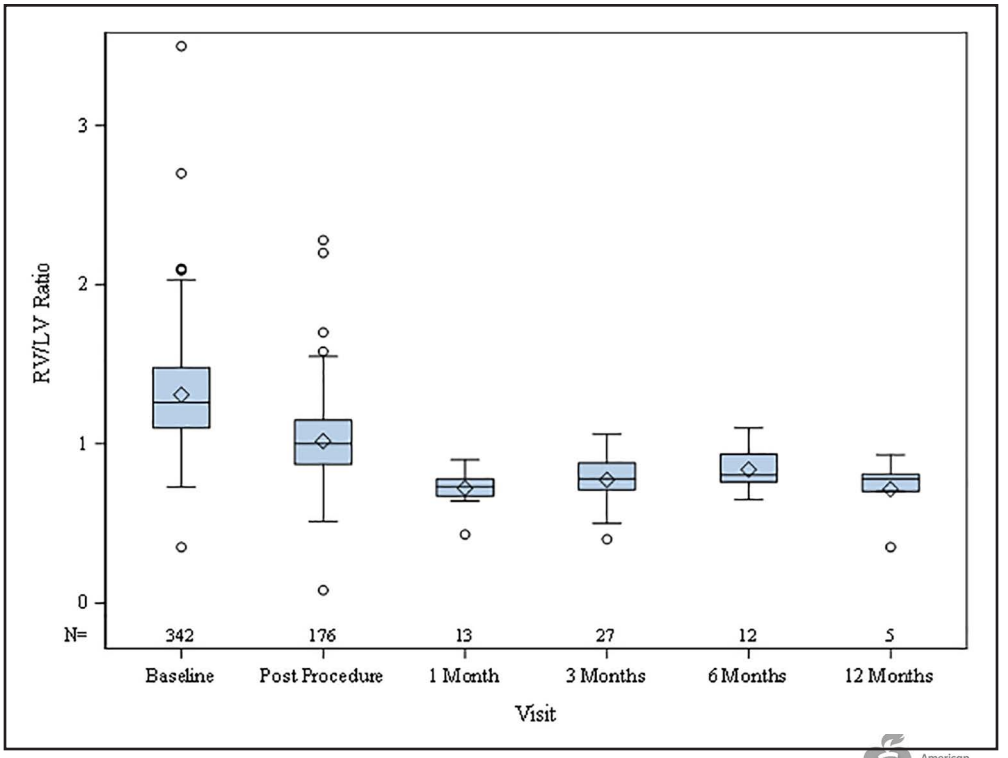

Figure. Change in right ventricular/left ventricular (RV/LV) ratio on echocardiogram in patients with intermediate-high and high-risk pulmonary embolism treated with ultrasound-facilitated catheter-directed thrombolysis in the KNOCOUT PE (The EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With Pulmonary Embolism) prospective registry study. For each boxplot, the upper and lower part of the blue box show the upper and lower quartiles; the upper line shows the maximum observation below the upper fence (+1.5×IQR); the lower line shows the minimum observation below the lower fence (−1.5×IQR); the horizontal line within the box shows the median; the diamond shape within the box shows the mean.

anticoagulation and USCDT, no other ICH events were reported. The echocardiographic outcome measure of change in RV/LV ratio demonstrated a mean relative reduction of 22.6% post-procedure and 41.8% 1-month post-procedure.

Previously published bleeding complication rates in some studies of USCDT have reported major bleeding rates approaching 10%.[7] In KNOCOUT PE, an International Society on Thrombosis and Haemostasias major bleeding rate of 1.6% was observed—lower than those previously reported in the ULTIMA and SEATTLE II studies, and comparable to that observed in OPTALYSE PE.[6–8,10] This is notable because the specific dosing and duration regimen were not prescribed, and there was no compulsory anticoagulation protocol. The low frequency of major bleeding in KNOCOUT PE reflected the procedure's safety in practice and was similar to rates of major bleeding reported with mechanical thrombectomy.[16–18] The reduction in the frequency of these serious adverse events may be attributable to multiple changes in practice, including the increased adoption of ultrasound for venous access, greater experience with the procedural technique, and the reduction in dose and duration of thrombolytic therapy.

In intermediate-high and high-risk patients, Bova and sPESI are 2 scoring systems used to predict short-term mortality at 30 days post-PE.[19–22] In KNOCOUT PE, 55.6% of patients had an sPESI score ≥1, which correlates with a 30-day mortality rate of 10.9%. Of the 477 patients in KNOCOUT PE with intermediate-high risk PE for whom Bova scores could be calculated, the mean score was 4.4 (SD=0.61); a Bova score of >4 correlates with 42% of patients experiencing PE-related complications and a 10% PE-related mortality. The 30-day mortality rate in the KNOCOUT PE prospective study was 1.0%, which is lower than would be predicted by the Bova and sPESI scoring systems; however, this may reflect the study population enrolled and selection bias. Furthermore, none of the patients who presented with high-risk PE died. These low mortality rates occurred during a time of increased implementation of organized PE response teams, increased use of catheter-based reperfusion strategies, and local protocolization of anticoagulation regimens.[23,24] Time in the ICU and length of hospital stay are also key considerations in evaluating interventional therapies for PE. In KNOCOUT PE, 90.8% of US patients and 45.6% of patients outside of the US required an ICU stay, with a mean ICU stay of 48.9 hours for the entire patient cohort. Although the patients in KNOCOUT PE had a mean thrombolytic infusion time of 10.5 hours, their longer stay in the ICU may be attributable to having clinically more severe PE (intermediate-high or high-risk

Table 6. Imaging Assessments (RV/LV, TAPSE, and eRSVP) in Patients in the KNOCOUT PE Prospective Registry Who Had Postprocedure-Matched Echocardiograms Before Discharge

	Baseline	Post-procedure*				1 mo	3 mo
		Overall (5 h to discharge)	5 to <24 h	24 to <48 h	≥48 h		
RV/LV							
N	176	176	65	77	32	13	27
Mean RV/LV (SD)	1.35 (0.32)	1.02 (0.26)	1.05 (0.24)	0.98 (0.27)	1.04 (0.28)	0.72 (0.11)	0.77 (0.15)
Mean absolute difference (SD) 2-sided *P* value†		−0.33 (0.32) <0.0001	−0.31 (0.34) <0.0001	−0.34 (0.29) <0.0001	−0.37 (0.38) <0.0001	−0.60 (0.35) <0.0001	−0.53 (0.30) <0.0001
Mean relative reduction (SD) 2-sided *P* value†		−22.64% (19.92) <0.0001	−20.06% (19.59) <0.0001	−24.57% (18.72) <0.0001	−23.48% (23.26) <0.0001	−41.79% (16.89) <0.0001	−37.99% (19.37) <0.0001
TAPSE							
N	67	67		36		6	13
Mean TAPSE (SD)	16.50 (17.91)	18.64 (5.94)		18.74 (6.38)		25.90 (3.66)	20.90 (7.08)
Mean absolute difference (SD) 2-sided *P* value†		2.14 (17.66) 0.3243		0.36 (22.85) 0.9250		5.98 (4.51) 0.0227	6.67 (5.37) 0.0008
Mean relative change (SD) 2-sided *P* value†		113.72% (299.69) 0.0028		82.58% (232.95) 0.0405		32.18% (25.87) 0.0285	57.71% (51.76) 0.0017
eRSVP							
N	62	62		31		6	4
Mean eRSVP (SD)	50.35 (15.34)	38.18 (14.45)		35.77 (16.73)		31.48 (9.81)	28.00 (8.12)
Mean absolute difference (SD) 2-sided *P* value†		−12.17 (18.16) <0.0001		−17.46 (17.54) <0.0001		−15.80 (20.41) 0.1165	−24.75 (5.06) 0.0023
Mean relative reduction (SD) 2-sided *P* value†		−17.31% (38.66) 0.0008		−28.55% (31.37) <0.0001		−24.44% (40.38) 0.1984	−47.43 (11.03) 0.0033

eRSVP indicates estimated right ventricular systolic pressure; KNOCOUT PE, The EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With Pulmonary Embolism; RV/LV, right ventricle/left ventricle ratio; and TAPSE, tricuspid annular plane systolic excursion.

*Post-procedure was defined as any assessments between 5.6 h post-procedure and discharge.

†Two-sided *P* value from *t* test.

PE) Additionally, decisions regarding patient placement in an ICU setting are subject to policies of individual hospitals and nursing competencies and not solely related to reperfusion therapy.

The mean RV/LV reduction of 22.6% on postprocedure echocardiogram was similar to observations in other single-arm prospective thrombectomy and catheter-directed thrombolysis trials (22.6%–34.9%).[6–10,16,18] In the stratified analyses by time of imaging post-intervention, the RV/LV ratio continues to improve and then stabilizes. Further reduction in RV/LV ratio was noted at 1-month post-intervention (41.8% mean improvement).

Limitations include those typically associated with an observational study, such as susceptibility to bias and confounding as well as uncertainty about causality. A major limitation is that, while screening logs were

Table 7. Quality of Life Outcomes Assessed in Patients With Intermediate-High and High-Risk Pulmonary Embolism Treated With Ultrasound-Facilitated Catheter-Directed Thrombolysis in the KNOCOUT PE Prospective Registry Study Over 12 Months Posttreatment Follow-Up

	3-mo post-procedure					12-mo post-procedure				
QoL measure	N	Post-procedure Mean (SD)	3-mo post-procedure Mean (SD)	Change Mean (SD)	2-sided *P* value*	N	Post-procedure Mean (SD)	12-mo post-procedure Mean (SD)	Change Mean (SD)	2-sided *P* value*
PEmb-QoL	243	38.5 (22.1)	16.0 (17.7)	41.1% (114.1)	<0.0001	153	38.9 (22.0)	14.1 (16.1)	44.2% (96.0)	<0.0001
VAS	242	63.1 (23.0)	75.5 (19.8)	56% (255.0)	<0.0001	152	66.2 (20.5)	77.4 (17.5)	30.3% (70.0)	<0.0001
EQ-5D-5 L Misery	243	10.2 (4.2)	7.4 (3.5)	17.8 (42.4)	<0.0001	152	9.8 (4.1)	7.1 (2.9)	18.6 (37.7)	<0.0001
EQ-5D-5 L Utility	243	0.64 (0.31)	0.83 (0.24)	0.2 (0.3)	<0.0001	152	0.67 (0.31)	0.86 (0.21)	0.2 (0.3)	<0.0001

EQ-5D-5 L indicates EuroQoL Five-Dimension Five-Level; KNOCOUT PE, The EKoSoNic Registry of the Treatment and Clinical Outcomes of Patients With Pulmonary Embolism; PEmb-QoL, pulmonary embolism quality of life; and VAS, visual analogue scale.

*2-sided *P* value from *t* test.

encouraged in KNOCOUT PE, they were not mandated. Without complete screening logs from each site, we were limited in ascertaining the extent of selection bias that may have occurred. The lack of follow-up echocardiographic data from some institutions was also a limitation. Conclusions regarding outcomes in improvement in echocardiographic measures are therefore exploratory. An additional limitation is that there was no core laboratory adjudication of imaging. Finally, the enrolled study population was predominantly White (60.5%), limiting the ability to generalize the study findings to other demographic populations.

CONCLUSIONS

USCDT is part of an increasingly diverse scope of interventional therapies for PE. This prospective study provides data on current practice and safety, which may be used by clinicians as part of the decision-making and consent processes when considering reperfusion for PE. Prospective randomized controlled trials, such as the currently enrolling HI-PEITHO (NCT04790370) and PE-TRACT trials (NCT05591118), support the evolution of evidence-based guidelines and clinical practice.[25]

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S5
Figure S1

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