

## ORIGINAL ARTICLE



# One-Year Echocardiographic, Functional, and Quality of Life Outcomes After Ultrasound-Facilitated Catheter-Based Fibrinolysis for Pulmonary Embolism

Gregory Piazza<sup>1</sup>, MD, MS\*; Keith M. Sterling, MD\*; Victor F. Tapson, MD; Kenneth Ouriel, MD; Andrew S.P. Sharp, MD; Ping-Yu Liu, PhD; Samuel Z. Goldhaber, MD; for the Optimum Duration and Dose of r-tPA with the Acoustic Pulse Thrombolysis Procedure for Intermediate-Risk Pulmonary Embolism (OPTALYSE-PE) Investigators

**BACKGROUND:** Accelerated tPA (tissue-type plasminogen activator) dosing regimens for ultrasound-facilitated, catheter-directed fibrinolysis improve short-term computed tomographic-measured right ventricular (RV)-to-left ventricular diameter ratio in massive and submassive pulmonary embolism. The impact on RV remodeling, functional status, and quality of life over the long-term remains unclear.

**METHODS:** To study 1-year changes in RV remodeling, functional status, and quality of life, we assessed patients with acute submassive pulmonary embolism randomly assigned to 1 of 4 tPA dosing regimens for ultrasound-facilitated, catheter-directed fibrinolysis in the OPTALYSE-PE trial (Optimum Duration and Dose of r-tPA With the Acoustic Pulse Thrombolysis Procedure for Intermediate-Risk Pulmonary Embolism; 8 mg/2 hours, 8 mg/4 hours, 12 mg/6 hours, and 24 mg/6 hours). Echocardiographic assessment included RV-to-left ventricular diameter ratio within 4 hours of treatment end, and at 48 hours, 30 days, 90 days, and 1 year. Functional status was assessed by 6-minute walk test at 30 days, 90 days, and 1 year and PROMIS-PF-6b scores at 30 days, 90 days, 180 days, 270 days, and 1 year. Quality of life was evaluated by PEm-QOL scores at 30 days, 90 days, 180 days, 270 days, and 1 year.

**RESULTS:** Mean RV-to-left ventricular diameter ratio decreased from baseline to 4 hours and further at 48 hours and 30 days, with reductions maintained at 90 days and 1 year in all groups. Mean 6-minute walk distance, PROMIS-PF-6b, and PEm-QOL scores improved over the course of 1 year in all groups.

**CONCLUSIONS:** Accelerated lower-dose tPA regimens for ultrasound-facilitated, catheter-directed fibrinolysis resulted in sustained recovery of RV-to-left ventricular diameter ratio and tricuspid annular plane systolic excursion and improvements in functional status and quality of life over 1 year.

**GRAPHIC ABSTRACT:** A [graphic abstract](#) is available for this article.

**REGISTRATION:** URL: <https://www.ClinicalTrials.gov>. Unique Identifier: NCT02396758.

**Key Words:** echocardiography ■ fibrinolysis ■ pulmonary artery ■ pulmonary embolism ■ quality of life

**A**lthough clinical trials have demonstrated short-term benefit of catheter-based therapies to improve right ventricular (RV) dysfunction following acute pulmonary embolism (PE),<sup>1–4</sup> a paucity of data regarding long-term RV remodeling, functional status, and quality of life exists to guide integration of these revascularization

Correspondence to: Gregory Piazza, MD, MS, Division of Cardiovascular Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. Email [gpiazza@partners.org](mailto:gpiazza@partners.org)

\*Drs Piazza and Sterling contributed equally to this work.

For Sources of Funding and Disclosures, see page 10.

© 2020 The Authors. *Circulation: Cardiovascular Interventions* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the [Creative Commons Attribution Non-Commercial-NoDerivs](#) License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited, the use is noncommercial, and no modifications or adaptations are made.

*Circulation: Cardiovascular Interventions* is available at [www.ahajournals.org/journal/circinterventions](http://www.ahajournals.org/journal/circinterventions)

### WHAT IS KNOWN

- Ultrasound-facilitated, catheter-based fibrinolytic therapy improves right ventricular (RV) dysfunction following acute pulmonary embolism.
- In the OPTALYSE-PE trial (Optimum Duration and Dose of r-tPA With the Acoustic Pulse Thrombolysis Procedure for Intermediate-Risk Pulmonary Embolism), 4 accelerated lower-dose ultrasound-assisted, catheter-based fibrinolysis regimens resulted in short-term reductions of computed tomographic-measured RV-to-left ventricular diameter ratio, a marker of RV dysfunction in pulmonary embolism, comparable to 24 mg of tPA (tissue-type plasminogen activator) administered over 12 to 24 hours studied in the SEATTLE II trial (Prospective, Single-Arm, Multi-Center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism).

### WHAT THE STUDY ADDS

- We observed improvement in short-, intermediate-, and long-term echocardiographic measures of RV remodeling and long-term functional status and quality of life in patients with submassive pulmonary embolism randomized to any of the four OPTALYSE-PE regimens.
- Reduction in echocardiographically-determined RV-to-left ventricular diameter ratio occurred in the short-term in all treatment groups and was maintained over 1 year.
- Mean 6-minute walk distance, PROMIS-PF-6b, and PEmb-QOL scores improved over 1 year in all treatment groups.

### Nonstandard Abbreviations and Acronyms

<b>CT</b>	computed tomography
<b>LV</b>	left ventricular
<b>PE</b>	pulmonary embolism
<b>RV</b>	right ventricular
<b>RVSP</b>	right ventricular systolic pressure
<b>TAPSE</b>	tricuspid annular plane systolic excursion
<b>tPA</b>	tissue-type plasminogen activator

strategies into evidence-based clinical practice.<sup>5-7</sup> An improved understanding of the complications of PE, including poor physical performance, impaired quality of life, and pulmonary hypertension, provides additional parameters to assess therapeutic response.<sup>8,9</sup> An analysis of 100 patients with acute PE from 5 Canadian hospitals demonstrated that almost half had exercise limitation at 1 year that adversely influenced quality of life, dyspnea, and walking distance.<sup>10</sup> This long-term

functional impairment after PE has become known as the "Post-PE Syndrome."

While computed tomographic (CT)-measured baseline and residual thrombus burden does not correlate with long-term functional limitation after PE,<sup>11</sup> assessment of poor recovery of RV function may identify patients with PE with an increased risk of adverse long-term outcomes.<sup>12</sup> In 203 patients with PE, increased RV-to-left ventricular (LV) diameter ratio at diagnosis correlated with reduced 6-minute walk distance in long-term follow-up.<sup>13</sup> Another study of 205 patients with submassive PE demonstrated that 41% had persistently abnormal RV function on echocardiography, functional limitation, or both at 6 months, and 20% had at least one index of poor quality-of-life.<sup>14</sup>

In short-term follow-up, ultrasound-assisted, catheter-based fibrinolysis improves RV function, reduces pulmonary artery pressures, and decreases thromboembolic burden.<sup>1-3</sup> In the dose-ranging OPTALYSE-PE trial (Optimum Duration and Dose of r-tPA With the Acoustic Pulse Thrombolysis Procedure for Intermediate-Risk Pulmonary Embolism), 4 ultrasound-assisted, catheter-based fibrinolysis regimens were evaluated in submassive PE.<sup>3</sup> All 4 regimens improved RV function comparable to 24 mg of tPA (tissue-type plasminogen activator) administered over 12 to 24 hours, based on the CT-calculated RV-to-LV diameter ratio from baseline to 48 hours. OPTALYSE-PE also provided detailed assessment of echocardiographic parameters of RV remodeling, functional status, and quality of life over 1 year. In this report, we assess short-, intermediate-, and long-term echocardiographic measures of RV remodeling and long-term functional status and quality of life in patients with submassive PE randomized to 1 of the 4 ultrasound-facilitated, catheter-based fibrinolysis regimens.

## METHODS

### Study Design

The study design of the OPTALYSE-PE trial has been described previously.<sup>3</sup> In brief, 101 trial participants were enrolled at 17 centers across the United States and Europe. Institutional Review Board approval was obtained at all sites, and written informed consent was obtained from all patients. The trial was a multicenter, parallel-group study in which participants were randomly assigned to 1 of 4 ultrasound-facilitated, catheter-based fibrinolysis regimens, varying in duration of infusion and total dose of tPA.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Population

Patients aged 18 to 75 years were eligible to participate if they had symptomatic, submassive (intermediate-risk), acute PE defined as PE symptoms for 14 days or fewer with normal systolic blood pressure (>90 mm Hg), RV-to-LV diameter ratio

≥0.9 on chest CT angiogram, and proximal PE located in at least one main or proximal lobar pulmonary artery.<sup>3</sup> Major exclusion criteria included stroke or transient ischemic attack, head trauma, other active intracranial or intraspinal disease within 1 year, active bleeding from a major organ within 1 month, major surgery within 7 days of screening, systolic blood pressure <90 mm Hg and/or use of vasopressors, hematocrit <30%, platelets <100 000/μL, INR >3; creatinine outside the normal range, and any hematologic disease potentially involving abnormal platelet number or function.

For the echocardiographic analyses, we included patients in the modified per protocol population who had bilateral catheters placed to treat bilateral PE and had technically adequate baseline and follow-up echocardiograms (Figure 1). For the functional status and quality of life analyses, we included patients in the intention-to-treat population who completed assessments at each time point and were treated with either bilateral or unilateral catheters.

### Ultrasound-Facilitated, Catheter-Based Fibrinolysis Procedure

Eligible patients were randomized to 1 of 4 study group assignments. Study group treatment arms corresponded to a specific tPA dose and duration regimen, as follows: 8 mg/2 hours (Arm 1), 8 mg/4 hours (Arm 2), 12 mg/6 hours (Arm 3), and 24 mg/6 hours (Arm 4).

All study patients received therapeutic anticoagulation. The heparin dose was reduced to 300 to 500 U/hour during the fibrinolytic infusion and increased to full therapeutic dosing after the conclusion of ultrasound-facilitated, catheter-based fibrinolysis. Patients who were prescribed low-molecular weight heparin received full therapeutic doses. After the procedure, the type and duration of anticoagulation were determined by the responsible physician. The procedure was performed in an angiographic suite by an experienced interventional radiologist, cardiologist, or vascular surgeon within 48 hours of the diagnostic chest CT angiogram. Eighty-six percent of patients had bilateral PE treated with bilateral catheters.

### Study Outcomes

The primary echocardiographic end point was mean change in RV-to-LV diameter ratio from baseline to within 4 hours after the end of the ultrasound-facilitated, catheter-based fibrinolytic procedure and 48±6 hours after its start. Secondary echocardiographic efficacy end points included mean change in tricuspid annular plane systolic excursion (TAPSE), mean change in estimated RV systolic pressure

(RVSP), and inferior vena cava collapse. All echocardiograms were analyzed at a dedicated, blinded imaging core laboratory (Syntactx, New York, NY).

Patient functional outcomes were determined by 6-minute walk test<sup>15</sup> at 30 days, 90 days, and 1 year and PROMIS-PF-6b scores (Patient-Reported Outcomes Measurement Information System Physical Function; www.commonfund.nih.gov/promis) at 30, 90, 180, 270 days, and 1 year. Before and at the conclusion of the 6-minute walk test, Borg Scale scores for dyspnea and fatigue were obtained.<sup>8</sup> Patients were asked to rate separately symptoms of dyspnea and fatigue on a scale of 0 to 10, with 0 signifying no shortness of breath and no difficulty walking; and 10 signifying maximal shortness of breath and difficulty walking.

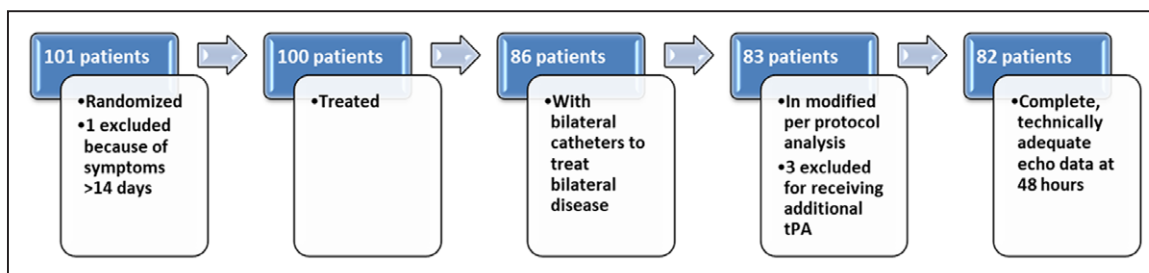
The PROMIS-PF-6b instrument measured self-reported physical functioning defined by upper extremity (dexterity), lower extremity (walking and mobility), and instrumental activities of daily living. Increases in PROMIS-PF-6b scores indicated improvement in physical functioning. A score of 50 is average for the general US population.

Quality of life was evaluated by PEmb-Quality of Life (QOL) scores at 30, 90, 180, 270 days, and 1 year.<sup>16</sup> The PEmb-QOL instrument is based on a validated 40-item questionnaire that quantifies health-related quality of life in patients with PE. The PEmb-QOL instrument includes questions related to frequency and intensity of complaints, activities of daily living, work-related problems, and emotional complaints. The minimal clinically important difference for changes in PEmb-QOL has been determined to be 15 points.<sup>17</sup> Since functional outcomes and quality of life were not assessed at the time of PE diagnosis and treatment with ultrasound-facilitated, catheter-based fibrinolysis, 6-minute walk test, Borg scale scores, PROMIS-PF-6b scores, and PEmb-QOL were compared with the initial assessments of each at 30 days (representing a post-PE baseline).

Symptomatic recurrent PE was defined as documented clinical symptoms and/or signs suggesting recurrent PE in combination with objective confirmation via chest CT angiogram, ventilation-perfusion lung scanning, or pulmonary arteriography.

### Statistical Analysis

All echocardiographic analyses were performed on the set of 82 modified per protocol patients who had bilateral catheters placed to treat bilateral PE and had complete, technically adequate echocardiograms, to ensure comparability of disease severity across treatment arms. The primary echocardiographic efficacy end point was the echocardiogram-measured RV-to-LV diameter ratio value. For each of the 4 treatment arms, the change in RV-to-LV diameter ratio over time was analyzed.



**Figure 1. Flow diagram for the echocardiographic analysis.**

tPA indicates tissue-type plasminogen activator.

TAPSE, estimated RVSP, 6-minute walk test distance, PROMIS-PF-6b scores, and PEmb-QOL scores were assessed using the same method. For RV-to-LV ratio, TAPSE, and estimated RVSP, a mixed model repeated measures (MMRM) analysis encompassing all 4 treatment arms was performed on the outcome values at baseline and 4 hours, 48 hours, 30 days, 90 days, and 1-year post procedure. Subject was a random effect for the model and the fixed effects included baseline value, assessment time point, treatment arm, and treatment versus time interaction. When treatment versus time interaction was not significant, results were presented for the model without the interaction. As nonlinear effects were expected over time and treatments were inherently ordered, time points and treatments were coded as ordinal variables: 1 to 6 for the 6 assessment time points in succession, and Arms 1 to 4 for 8 mg/2 hours, 8 mg/4 hours, 12 mg/6 hours, and 24 mg/6 hours, respectively for treatments. A similar MMRM analysis was performed for 6-minute walk test distance, PROMIS-PF-6b scores, and PEmb-QOL scores. For RV-to-LV ratio, TAPSE, estimated RVSP, 6-minute walk test distance, PROMIS-PF-6b scores, and PEmb-QOL scores, the actual data distribution at baseline and each follow-up time points were presented as box plots for each treatment.

All statistical analyses were performed using the SAS statistical software version 9.4 (SAS Institute, Cary, NC).

### Role of Funding

The sponsor had no role in data interpretation or writing the manuscript. Drs Piazza, Sterling, and Goldhaber had full access to the data, take responsibility for the integrity of the data and the analysis, and had final responsibility for the decision to submit for publication. The sponsor of the trial was in possession of the database.

## RESULTS

### Baseline Demographics and Treatment Groups

The mean age of the study population was 57.6 years. Women comprised 48% of the study population. The mean body mass index was 35.8 kg/m<sup>2</sup>.

Eighty-three patients were included in the modified per protocol population for the echocardiographic

analyses. Eighty-two had complete technically adequate data for the primary echocardiographic end point analysis (Figure 1). Complete technically adequate longer-term echocardiographic follow-up was available for 76, 70, and 64 patients at 30 days, 90 days, and 1 year, respectively (Table). There were no differences in demographic or clinical characteristics between subjects with complete longer-term echocardiographic follow-up and those excluded from the analyses due to incomplete follow-up.

Follow-up 6-minute walk test data, PROMIS-PF-6b scores, and PEmb-QOL scores were available for 78, 101, and 91 patients, respectively.

### Change in RV-to-LV Diameter Ratio

The mean echocardiographic baseline RV-to-LV diameter ratio was 1.16, 1.19, 1.14, and 1.24 in the 8 mg/2 hours (Arm 1), 8 mg/4 hours (Arm 2), 12 mg/6 hours (Arm 3), and 24 mg/6 hours (Arm 4) groups, respectively. A downward trend was observed in RV-to-LV diameter ratio over the year in all treatment groups (Figure 2). There were no significant differences between treatment groups. The MMRM analysis indicated a constant,  $\approx 0.08$  decrease in mean RV-to-LV diameter ratio from one time point to the next time point, that is, from baseline to 4 hours, 48 hours, 30 days, 90 days, and 1-year post-procedure in all treatment groups (all treatments combined  $P < 0.0001$ ).

### Tricuspid Annular Plane Systolic Excursion

The mean baseline TAPSE was 16.4, 16.8, 17.0, and 17.4 mm in the 8 mg/2 hours (Arm 1), 8 mg/4 hours (Arm 2), 12 mg/6 hours (Arm 3), and 24 mg/6 hours (Arm 4) groups, respectively. TAPSE increased after the ultrasound-facilitated, catheter-based fibrinolytic procedure in all treatment groups (Figure 3). The MMRM analysis predicted a mean TAPSE increase of 1.56, 1.31, 1.00, and 0.65 ( $P < 0.02$  for all treatments) from one time point to the next time point for 8 mg/2 hours (Arm 1), 8 mg/4 hours (Arm 2), 12 mg/6 hours (Arm 3), and 24 mg/6 hours (Arm 4), respectively.

### Estimated Right Ventricular Systolic Pressure

The mean echocardiographically-estimated baseline RVSP was 25.9, 30.3, 38.2, and 25.5 mmHg in the 8 mg/2 hours (Arm 1), 8 mg/4 hours (Arm 2), 12 mg/6 hours (Arm 3), and 24 mg/6 hours (Arm 4) groups, respectively (Figure 4). The MMRM analysis indicated a constant,  $\approx 2.46$  mmHg decrease in mean RVSP from one time point to the next time point in all treatment groups (all treatments combined  $P < 0.0001$ ).

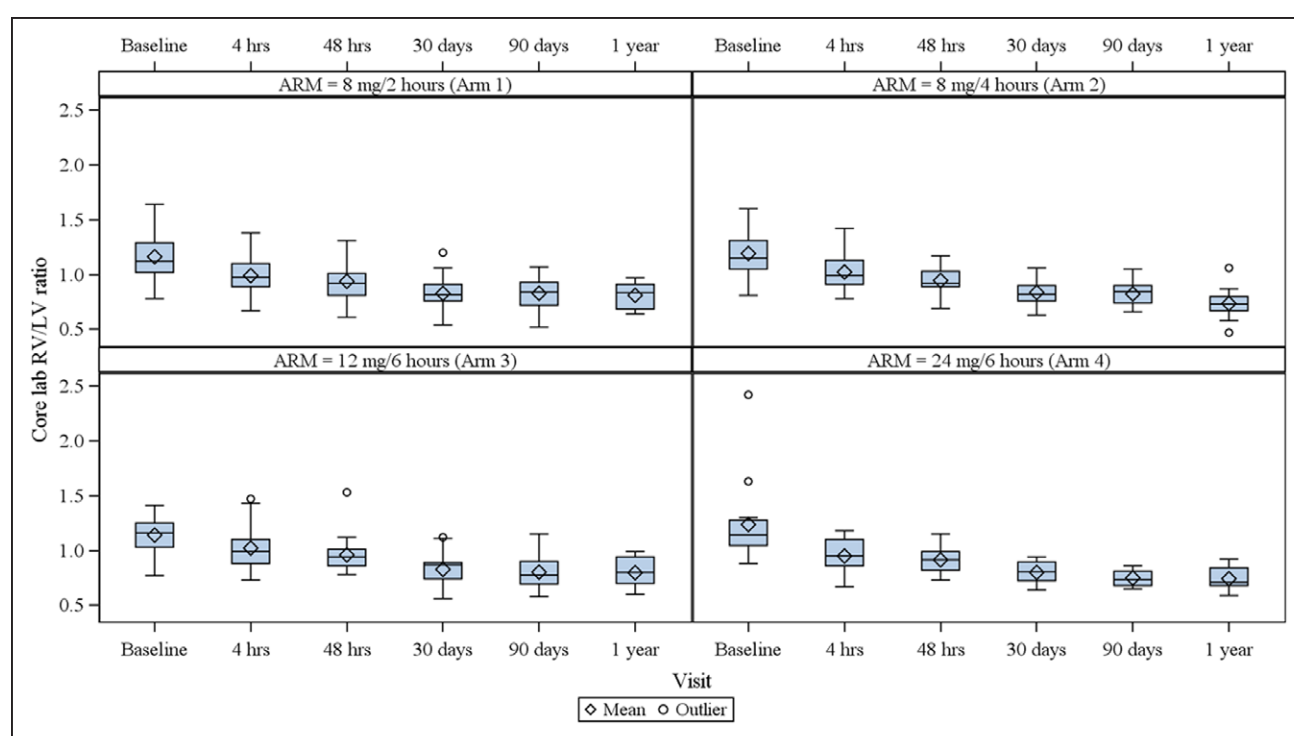
**Table. Treatment Assignments for Patients in the OPTALYSE-PE Trial Included in the Primary Echocardiographic End Point Analysis**

Fibrinolytic Regimen	Number of Patients in MPP Population With Adequate Echocardiographic Follow-Up Data*				
	4 h	48 h	30 d	90 d	1 y
8 mg/2 h	22	22	22	19	16
8 mg/4 h	21	21	19	18	17
12 mg/6 h	22	23	23	23	21
24 mg/6 h	15	16	12	10	10
Total	80	82	76	70	64

MPP indicates modified-per-protocol; and OPTALYSE-PE, Optimum Duration and Dose of r-tPA With the Acoustic Pulse Thrombolysis Procedure for Intermediate-Risk Pulmonary Embolism.

\*Patients with bilateral catheters to treat bilateral pulmonary embolism and who received protocol specified dose of tPA (tissue-type plasminogen activator).





**Figure 2.** Right ventricular (RV)-to-left ventricular (LV) diameter ratio at baseline and 4 h, 48 h, 30 d, 90 d, and 1 y after the ultrasound-facilitated, catheter-based fibrinolytic procedure.

## Respirophasic Collapse of the Inferior Vena Cava

Respirophasic inferior vena cava collapse was observed in 94%, 93.3%, 96.7%, 94.8%, 96.2%, and 86.4% at baseline, within 4 hours, 48 hours, 30 days, 90 days, and 1 year, respectively. The frequency of respirophasic collapse remained similar among the treatment groups at each time point.

## Functional Performance Assessment

Mean 6-minute walk test distance at 30 days was  $351.6 \pm 91.1$  meters (Arm 1),  $352.2 \pm 148.2$  meters (Arm 2),  $343.1 \pm 110.2$  meters (Arm 3), and  $327.3 \pm 99.7$  meters (Arm 4). Mean 6-minute walk distance increased over 1 year in all treatment groups (Figure 5). The MMRM analysis indicated no differences among treatment arms and a mean 6-minute walk distance increase of  $\approx 26.7$  meters from 30 days to 90 days and from 90 days to 1 year (all treatments combined  $P=0.0148$ ).

The proportion of patients reporting Borg Scale scores for dyspnea of 0 before the 6-minute walk test numerically increased over 1 year in Arm 2, Arm 3, and Arm 4 (Figure 6). The proportion of patients reporting Borg Scale scores for dyspnea of 0 following the 6-minute walk test numerically increased over one year in Arm 1, Arm 3, and Arm 4. The proportion of patients reporting Borg Scale scores for fatigue of 0 before and following the 6-minute walk test numerically increased over 1 year in Arm 1, Arm 2, and Arm 3 (Figure 6).

Mean PROMIS-PF-6b scores improved over the course of 1 year in all treatment groups (Figure 5). The MMRM analysis indicated no differences among treatment arms and a mean PROMIS-PF-6b score increase of  $\approx 1.0$  point from 1 follow-up time point to the next time point (all treatments combined  $P=0.0002$ ).

## Quality of Life

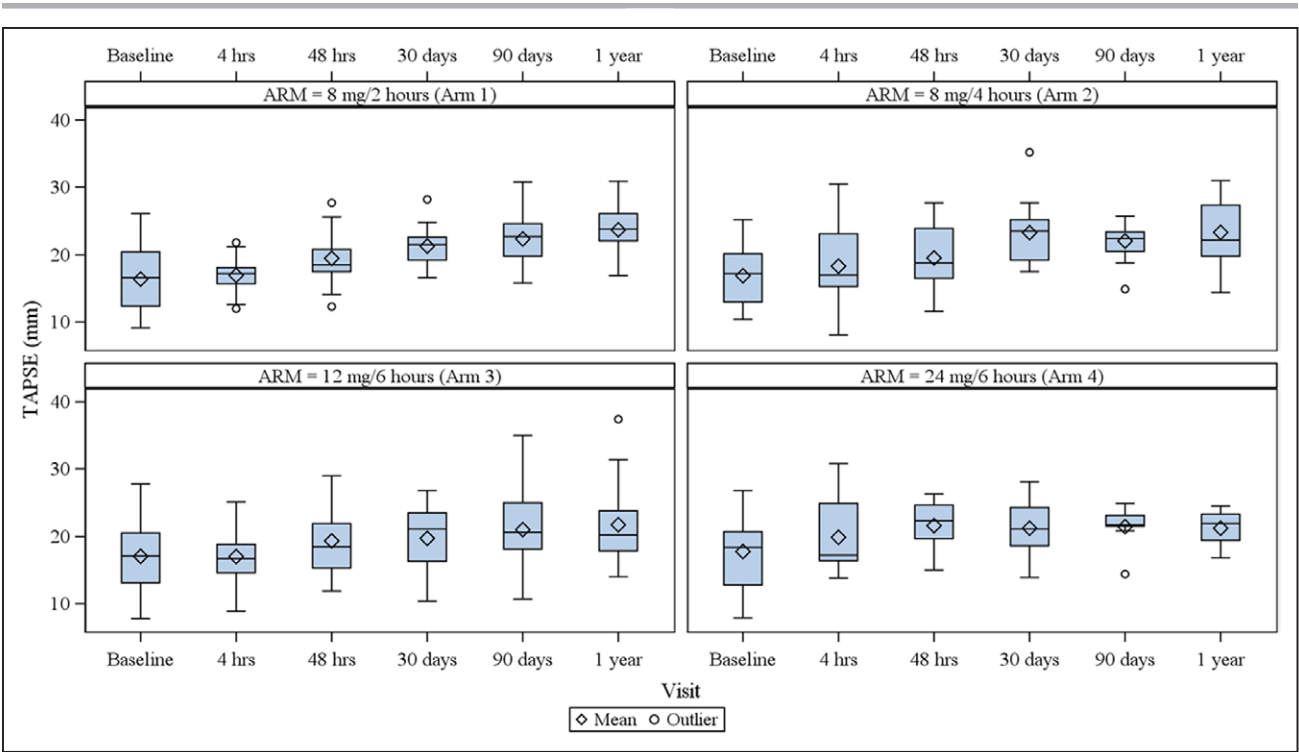
Quality of life as measured by the mean PEmb-QOL score improved over 1 year in all treatment groups (Figure 5). The MMRM analysis indicated no differences among treatment arms and a mean PEmb-QOL score decrease of  $\approx 3.1$  point from 1 follow-up time point to the next time point (all treatments combined  $P<0.0001$ ).

## One-Year Safety Outcomes

In the overall safety population (Arms 1–4), symptomatic recurrent PE occurred in 1 patient by 30 days and 1 patient by 1 year for a total frequency of 2%. All-cause mortality was observed in 1 patient by 30 days (cardiac arrest 11 days after treatment) and 1 patient by 1 year (respiratory failure due to chronic obstructive pulmonary disease 6 months after treatment) for a total mortality rate of 2%.

## DISCUSSION

We observed improvement in short-, intermediate-, and long-term echocardiographic measures of RV

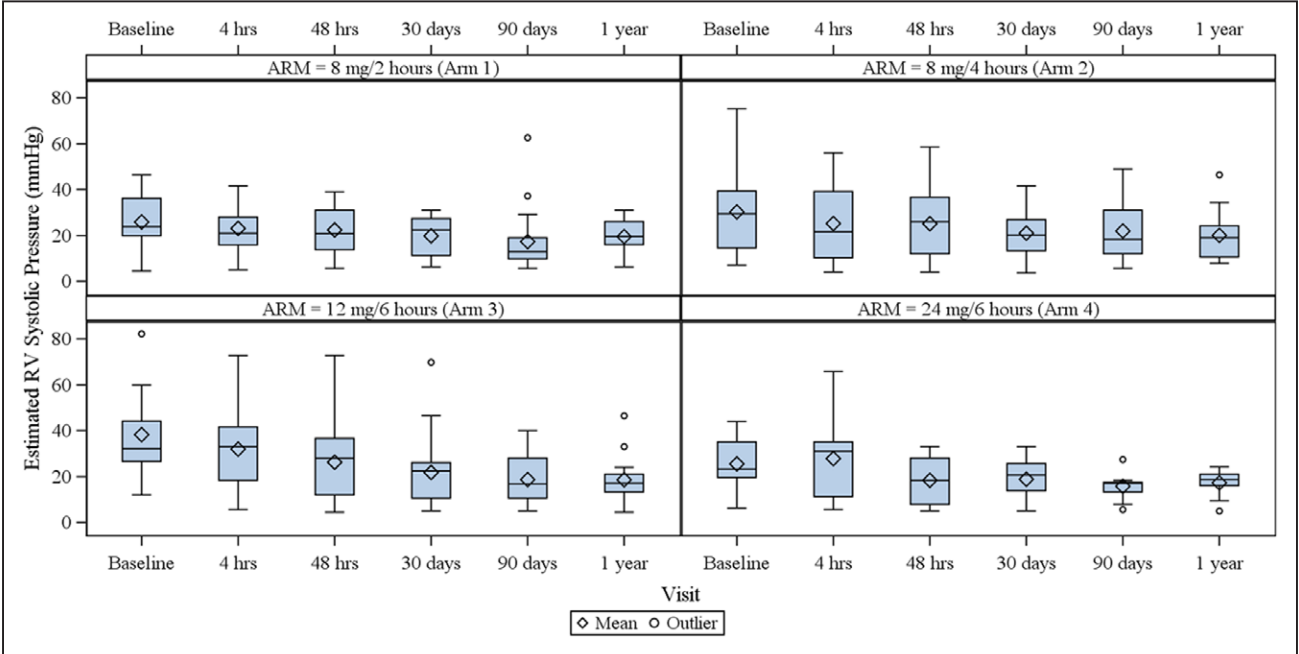


**Figure 3.** Tricuspid annular plane systolic excursion (TAPSE) at baseline and 4 h, 48 h, 30 d, 90 d, and 1 y after the ultrasound-facilitated, catheter-based fibrinolytic procedure.

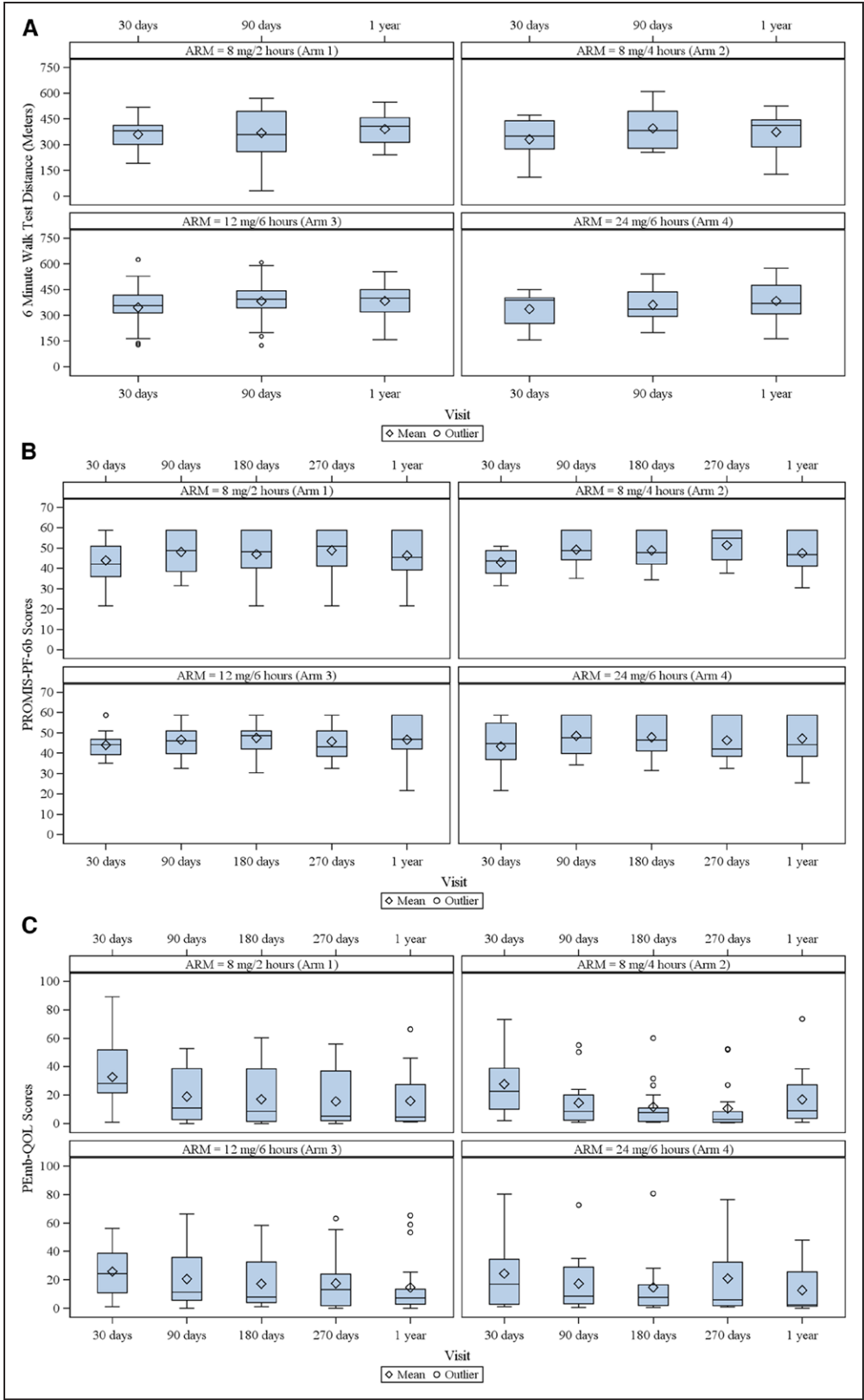
remodeling and long-term functional status and quality of life in patients with submassive PE randomized to any of the 4 ultrasound-facilitated, catheter-based fibrinolysis regimens. Reduction in the RV-to-LV diameter ratio occurred in the short-term in all accelerated lower-dose regimens and was maintained at one year.

Mean 6-minute walk distance, PROMIS-PF-6b, and PEmb-QOL scores improved over the course of 1 year in all treatment groups.

The most comprehensively studied of advanced therapies for acute PE, full-dose intravenous fibrinolysis, has demonstrated efficacy for prevention of early morbidity

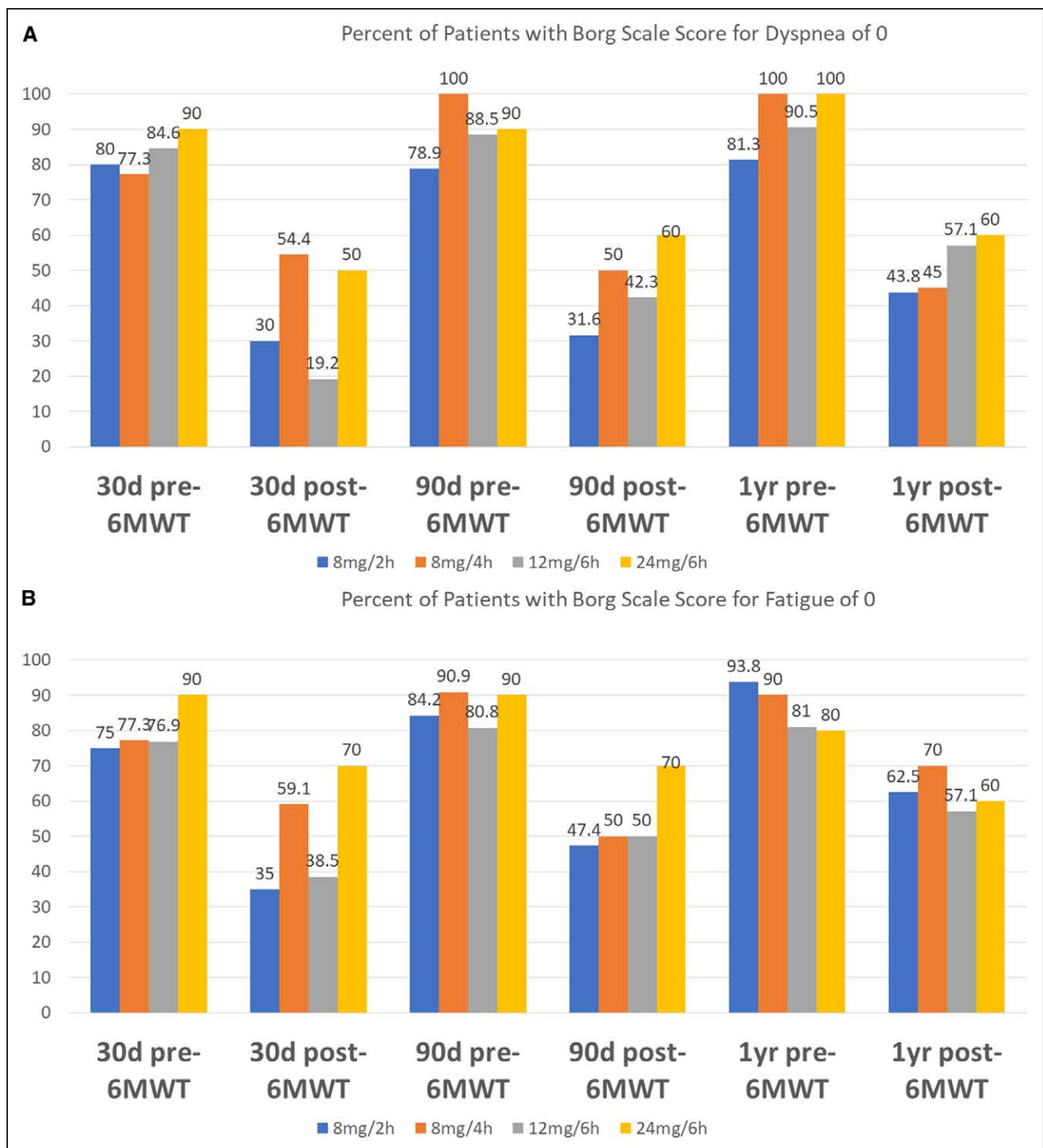


**Figure 4.** Estimated right ventricular (RV) systolic pressure at baseline and 4 h, 48 h, 30 d, 90 d, and 1 y after the ultrasound-facilitated, catheter-based fibrinolytic procedure.



**Figure 5. Functional performance and quality of life assessments.**

Six-minute walk test at 30 d, 90 d, and 1 y after the ultrasound-facilitated, catheter-based fibrinolytic procedure (A). \*PROMIS-PF-6b scores at 30 d, 90 d, 180 d, 270 d, and 1 y after the ultrasound-facilitated, catheter-based fibrinolytic procedure (B). PEmb-QOL scores at 30 d, 90 d, 180 d, 270 d, and 1 y after the ultrasound-facilitated, catheter-based fibrinolytic procedure (C). \*Note: one outlier of 1400 m for Arm 3 at 1 y.



**Figure 6.** Proportion of patients reporting Borg Scale scores for dyspnea and fatigue of 0 at 30, 90 d, and 1 y after the ultrasound-facilitated, catheter-based fibrinolytic procedure. 6MWT indicates six-minute walk test.

and mortality.<sup>18–20</sup> However, peripheral intravenous fibrinolysis provides limited net clinical benefit because of the increased risk of intracranial hemorrhage<sup>21,22</sup> and lack of impact on long-term mortality rates, residual dyspnea, pulmonary hypertension, and RV dysfunction.<sup>23</sup> Catheter-directed therapy facilitates lower-dose fibrinolytic regimens that improve RV recovery while reducing the risk of major bleeding.<sup>1–3,24–30</sup> A single-center prospective

study of 25 patients with submassive PE, treated with ultrasound-facilitated, catheter-directed fibrinolysis, demonstrated significant reduction in echocardiographically measured RV-to-LV diameter ratio from baseline to 72 hours after the procedure and preservation of RV recovery at 90 days.<sup>31</sup> In the current study, we demonstrated that accelerated lower-dose regimens improved echocardiographic markers of RV remodeling, including



RV-to-LV diameter ratio and TAPSE, in the short-term and at 1 year.

Sustained echocardiographic improvement seems to be important for preventing the post-PE syndrome by enabling more complete functional recovery.<sup>32</sup> Kahn et al<sup>8</sup> examined 100 patients at 1 and 12 months after PE. Nearly half had exercise limitation and echocardiographic abnormalities at 1 year. In a subsequent study of 20 patients with massive or submassive PE, Albaghdadi et al<sup>33</sup> showed that at 6 months, persistent symptoms, abnormalities of RV structure and function, and exercise limitation were common. In meta-analysis, systemic full-dose fibrinolytic therapy has not been shown to reduce the risk of at least moderate functional impairment compared with anticoagulation alone.<sup>34</sup> In contrast, a separate meta-analysis of ultrasound-assisted catheter-directed versus systemic fibrinolysis for massive and submassive PE showed that ultrasound-assisted catheter-directed therapy was associated with a lower rate of major bleeding.<sup>35</sup>

From the interval of 1 month to 1 year after initial therapy, patients in the OPTALYSE-PE trial demonstrated increased 6-minute walk test distance, a greater proportion of patients without symptoms of dyspnea or fatigue following 6-minute walk test, improved functional performance scores, and better quality of life. Although the current trial did not include an anticoagulation alone comparator group, the 1-year improvement in functional performance and quality of life across all treatment groups mirrored the recovery of RV function as assessed by serial echocardiography. A prospective, multicenter cohort study of 100 patients with acute PE, two-thirds of whom had normal RV function at time of diagnosis, and treated predominantly with anticoagulation alone, has also observed improvement in functional performance and quality of life over 1 year.<sup>8</sup> In our higher-risk OPTALYSE-PE cohort, patients treated with accelerated lower-dose regimens demonstrated an improvement in mean 6-minute walk test distance of nearly 40 meters, increases in PROMIS-PF-6b scores approaching 50 (average for the general US population), and reductions in PEmb-QOL scores of  $\approx 15$ , signifying a clinically important difference.

In a separate study, we used a CT-based, 3-dimensional reconstruction technique to analyze the pulmonary vascular response to ultrasound-facilitated, catheter-directed fibrinolysis for PE in the SEATTLE II trial (Prospective, Single-Arm, Multi-Center Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism). We found that post-PE RV enlargement was related to decreased distal pulmonary arterial blood volume, even when adjusted for central thromboembolic burden.<sup>36</sup> After ultrasound-facilitated, catheter-directed fibrinolysis, there was an increase in distal pulmonary arterial blood volume. The increase in the distal, but not proximal, pulmonary arterial blood

volume correlated with RV decompression after intervention. This finding may explain why there was not a dose-response effect in OPTALYSE-PE. The impact of ultrasound-facilitated, catheter-directed fibrinolysis on the distal pulmonary vasculature may provide a potential mechanism for the long-term RV remodeling, functional performance recovery, and improved quality of life observed in the current study.

Our results must be interpreted within the context of the study design. Relatively small sample sizes within each study arm limited our ability to discern significant differences in echocardiographic parameters, functional performance, and quality of life across study groups. We did not evaluate more advanced echocardiographic techniques such as strain and strain rate, which carry short-term prognostic value.<sup>37,38</sup> While echocardiography is more widely available, less costly, and more practical for this study, cardiac magnetic resonance is considered the gold standard for assessment of RV structure and function because of enhanced precision for detecting small changes in RV function and overall greater reproducibility.<sup>39,40</sup> Nevertheless, echocardiography has been validated for long-term follow-up of RV size and function in clinical trials of pulmonary vasodilators for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.<sup>41</sup>

We observed attrition of echocardiographic, functional performance, and quality life assessments in follow-up for the longer-term time points across all the study groups. Because there was neither a systemic or catheter-directed fibrinolytic infusion arm nor anticoagulation only comparator, we cannot determine how these accelerated regimens for ultrasound-facilitated, catheter-directed fibrinolysis may compare with other therapeutic strategies. While ultrasound-facilitated, catheter-directed fibrinolysis accelerates short-term recovery of RV function, a "catch-up" phenomenon has been reported in patients with PE treated with anticoagulation alone compared with catheter-directed fibrinolysis after 30 days.<sup>1,24</sup> Prospective studies comparing ultrasound-facilitated, catheter-directed fibrinolysis with systemic and other catheter-based systems will be needed to determine the impact of ultrasound itself on the pulmonary vasculature, RV remodeling, and patient-centered clinical and functional outcomes.<sup>26,28,29</sup>

Serial assessments of RV remodeling in the short- (4 hours and 48 hours), intermediate- (30 and 90 days), and long-term (1 year) and functional performance and quality of life in the intermediate term and long term are the main strengths of our analysis. While a similar study of patients with submassive PE evaluated a subset with echocardiography at 6 months,<sup>14</sup> no other study has performed similarly rigorous and extensive short-, intermediate-, and long-term echocardiographic evaluation and functional performance and quality of life assessment after catheter-based therapy for PE. We used

well-validated tools for measurement of functional performance (6-minute walk test and PROMIS-PF-6b) and quality of life (PEmb-QOL). Finally, all echocardiographic parameters were analyzed by a central core imaging laboratory with blinded interpretation.

In conclusion, accelerated lower-dose tPA regimens for ultrasound-facilitated, catheter-directed fibrinolysis resulted in sustained recovery over 1 year of follow-up of the echocardiographically determined RV function in all treatment groups. Improvements in long-term functional status and quality of life paralleled RV recovery.

## ARTICLE INFORMATION

Received January 21, 2020; accepted June 3, 2020.

### Affiliations

Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (G.P.). Department of Cardiovascular and Interventional Radiology, INOVA Alexandria Hospital, VA (K.M.S.). Pulmonary/Critical Care Division, Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA (V.F.T.). Syntactx, New York (K.O.). University Hospital of Wales, Cardiff, United Kingdom (A.S.P.S.). University of Exeter, United Kingdom (A.S.P.S.). Fred Hutchinson Cancer Center, Seattle, WA (P.-Y.L.). Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (S.Z.G.).

### Sources of Funding

This study was funded by a research grant from BTG International.

### Disclosures

Dr Piazza receives significant research grant support from BTG International, Bristol Myers Squibb, Daiichi-Sankyo, Bayer, Portola, and Janssen and has received modest consulting fees from Pfizer. Dr Tapson receives significant research grant support from Bio2 Medical, Bayer, BTG International, Daiichi-Sankyo, Inari, Janssen, and Portola and has received modest consulting fees from Bayer and Janssen. Dr Sterling receives significant research support from BTG International. Dr Ouriel holds significant equity in and is an employee of Syntactx which receives significant fees for core laboratory activities from BTG International. Dr Sharp receives significant research support and modest consulting fees from BTG International. Dr Liu receives significant consulting fees from BTG International. Dr Goldhaber receives significant research grant support from BTG International, Bristol Myers Squibb, Daiichi-Sankyo, Bayer, Portola, and Janssen.

## REFERENCES

- Kucher N, Boekstegers P, Müller OJ, Kupatt C, Beyer-Westendorf J, Heitzer T, Tebbe U, Horstkotte J, Müller R, Blessing E, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. *Circulation*. 2014;129:479–486. doi: 10.1161/CIRCULATIONAHA.113.005544
- Piazza G, Hohlfelder B, Jaff MR, Ouriel K, Engelhardt TC, Sterling KM, Jones NJ, Gurley JC, Bhatheja R, Kennedy RJ, et al; SEATTLE II Investigators. A prospective, single-arm, multicenter trial of ultrasound-facilitated, catheter-directed, low-dose fibrinolysis for acute massive and submassive pulmonary embolism: the SEATTLE II study. *JACC Cardiovasc Interv*. 2015;8:1382–1392. doi: 10.1016/j.jcin.2015.04.020
- Tapson VF, Sterling K, Jones N, Elder M, Tripathy U, Brower J, Maholic RL, Ross CB, Natarajan K, Fong P, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE trial. *JACC Cardiovasc Interv*. 2018;11:1401–1410. doi: 10.1016/j.jcin.2018.04.008
- Tu T, Toma C, Tapson VF, Adams C, Jaber WA, Silver M, Khandhar S, Amin R, Weinberg M, Engelhardt T, et al; FLARE Investigators. A prospective, single-arm, multicenter trial of catheter-directed mechanical thrombectomy for intermediate-risk acute pulmonary embolism: the FLARE study. *JACC Cardiovasc Interv*. 2019;12:859–869. doi: 10.1016/j.jcin.2018.12.022
- Giri J, Sista AK, Weinberg I, Kearon C, Kumbhani DJ, Desai ND, Piazza G, Gladwin MT, Chatterjee S, Kobayashi T, et al. Interventional therapies for acute pulmonary embolism: current status and principles for the development of novel evidence: a scientific statement from the American Heart Association. *Circulation*. 2019;140:e774–e801. doi: 10.1161/CIR.0000000000000707
- Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149:315–352. doi: 10.1016/j.chest.2015.11.026
- Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman M, Humbert M, Jennings CS, Jiménez D, et al; ESC Scientific Document Group. 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;41:543–603. doi: 10.1093/eurheartj/ehz405
- Kahn SR, Akaberi A, Granton JT, Anderson DR, Wells PS, Rodger MA, Solymoss S, Kovacs MJ, Rudski L, Shimony A, et al. Quality of life, dyspnea, and functional exercise capacity following a first episode of pulmonary embolism: results of the ELOPE cohort study. *Am J Med*. 2017;130:990.e9–990.e21. doi: 10.1016/j.amjmed.2017.03.033
- Konstantinides SV, Barco S, Rosenkranz S, Lankeit M, Held M, Gerhardt F, Bruch L, Ewert R, Faehling M, Freise J, et al. Late outcomes after acute pulmonary embolism: rationale and design of FOCUS, a prospective observational multicenter cohort study. *J Thromb Thrombolysis*. 2016;42:600–609. doi: 10.1007/s11239-016-1415-7
- Kahn SR, Hirsch AM, Akaberi A, Hernandez P, Anderson DR, Wells PS, Rodger MA, Solymoss S, Kovacs MJ, Rudski L, et al. Functional and exercise limitations after a first episode of pulmonary embolism: results of the ELOPE prospective cohort study. *Chest*. 2017;151:1058–1068. doi: 10.1016/j.chest.2016.11.030
- Ma KA, Kahn SR, Akaberi A, Dennie C, Rush C, Granton JT, Anderson D, Wells PS, Rodger MA, Solymoss S, et al; ELOPE Study group. Serial imaging after pulmonary embolism and correlation with functional limitation at 12 months: Results of the ELOPE Study. *Res Pract Thromb Haemost*. 2018;2:670–677. doi: 10.1002/rth.2.12123
- Jaff MR, McMurtry MS, Archer SL, Cushman M, Goldenberg N, Goldhaber SZ, Jenkins JS, Kline JA, Michaels AD, Thistlethwaite P, et al; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; American Heart Association Council on Peripheral Vascular Disease; American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation*. 2011;123:1788–1830. doi: 10.1161/CIR.0b013e318214914f
- Tavoly M, Wik HS, Sirnes PA, Jelsness-Jørgensen LP, Ghanima JP, Klok FA, Sandset PM, Ghanima W. The impact of post-pulmonary embolism syndrome and its possible determinants. *Thromb Res*. 2018;171:84–91. doi: 10.1016/j.thromres.2018.09.048
- Stevenson BG, Hernandez-Nino J, Rose G, Kline JA. Echocardiographic and functional cardiopulmonary problems 6 months after first-time pulmonary embolism in previously healthy patients. *Eur Heart J*. 2007;28:2517–2524. doi: 10.1093/eurheartj/ehm295
- Chow V, Ng AC, Secombe L, Chung T, Thomas L, Celermajer DS, Peters M, Kriharides L. Impaired 6-min walk test, heart rate recovery and cardiac function post pulmonary embolism in long-term survivors. *Respir Med*. 2014;108:1556–1565. doi: 10.1016/j.rmed.2014.08.002
- Klok FA, Cohn DM, Middeldorp S, Scharloo M, Büller HR, van Kralingen KW, Kaptein AA, Huisman MV. Quality of life after pulmonary embolism: validation of the PEmb-QoL Questionnaire. *J Thromb Haemost*. 2010;8:523–532. doi: 10.1111/j.1538-7836.2009.03726.x
- Akaberi A, Klok FA, Cohn DM, Hirsch A, Granton J, Kahn SR. Determining the minimal clinically important difference for the PEmbQoL questionnaire, a measure of pulmonary embolism-specific quality of life. *J Thromb Haemost*. 2018;16:2454–2461. doi: 10.1111/jth.14302
- Chatterjee S, Chakraborty A, Weinberg I, Kadakia M, Wilensky RL, Sardar P, Kumbhani DJ, Mukherjee D, Jaff MR, Giri J. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. *JAMA*. 2014;311:2414–2421. doi: 10.1001/jama.2014.5990
- Marti C, John G, Konstantinides S, Combescure C, Sanchez O, Lankeit M, Meyer G, Perrier A. Systemic thrombolytic therapy for acute

- pulmonary embolism: a systematic review and meta-analysis. *Eur Heart J*. 2015;36:605–614. doi: 10.1093/eurheartj/ehu218
20. Meyer G, Vicaute E, Danays T, Agnelli G, Becattini C, Beyer-Westendorf J, Bluhmki E, Bouvaist H, Brenner B, Couturaud F, et al; PEITHO Investigators. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370:1402–1411. doi: 10.1056/NEJMoa1302097
  21. Fiumara K, Kucher N, Fanikos J, Goldhaber SZ. Predictors of major hemorrhage following fibrinolysis for acute pulmonary embolism. *Am J Cardiol*. 2006;97:127–129. doi: 10.1016/j.amjcard.2005.07.117
  22. Piazza G. Submassive pulmonary embolism. *JAMA*. 2013;309:171–180. doi: 10.1001/jama.2012.164493
  23. Konstantinides SV, Vicaute E, Danays T, Becattini C, Bertoletti L, Beyer-Westendorf J, Bouvaist H, Couturaud F, Dellas C, Dierschmied D, et al. Impact of thrombolytic therapy on the long-term outcome of intermediate-risk pulmonary embolism. *J Am Coll Cardiol*. 2017;69:1536–1544. doi: 10.1016/j.jacc.2016.12.039
  24. Avgerinos ED, Abou Ali AN, Liang NL, Rivera-Lebron B, Toma C, Maholic R, Makaroun MS, Chaer RA. Catheter-directed interventions compared with systemic thrombolysis achieve improved ventricular function recovery at a potentially lower complication rate for acute pulmonary embolism. *J Vasc Surg Venous Lymphat Disord*. 2018;6:425–432. doi: 10.1016/j.jvsv.2017.12.058
  25. Kaymaz C, Akbal OY, Hakgor A, Tokgoz HC, Karagoz A, Tanboga IH, Tanyeri S, Keskin B, Turkday S, Demir D, et al. A five-year, single-centre experience on ultrasound-assisted, catheter-directed thrombolysis in patients with pulmonary embolism at high risk and intermediate to high risk. *EuroIntervention*. 2018;14:1136–1143. doi: 10.4244/EIJ-D-18-00371
  26. Klein AJ, Shishehbor MH. Ultrasound-assisted catheter directed therapy (CDT) for pulmonary embolism versus standard CDT: sounds of a cry for data! *Vasc Med*. 2019;24:248–250. doi: 10.1177/1358863X19838346
  27. Kuo WT, Banerjee A, Kim PS, DeMarco FJ, Jr, Levy JR, Facchini FR, Unver K, Bertini MJ, Sista AK, Hall MJ, et al. Pulmonary embolism response to fragmentation, embolectomy, and catheter thrombolysis (PERFECT): initial results from a prospective multicenter registry. *Chest*. 2015;148:667–673. doi: 10.1378/chest.15-0119
  28. Rao G, Xu H, Wang JJ, Galmer A, Giri J, Jaff MR, Kolluri R, Lau JF, Selim S, Weinberg I, et al. Ultrasound-assisted versus conventional catheter-directed thrombolysis for acute pulmonary embolism: a multicenter comparison of patient-centered outcomes. *Vasc Med*. 2019;24:241–247. doi: 10.1177/1358863X19838334
  29. Rothschild DP, Goldstein JA, Ciacci J, Bowers TR. Ultrasound-accelerated thrombolysis (USAT) versus standard catheter-directed thrombolysis (CDT) for treatment of pulmonary embolism: a retrospective analysis. *Vasc Med*. 2019;24:234–240. doi: 10.1177/1358863X19838350
  30. Sadiq I, Goldhaber SZ, Liu PY, Piazza G. Submassive and Massive Pulmonary Embolism Treatment with Ultrasound Accelerated Thrombolysis Therapy (SEATTLE II) Investigators. Risk factors for major bleeding in the SEATTLE II trial. *Vasc Med*. 2017;22:44–50. doi: 10.1177/1358863X16676355
  31. Knox MF, Langholz DE, Berjaoui WK, Eberhart L. Preservation of cardiopulmonary function in patients treated with ultrasound-accelerated thrombolysis in the setting of submassive pulmonary embolism. *J Vasc Interv Radiol*. 2019;30:734–741. doi: 10.1016/j.jvir.2018.08.027
  32. Barco S, Russo M, Vicaute E, Becattini C, Bertoletti L, Beyer-Westendorf J, Bouvaist H, Couturaud F, Danays T, Dellas C, et al. Incomplete echocardiographic recovery at 6 months predicts long-term sequelae after intermediate-risk pulmonary embolism. A post-hoc analysis of the Pulmonary Embolism Thrombolysis (PEITHO) trial. *Clin Res Cardiol*. 2019;108:772–778. doi: 10.1007/s00392-018-1405-1
  33. Albaghdadi MS, Dudzinski DM, Giordano N, Kabrhel C, Ghoshhajra B, Jaff MR, Weinberg I, Baggish A. Cardiopulmonary exercise testing in patients following massive and submassive pulmonary embolism. *J Am Heart Assoc*. 2018;7:e006841. doi: 10.1161/JAHA.117.006841
  34. Sista AK, Miller LE, Kahn SR, Kline JA. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: systematic review with meta-analysis. *Vasc Med*. 2017;22:37–43. doi: 10.1177/1358863X16670250
  35. Kaymaz C, Akbal OY, Tanboga IH, Hakgor A, Yilmaz F, Ozturk S, Poci N, Turkday S, Ozdemir N, Konstantinides S. Ultrasound-assisted catheter-directed thrombolysis in high-risk and intermediate-high-risk pulmonary embolism: a meta-analysis. *Curr Vasc Pharmacol*. 2018;16:179–189. doi: 10.2174/157016115666170404122535
  36. Rahaghi FN, San José Estépar R, Goldhaber SZ, Minhas JK, Nardelli P, Vegas Sanchez-Ferrero G, De La Bruere I, Hassan SM, Mason S, Ash SY, et al. Quantification and significance of pulmonary vascular volume in predicting response to ultrasound-facilitated, catheter-directed fibrinolysis in acute pulmonary embolism (SEATTLE-3D). *Circ Cardiovasc Imaging*. 2019;12:e009903. doi: 10.1161/CIRCIMAGING.119.009903
  37. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, Kociol RD, Lewis EF, Mehra MR, Pagani FC, et al; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. *Circulation*. 2018;137:e578–e622. doi: 10.1161/CIR.0000000000000560
  38. Lee K, Kwon O, Lee EJ, Sin MJ, Lee JS, Lee S, Kang DH, Song JK, Song JM. Prognostic value of echocardiographic parameters for right ventricular function in patients with acute non-massive pulmonary embolism. *Heart Vessels*. 2019;34:1187–1195. doi: 10.1007/s00380-019-01340-1
  39. Bax JJ, Di Carli M, Narula J, Delgado V. Multimodality imaging in ischaemic heart failure. *Lancet*. 2019;393:1056–1070. doi: 10.1016/S0140-6736(18)33207-0
  40. Lahm T, Douglas IS, Archer SL, Bogaard HJ, Chesler NC, Haddad F, Hemnes AR, Kawut SM, Kline JA, Kolb TM, et al; American Thoracic Society Assembly on Pulmonary Circulation. Assessment of right ventricular function in the research setting: knowledge gaps and pathways forward. an official american thoracic society research statement. *Am J Respir Crit Care Med*. 2018;198:e15–e43. doi: 10.1164/rccm.201806-1160ST
  41. Marra AM, Halank M, Benjamin N, Bossone E, Cittadini A, Eichstaedt CA, Egenlauf B, Harutyunova S, Fischer C, Gall H, et al. Right ventricular size and function under riociguat in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (the RIVER study). *Respir Res*. 2018;19:258. doi: 10.1186/s12931-018-0957-y