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Intravascular Ultrasound Pulmonary Artery Denervation to Treat Pulmonary Arterial Hypertension (TROPHY1)

Multicenter, Early Feasibility Study

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ABSTRACT

OBJECTIVES The aim of this study was to investigate whether therapeutic intravascular ultrasound pulmonary artery denervation (PDN) is safe and reduces pulmonary vascular resistance (PVR) in patients with pulmonary arterial hypertension (PAH) on a minimum of dual oral therapy.

BACKGROUND Early studies have suggested that PDN can reduce PVR in patients with PAH.

METHODS TROPHY1 (Treatment of Pulmonary Hypertension 1) was a multicenter, international, open-label trial undertaken at 8 specialist centers. Patients 18 to 75 years of age with PAH were eligible if taking dual oral or triple nonparenteral therapy and not responsive to acute vasodilator testing. Eligible patients underwent PDN (TIVUS System). The primary safety endpoint was procedure-related adverse events at 30 days. Secondary endpoints included procedure-related adverse events, disease worsening and death to 12 months, and efficacy endpoints that included change in pulmonary hemodynamic status, 6-min walk distance, and quality of life from baseline to 4 or 6 months. Patients were to remain on disease-specific medication for the duration of the study.

RESULTS Twenty-three patients underwent PDN, with no procedure-related serious adverse events reported. The reduction in PVR at 4- or 6-month follow-up was 94 ± 151 dyn·s·cm^{-5} ($p = 0.001$) or 17.8%, which was associated with a 42 ± 63 m ($p = 0.02$) increase in 6-min walk distance and a 671 ± 1,555 step ($p = 0.04$) increase in daily activity.

CONCLUSIONS In this multicenter early feasibility study, PDN with an intravascular ultrasound catheter was performed without procedure-related adverse events and was associated with a reduction in PVR and increases in 6-min walk distance and daily activity in patients with PAH on background dual or triple therapy. (J Am Coll Cardiol Intv 2020;13:989–99)

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ABBREVIATIONS AND ACRONYMS

PAH = pulmonary arterial hypertension

PDN = pulmonary artery denervation

PVR = pulmonary vascular resistance

Patients with pulmonary arterial hypertension (PAH) manifest signs of sympathetic overdrive (1) that are associated with poor outcomes (2). The lungs are a major source of catecholamines and both release and metabolize >40% of circulating levels (3). It is unknown whether activation of the sympathetic nervous system is a secondary phenomenon or whether it may play an exacerbating and/or pathogenic role in the progression of disease. In experimental models of pulmonary hypertension, therapies that target the sympathetic (4,5) and renin-angiotensin-aldosterone (6) systems reduce small-vessel remodeling and improve hemodynamic status. However, in patients with PAH, the few studies undertaken thus far have demonstrated modulation of both pulmonary and systemic hemodynamic status, with no evidence of clinical benefit (7–9). Furthermore, beta-adrenergic blockade may produce deterioration in patients with PAH resulting from the systemic hemodynamic effects (hypotension, reduced heart rate, and cardiac output).

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Catheter-based renal denervation in patients with systemic hypertension reduces blood pressure (10–12). Such technologies offer the opportunity to modulate sympathetic activity through targeted denervation of the pulmonary vasculature, potentially avoiding the adverse effects of systemically active therapies. Nerves surrounding the pulmonary vasculature are present to a depth of 4 mm in large animals (13,14) and 10 mm in human samples (15). In patients with PAH, the application of radiofrequency energy to a specific location at the bifurcation is reported to provide an acute improvement in hemodynamic status that persists to 3 months despite the withdrawal of disease-specific therapy (16). Current guidelines indicate that patients with PAH and high-risk indicators should be treated with 2 disease-specific therapies (17). As such, the effect of pulmonary artery denervation (PDN) in patients on best medical therapy is unknown, as is the feasibility of ultrasound energy delivery for PDN.

The TIVUS System (SoniVie, Rosh Haayin, Israel) is a percutaneous, noncontact catheter that provides a fenestrated ring of thermal effect to a depth of 10 mm, which is the expected location of the efferent and afferent autonomic nerves in the pulmonary artery adventitia (15). We designed this preliminary study to investigate for the first time the feasibility of therapeutic intravascular ultrasound PDN, to monitor early safety, and to determine whether the procedure would lower pulmonary vascular resistance (PVR) in patients with PAH established on a minimum of dual oral therapy.

METHODS

STUDY DESIGN AND PARTICIPANTS. TROPHY1 (Treatment of Pulmonary Hypertension 1) was a multicenter, open-label, early feasibility study. Participants were recruited from 5 hospitals in Europe and Israel and 3 in the United States. The study was undertaken in accordance with the Declaration of Helsinki and was approved by local ethics committees or Institutional Review Boards. All participants provided written informed consent. Briefly, eligible patients were men or women 18 to 75 years of age with PAH that did not respond to vasodilator testing, on a minimum of dual oral disease-specific therapy (17), with estimated glomerular filtration rate ≥30 ml/min/1.73 m^2.

PROCEDURES. After qualifying hemodynamic evaluation and pulmonary angiography, patients underwent immediate therapeutic intravascular ultrasound PDN (TIVUS System). A maximum of 18 activations were delivered to nonoverlapping segments of the main (n = 8), right (n = 8), and left (n = 2) pulmonary arteries. The number of activations and distance from the pulmonary artery bifurcation was limited on the left by the recurrent laryngeal nerve (15). Continuous monitoring of energy output, vessel wall distance, and temperature was used to optimize each activation, with automated safety cut-outs. Patients were sedated and received pain-controlling medication at the discretion of the responsible physician. The target activated coagulation time of >250 s was achieved with intravenous heparin to prevent coagulum buildup on the ultrasound probe.

Post-procedural follow-up was at 1 month, 4 or 6 months (Europe and Israel, 4 months; United States, 6 months; mean 4.8 ± 1.3 months), 8 months, and 12 months. Systemic blood pressure and heart

Medical. Dr. McLaughlain has received research support and fees from Acceleron, Actelion, and Bayer; has received research support from Eiger BioPharmaceuticals and Reta Pharmaceuticals; and has received fees from Arena, Caremark, Corsair Pharma, Merck, and United Therapeutics. Drs. Shav and Shabtay are employees of SoniVie. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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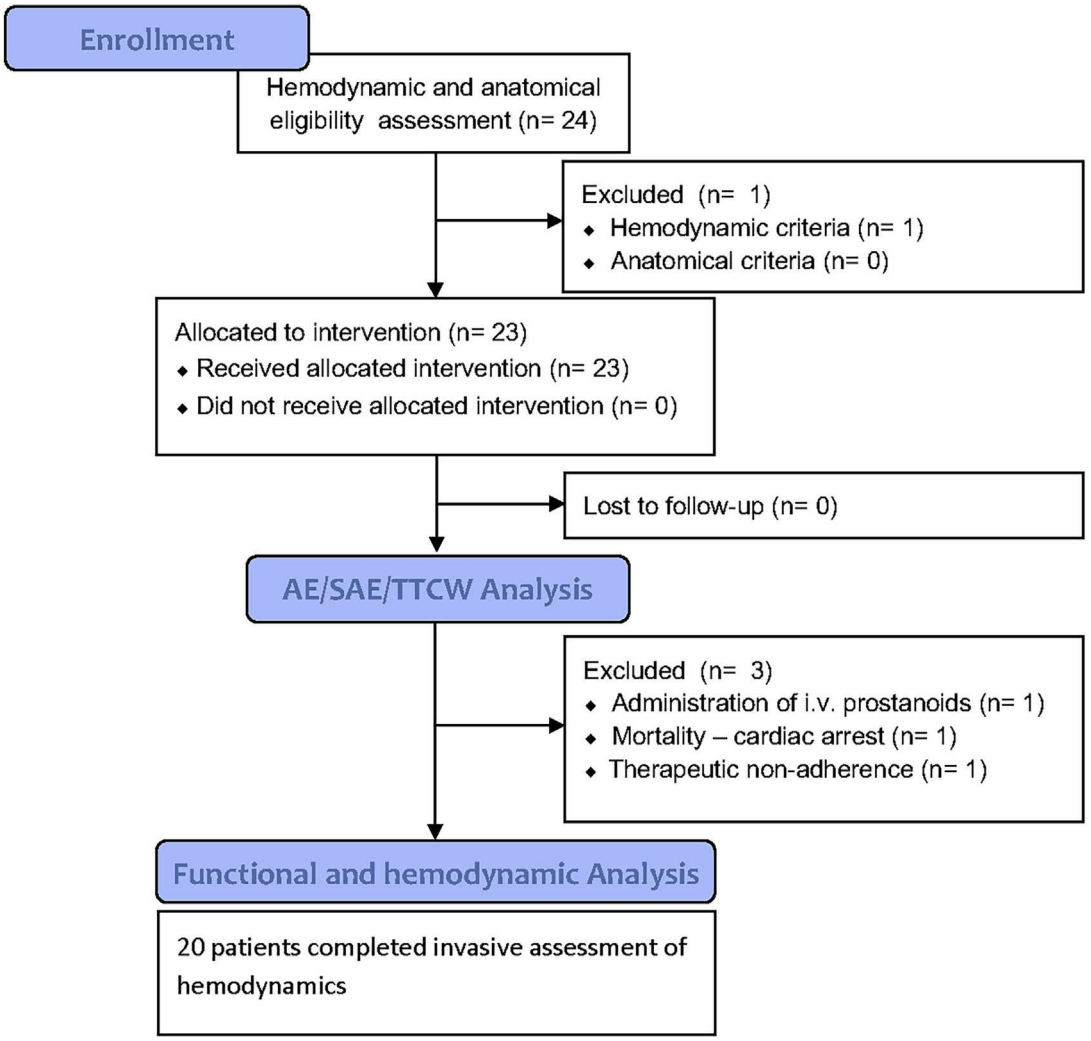
FIGURE 1 **Consolidated Standards of Reporting Trials Diagram**



Hemodynamic and anatomic eligibility assessment was undertaken in 24 patients. One was excluded at right heart catheterization, and 23 underwent ultrasound pulmonary artery denervation. All patients were included in adverse event (AE), serious AE (SAE), and time to clinical worsening (TTCW) analysis. Twenty patients underwent invasive assessment of hemodynamic status at 4 or 6 months, with 3 excluded (1 receiving intravenous [i.v.] prostanoid therapy, 1 who died, and 1 with nonadherence to therapy).

rate, adverse events, 6-min walk distance, and medications were recorded and laboratory assessments undertaken at each visit. Right heart catheterization was performed at baseline and 4- or 6-month and 12-month follow-up in the supine position, with pulmonary pressure and flow measurements repeated in triplicate. Magnetic resonance imaging or computed tomography was performed at 1 and 6 or 12 months. Wrist-based activity monitoring was undertaken for 14 days (ActiGraph GT9X Link, ActiGraph, Pensacola, Florida) prior to baseline, 4- or 6-month, 8-month, and 12-month visits.

OUTCOMES. The primary endpoint was procedure-related adverse events at 30 days (pulmonary artery perforation, dissection, aneurysm, or stenosis; hemoptysis; and disease- or procedure-related death). Secondary endpoints included PAH worsening and death to 12 months and change from baseline to 4- or 6-month follow-up in PVR, mean pulmonary artery pressure, right atrial pressure, 6-min walk distance, quality of life (emPHasis-10), N-terminal pro-brain natriuretic peptide, disease-specific medication, and actigraphy. The time-to-event endpoint was a composite of death, disease-related hospitalization,

TABLE 1 Baseline Characteristics of Patients Enrolled (N = 23)

Age, yrs	60.0 ± 11.4
Female	18 (78)
Race	
Caucasian	19 (83)
Black	1 (4)
Hispanic	2 (9)
Middle East	1 (4)
Time from diagnosis, yrs	6.1 ± 5.7
Type of PAH	
Associated with connective tissue disease	12 (52)
Associated with drug use	3 (13)
Idiopathic	8 (35)
WHO functional class III	23 (100)

Values are mean ± SD or n (%).
PAH = pulmonary arterial hypertension; WHO = World Health Organization.

initiation of parenteral prostanoid therapy, lung transplantation, or atrial septostomy, whichever occurred first, to 12 months (18). Risk assessment was undertaken using the French invasive score with low-risk criteria defined as World Health Organization functional class I or II, 6-min walk distance >440 m, right atrial pressure <8 mm Hg, and cardiac index ≥2.5 l/min/m^2 (19). An independent data and safety monitoring board reviewed all potential procedure-related serious adverse events and adverse events.

BLINDED DATA ANALYSIS. Hemodynamic data were analyzed blinded to participant and time point by an independent core laboratory (Cardiovascular Research Foundation, New York, New York).

TABLE 2 Medical Therapy of Patients at Baseline and 4- or 6-Month Follow-Up (N = 20)

Disease-Specific Therapy	Baseline	4 or 6 Months
ERA/PDE5 inhibitor	10 (50)	10 (50)
ERA/sGC	4 (20)	4 (20)
ERA/PDE5 inhibitor/inhaled prostacyclin	3 (15)	3 (15)
ERA/sGC/inhaled prostacyclin	2 (10)	2 (10)
ERA/sGC/oral IP agonist	1 (5)	1 (5)
Diuretic agents		
None	3 (15)	3 (15)
Loop	7 (35)	6 (30)
Loop/aldosterone antagonist	7 (35)	8 (40)
Loop/aldosterone antagonist/thiazide	3 (15)	3 (15)

Values are n (%).
ERA = endothelin receptor antagonist; IP = prostacyclin; PDE5 = phosphodiesterase type 5; sGC = soluble guanylate cyclase.

STATISTICAL ANALYSIS. Statistical analyses were performed using 1-way analysis of variance, the Wilcoxon matched-pairs signed rank test, Student's paired *t*-test, and the chi-square test as appropriate in accordance with the pre-specified statistical analysis plan. Reported adverse events are of all patients enrolled, but patients who did not undergo follow-up right heart catheterization were excluded in the reporting of hemodynamic and functional endpoints (Figure 1). Expected survival was modeled from 6-min walk distance, sex, and cardiac output using the French registry equation (20).

The study is registered at ClinicalTrials.gov (NCT02516722, NCT02835950).

FUNDING. The study was funded by SoniVie. The advisory committee and sponsor designed the study. Independent data collection and monitoring were undertaken by site-specific contract research organizations. Statistical analyses were performed by the Cardiovascular Research Foundation. All authors had access to data and were responsible for the decision to submit.

RESULTS

Between March 2015 and April 2018, 24 patients with PAH on a minimum of dual oral therapy were enrolled in TROPHY1. After qualifying right heart catheterization, 23 patients underwent PDN.

Baseline characteristics are shown in Table 1. The mean age was 60.0 ± 11.4 years, 18 patients (78%) were women, and 19 (83%) were Caucasian. At the time of enrollment, all patients were receiving dual oral therapy, and 7 (30%) were also receiving an inhaled prostanoid or oral prostacyclin agonist (Table 2).

Patients received an average of 10.0 (minimum 7, maximum 16) ultrasound activations, with 4.5 (range: 2 to 7), 1.9 (range: 1 to 2), and 4.0 (range: 1 to 8) in the right, left, and main pulmonary arteries, respectively, with all patients receiving the pre-specified minimum (2 right, 1 left, and 2 main). The duration of the denervation procedure was 32.0 ± 9.8 min, with a mean fluoroscopy time of 8.1 ± 5.4 min.

There were no procedure-related serious adverse events. Serious adverse events and adverse events are shown in Table 3. No patients reported procedure-related pain lasting longer than 2 days, and no perforation, dissection, aneurysm, or stenosis was identified by pulmonary angiography post-procedure or magnetic resonance imaging or computed tomography at 1 and 12 months. There was no acute reduction in mean pulmonary artery pressure

(+0.7 ± 10.0 mm Hg; p = NS), and no change in estimated glomerular filtration rate was apparent at 1 month (6.1 ± 27.0 ml/min/1.73 m^2; p = NS). Three subjects did not undergo follow-up right heart catheterization and were not included in efficacy analysis: 1 transitioned to intravenous prostanoid, 1 died (unrelated to the procedure), and 1 was nonadherent to therapy (**Figure 1**). Survival at 4 or 6 and 12 months was 96%. The French registry equation was used to estimate expected survival on the basis of patient data at the point of study entry; expected survival was 93% and 87% at 6 and 12 months, respectively (20). Disease-specific therapy was unchanged between baseline and 4- or 6-month follow-up in patients included in the efficacy analysis (**Table 2**). Diuretic therapy was consistent between time points (**Table 2**): furosemide equivalent 54 mg/day (range: 0 to 160 mg/day) versus 59 mg/day (range: 0 to 160 mg/day), aldosterone antagonist 15 mg/day (range: 0 to 50 mg/day) versus 16.25 mg/day (range: 0 to 50 mg/day), and thiazide 0.5 mg/day (range: 0 to 5 mg/day) versus 0.5 mg/day (range: 0 to 5 mg/day).

At 4- or 6-month follow-up, hemodynamic and functional endpoints improved: PVR was reduced by 94 ± 151 dyn·s·cm^{-5} (p = 0.001), or 17.8%, and 6-min walk distance increased by 42 ± 63 m (p = 0.02) (**Figures 2 to 4, Central Illustration, Table 4**). Improvements in mean pulmonary artery pressure (−5.1 ± 7.4 mm Hg; p < 0.01), right atrial pressure (−2.4 ± 3.5 mm Hg; p = 0.01), and pulmonary arterial compliance (+0.39 ± 0.83 ml/mm Hg; p < 0.01) were also observed (**Figure 2, Central Illustration, Table 4**). Reductions from baseline PVR of >10% were observed in 14 patients (70%), and of those, 8 (40%) had reductions of >20% (**Figure 3**). At 4 or 6 months, daily activity was increased by 671 ± 1,555 steps (p = 0.04), but no alteration was identified in cardiac output (+0.3 ± 0.9 l/min; p = NS), stroke volume index (+4.85 ± 11.5 ml/min/m^2; p = 0.09), quality of life (emPHasis-10 score −5.1 ± 12.4; p = 0.20), N-terminal pro-brain natriuretic peptide (−263.5 ± 1,120 pg/ml; p = 0.2), systemic blood pressure (+4.8 ± 24.4 mm Hg; p = NS), and heart rate (+0.05 ± 8.2 beats/min; p = NS) (**Figures 2 and 4**, Supplemental Figure 1, **Table 4**). Hemodynamic and functional improvements were reflected in an increased number of European Society of Cardiology low-risk indicators achieved at 4- or 6-month follow-up (European Society of Cardiology/French invasive risk score 0.4 ± 0.6; p < 0.001) (**Figure 4, Central Illustration**). Following PDN, clinical worsening events occurred in 6 patients, which were distributed throughout the follow-up period (**Figure 4**).

TABLE 3 Serious Adverse Events and Adverse Events (All Patients Enrolled, N = 23)

Event	n	Description
Serious adverse events		
PAH hospitalization	11	Right ventricular failure/volume overload, syncope, initiation of IV prostacyclin
Non-PAH hospitalization	3	Digoxin overdose, vasovagal episode, exacerbation of lung disease
Death	1	Cardiac arrest
Adverse events		
Anemia	2	
Cardiac/PAH	32	Edema, chest pain, ECG changes, palpitations, breathlessness, PAH progression/worsening
Infection	16	Urinary, respiratory, gastroenterological, dermatological, dental
Pain	10	Pain during procedure, neck pain
Procedure related	7	Bleeding, hematoma, bruising, low saturation
Renal impairment	3	

ECG = electrocardiographic; IV = intravenous; PAH = pulmonary arterial hypertension.

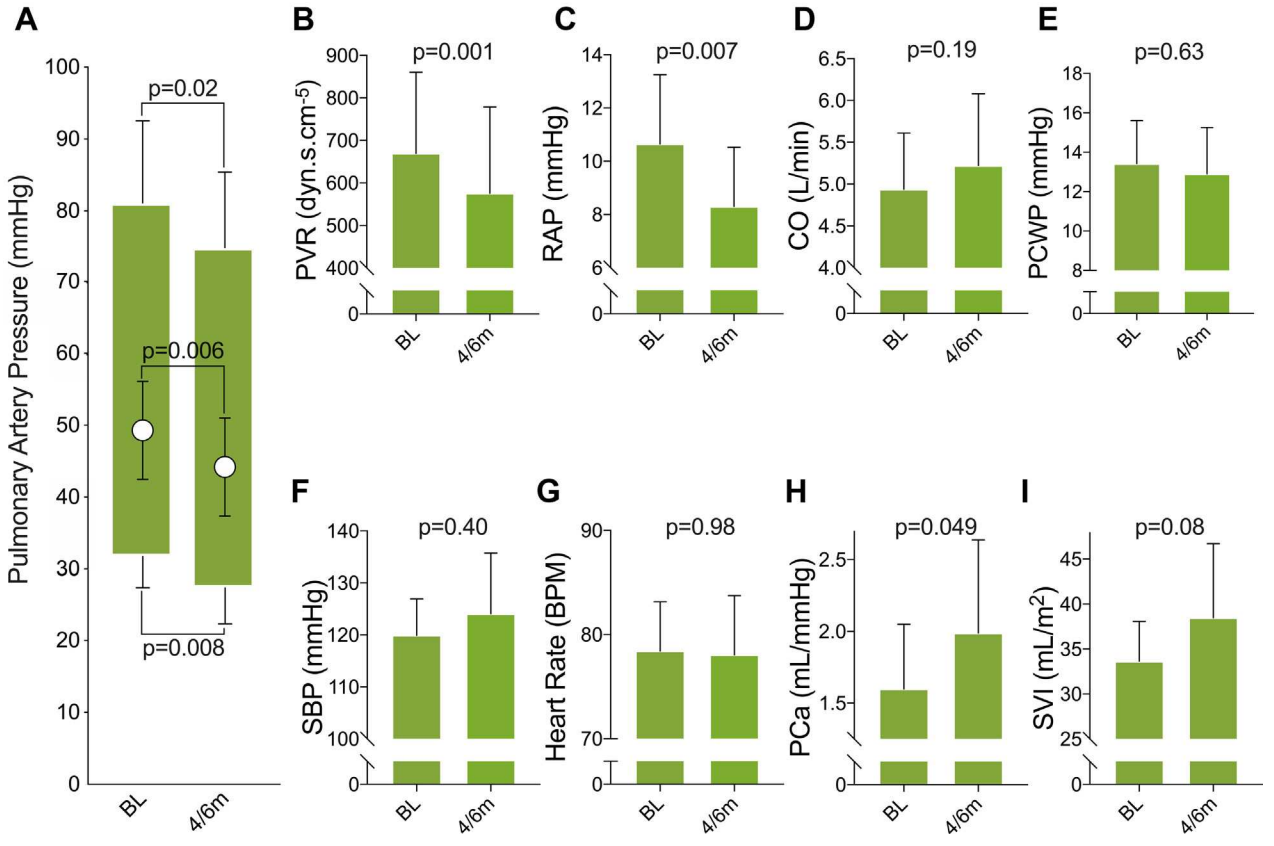
DISCUSSION

This is the first study to examine the feasibility of therapeutic intravascular ultrasound PDN and describe early safety and clinical outcome indicators. Following qualifying right heart catheterization, patients with PAH on a minimum of dual oral therapy underwent immediate PDN. No procedure-related serious adverse events were reported, and pulmonary hemodynamic status, 6-min walk distance, and daily activity improved at 4 or 6 months.

Patients were recruited from specialist pulmonary hypertension centers, and the female predominance, hemodynamic severity, and background therapy are similar to those of large registries (21,22). The mean age of 60 years, lengthy diagnosis-to-enrollment duration, large number of patients on triple therapy, and high proportion of connective tissue disease-associated PAH also suggest that patients enrolled were those established on guideline-directed therapy with limited options for therapeutic escalation or transplantation.

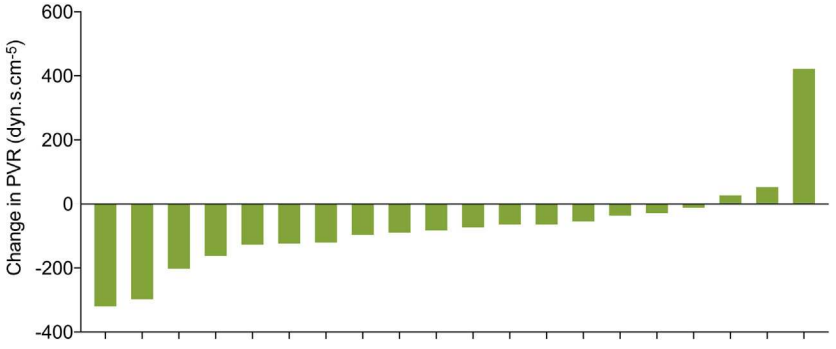
Ultrasound PDN was undertaken with no procedure-related serious adverse events reported. Of the 15 severe adverse events, 11 were disease-related deterioration. At 12-month follow-up, clinical worsening events had occurred in 6 of the 23 patients enrolled, a number typical for patients in World Health Organization functional class III or IV (23,24). As such, procedural feasibility and early safety appear acceptable. Disease-specific and diuretic therapy were maintained from baseline to follow-up. At 4 or 6 months following PDN, a

FIGURE 2 **Pulmonary Vascular Hemodynamic Status at Baseline and 4 or 6 Months**



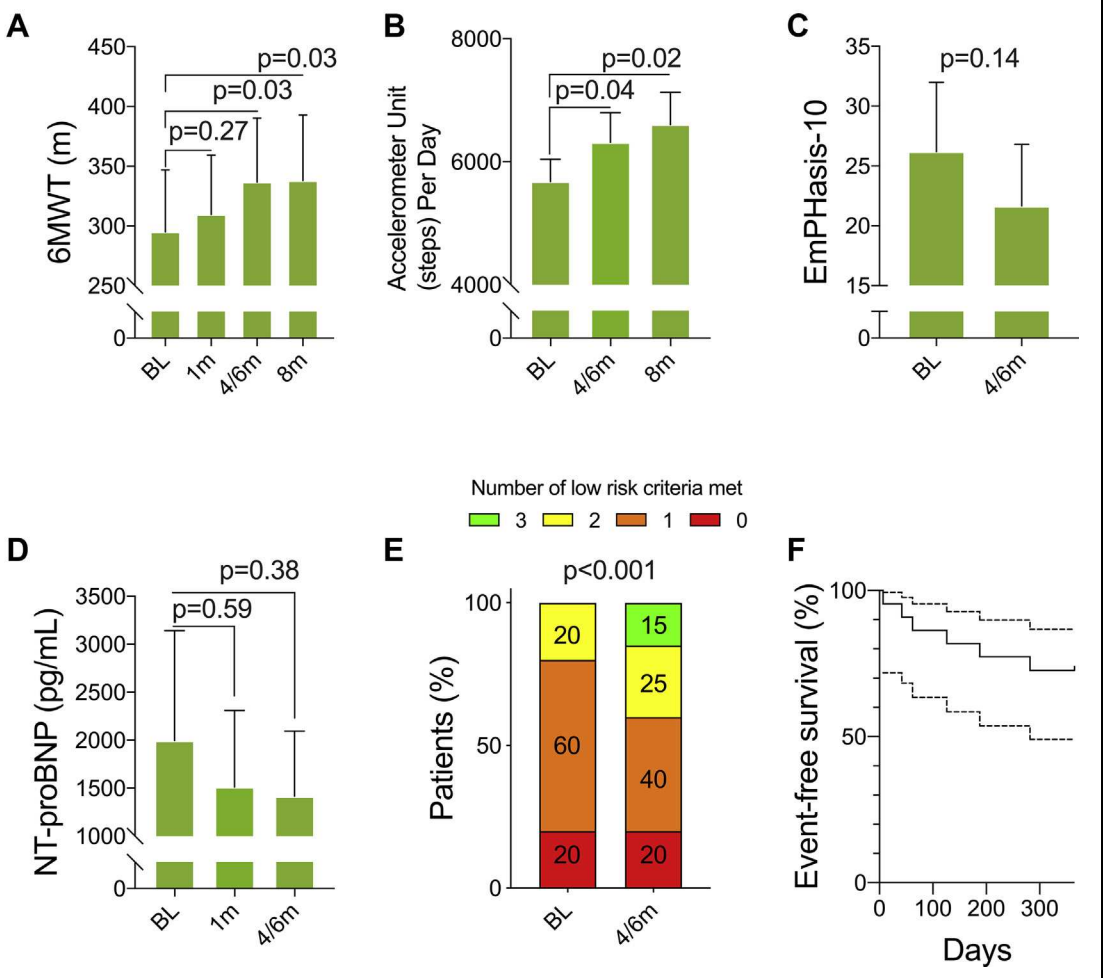
(A) Pulmonary artery pressure (mean systolic pulmonary artery pressure: **upper**, +95% confidence interval [CI]; mean of mean pulmonary artery pressure: **white circles**, ±95% CI; mean diastolic pulmonary artery pressure: **lower**, −95% CI). **(B)** Pulmonary vascular resistance (PVR). **(C)** Right atrial pressure (RAP). **(D)** Cardiac output (CO). **(E)** Pulmonary capillary wedge pressure (PCWP). **(F)** Systolic blood pressure (SBP). **(G)** Heart rate. **(H)** Pulmonary arterial compliance (PCa). **(I)** Stroke volume index (SVI). n = 20, mean ± 95% CI, Wilcoxon matched-pairs signed rank test or Student's paired *t*-test as appropriate.

FIGURE 3 **Change in PVR at 4 or 6 Months**



Individual patient change in pulmonary vascular resistance (PVR) from baseline to 4 or 6 months following pulmonary artery denervation.

FIGURE 4 Functional and Clinical Outcomes



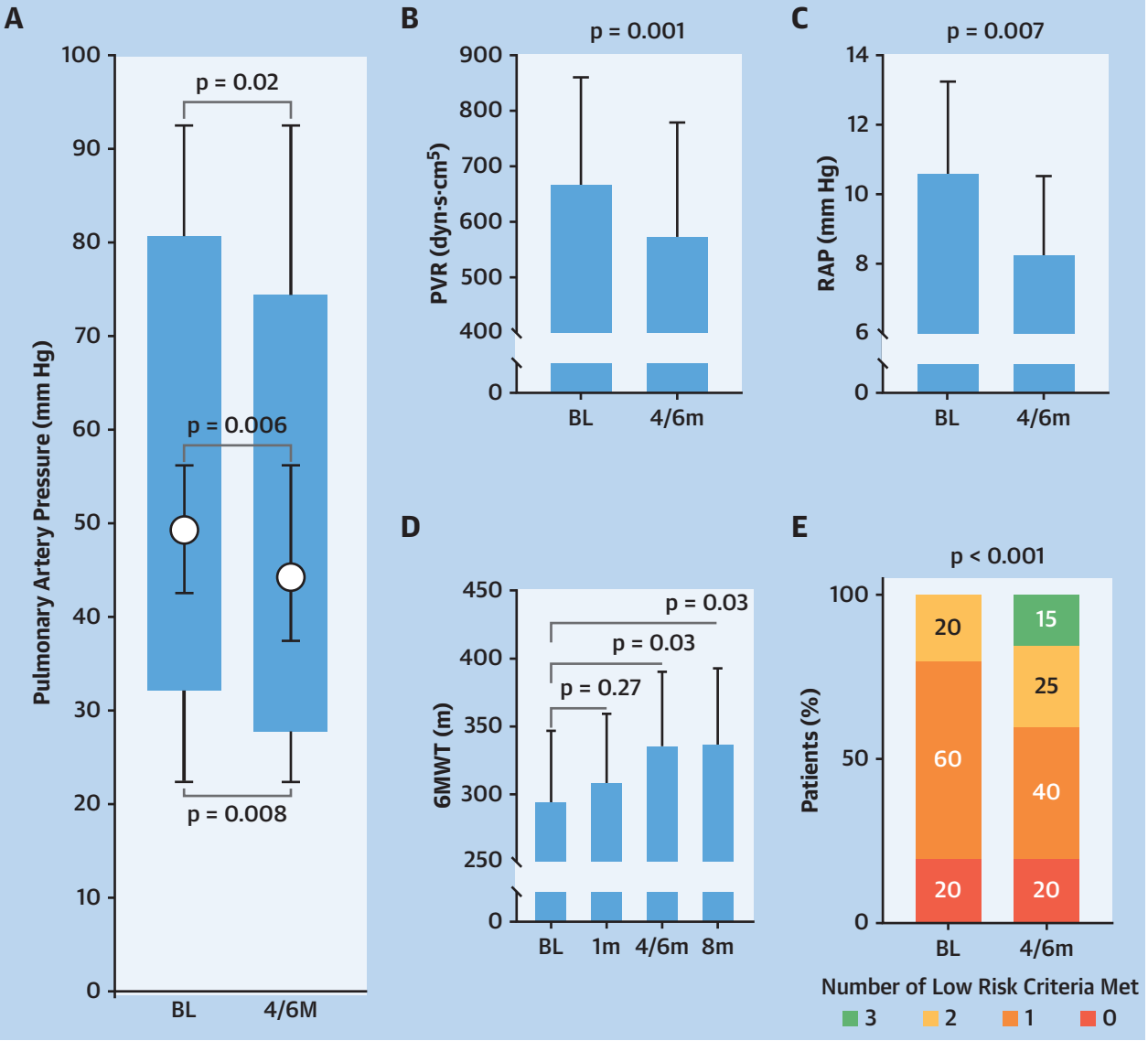
At 4 or 6 and 8 months following pulmonary artery denervation, distance walked on 6-min walk test (6MWT) **(A)** and daily activity (steps per day) **(B)** were increased. Quality-of-life score **(C)** and N-terminal pro-brain natriuretic peptide (NT-proBNP) **(D)** were not changed. The number of European Society of Cardiology low-risk criteria increased **(E)**. Clinical worsening events were distributed throughout follow-up. In **A to E**, n = 20, mean ± 95% confidence interval, 1-way analysis of variance or chi-square test as appropriate. In **F**, n = 23.

94 dyn·s·cm^{-5} reduction in PVR was observed, 6-min walk distance was increased by 42 m, and systemic blood pressure and heart rate were not altered. In keeping with the observed reduction in PVR, both right atrial pressure and pulmonary artery compliance were improved (22). Although not statistically significant, stroke volume index increased to a level above the optimal absolute cutoff threshold associated with mortality or transplantation (38 ml/min/m^2) (22). In comparison with prior reports of PDN in patients with PAH (PADN-1 [First-in-Man Pulmonary Artery Denervation for Treatment of Pulmonary Artery Hypertension]) (16), patients enrolled in TROPHY1 were older, with a longer time from diagnosis and a high predominance of connective tissue disease, and were all established on guideline-directed therapy. Consistent with PADN-1 (16), PDN improved PVR in a manner driven primarily by a reduction in pulmonary artery pressure. However, in TROPHY1, no on-table reduction in pulmonary artery pressure was apparent, and the magnitude of changes was less marked. The observed reduction in PVR and increase in 6-min walk distance achieved at 4 or 6 months in TROPHY1 are in line with hemodynamic

CENTRAL ILLUSTRATION **Pulmonary Vascular Hemodynamic and Functional Indicators at Baseline and Follow-Up**

Intravascular ultrasound pulmonary artery denervation to treat pulmonary arterial hypertension

An open-label, early feasibility study of ultrasound pulmonary artery denervation in 23 patients with pulmonary arterial hypertension established on guideline-directed medical therapy



Rothman, A.M.K. et al. J Am Coll Cardiol Intv. 2020;13(8):989-99.

(A) Pulmonary artery pressure (mean systolic pulmonary artery pressure: **upper**, +95% confidence interval [CI]; mean of mean pulmonary artery pressure: **white circles**, ±95% CI; mean diastolic pulmonary artery pressure: **lower**, −95% CI). **(B)** Pulmonary vascular resistance (PVR). **(C)** Right atrial pressure (RAP). **(D)** Distance walked on 6-min walk test (6MWT). **(E)** European Society of Cardiology risk score. n = 20, mean ± 95% CI, 1-way analysis of variance, Student's paired *t*-test, and chi-square test as appropriate.

outcomes of approved drug therapies and compare favorably with a minimally important clinical difference in 6-min walk distance of 33 m (25). The observed increase in daily activity and improved clinical risk score provide further indication of potential benefit on a background of guideline-directed medical therapy.

Markers of neurohormonal activity are increased in patients with PAH and are associated with adverse clinical events (1,2). The pulmonary vasculature is highly innervated, releasing and metabolizing >40% of circulating catecholamines (3). The pulmonary (nerve) plexus is predominantly sympathetic and is innervated by fibers from the spinal ganglions (sympathetic) and vagus nerve (parasympathetic) (15). Baroreceptor structures have been described at the pulmonary artery bifurcation (26), and balloon distention of the main pulmonary artery increases pulmonary artery pressure and PVR (27). These acute changes are abrogated by surgical denervation and chemical sympathectomy implicating sympathetic nerves in the reflex (27). Furthermore, sympathetic inhibition, through cervical ganglion block, reduces pulmonary artery pressure in the context of acute pulmonary embolism (28). In experimental models, denervation of the pulmonary artery induces persistent structural and functional changes within associated nerves and improves hemodynamic changes driven by balloon distention (29), vasoconstriction (13,15), and small-vessel remodeling (14). The elevated PVR apparent in patients with PAH is driven by small-vessel remodeling but also leads to increased pulmonary artery pressure. The present study demonstrates improvements in pulmonary vascular hemodynamic status and functional capacity 4 or 6 months following PDN. In contrast to prior reports of radiofrequency PDN, no acute reduction in pulmonary artery pressure was observed with ultrasound PDN in this study, suggesting a potential remodeling effect.

The health-economic cost of PAH-specific therapy and clinical deterioration is high (30); dual oral therapy is priced at $30,000 to $50,000 per year per patient and triple therapy at $50,000 to $160,000 per patient per year (31,32). As such, a single, or repeated-interval, catheterization laboratory-based procedure may provide an alternative to therapeutic escalation or an addition to combination therapy.

STUDY STRENGTHS AND LIMITATIONS. The study was open label, with no placebo arm. Patients and responsible physicians were not blinded, and the potential effect of placebo cannot be quantified.

TABLE 4 Hemodynamics at Baseline and 4- or 6-Month Follow-Up (N = 20)

	Baseline	4 or 6 Months	p Value
Right atrial pressure (mm Hg)	10.7 (8.1–13.3)	8.3 (6.1–10.5)	0.008
Pulmonary artery pressure (mm Hg)			
Systolic	80.7 (68.8–92.5)	74.3 (63.1–85.4)	0.02
Mean	49.3 (42.5–56.1)	44.2 (37.4–51.0)	0.006
Diastolic	32.1 (27.3–36.8)	27.7 (22.3–33.1)	0.007
Pulmonary arterial wedge pressure (mm Hg)	13.4 (11.2–15.6)	12.9 (10.6–15.3)	0.63
Cardiac output (l/min)	4.9 (4.3–5.6)	5.2 (4.4–6.1)	0.41
Pulmonary vascular resistance (dyn·s·cm^{-5})	670 (479–861)	576 (373–779)	0.001
Systemic blood pressure (mm Hg)			
Systolic	120 (113.0–126.9)	124.1 (112.4–135.7)	0.72
Diastolic	75.4 (69.7–81.1)	75.7 (69.5–81.9)	0.74
Heart rate (beats/min)	78.4 (73.7–83.2)	78.1 (72.4–83.8)	0.87

Values are mean (95% confidence interval).

Patients were recruited from specialist centers at which serial walk testing was part of routine care, thereby reducing potential training and learning effects. To minimize potential bias, hemodynamic studies were assessed by an independent core laboratory, blinded to subject and sequence, and data were analyzed by an independent statistician in accordance with the pre-specified analysis plan. Additionally, for this procedure, there is no immediate feedback to the operator to indicate successful denervation.

CONCLUSIONS

Intravascular ultrasound PDN was feasible, reduced PVR, and increased 6-min walk distance and daily activity in patients with PAH treated with dual oral or triple therapy. Further studies are required to evaluate the efficacy, durability, safety, and long-term clinical impact of PDN in patients with pulmonary hypertension of various forms.

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PERSPECTIVES

WHAT IS KNOWN? Early studies have suggested that PDN reduces PVR in patients with PAH.

WHAT IS NEW? In this multicenter early feasibility study, ultrasound PDN was performed without procedure-related adverse events and was associated with a reduction PVR and increases in 6-min walk distance and daily activity in patients with PAH on a minimum of dual oral therapy.

WHAT IS NEXT? Further studies are required to evaluate the efficacy, durability, safety, and long-term clinical impact of PDN in patients with pulmonary hypertension of various forms.

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APPENDIX For a supplemental figure, please see the online version of this paper.