Characterization of Connective Tissue Disease-Associated Pulmonary Arterial Hypertension From REVEAL

Identifying Systemic Sclerosis as a Unique Phenotype

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Background: REVEAL (the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) is the largest US cohort of patients with pulmonary arterial hypertension (PAH) confirmed by right-sided heart catheterization (RHC), providing a more comprehensive subgroup characterization than previously possible. We used REVEAL to analyze the clinical features of patients with connective tissue disease-associated PAH (CTD-APAH).

Methods: All newly and previously diagnosed patients with World Health Organization (WHO) group 1 PAH meeting RHC criteria at 54 US centers were consecutively enrolled. Cross-sectional and 1-year mortality and hospitalization analyses from time of enrollment compared CTD-APAH to idiopathic disease and systemic sclerosis (SSc) to systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), and rheumatoid arthritis (RA).

Results: Compared with patients with idiopathic disease ($n = 1,251$), patients with CTD-APAH ($n = 641$) had better hemodynamics and favorable right ventricular echocardiographic findings but a higher prevalence of pericardial effusions, lower 6-min walk distance (300.5 ± 118.0 vs 329.4 ± 134.7 m, $P = .01$), higher B-type natriuretic peptide (BNP) levels (432.8 ± 789.1 vs 245.6 ± 427.2 pg/mL, $P < .0001$), and lower diffusing capacity of carbon monoxide (DLCO) ($44.9\% \pm 18.0\%$ vs $63.6\% \pm 22.1\%$ predicted, $P < .0001$). One-year survival and freedom from hospitalization were lower in the CTD-APAH group (86% vs 93%, $P < .0001$; 67% vs 73%, $P = .03$). Compared with patients with SSc-APAH ($n = 399$), those with other CTDs (SLE, $n = 110$; MCTD, $n = 52$; RA, $n = 28$) had similar hemodynamics; however, patients with SSc-APAH had the highest BNP levels (552.2 ± 977.8 pg/mL), lowest DLCO ($41.2\% \pm 16.3\%$ predicted), and poorest 1-year survival (82% vs 94% in SLE-APAH, 88% in MCTD-APAH, and 96% in RA-APAH).

Conclusions: Patients with SSc-APAH demonstrate a unique phenotype with the highest BNP levels, lowest DLCO, and poorest survival of all CTD-APAH subgroups.

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Abbreviations: 6MWD = 6-min walk distance; BNP = B-type natriuretic peptide; CTD = connective tissue disease; CTD-APAH = connective tissue disease-associated pulmonary arterial hypertension; DLCO = diffusing capacity of carbon monoxide; EDC = electronic data capture; HRCT = high-resolution CT; ILD = interstitial lung disease; IPAH = idiopathic pulmonary arterial hypertension; MCTD = mixed connective tissue disease; NT-proBNP = N-terminal-pro B-type natriuretic peptide; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; RA = rheumatoid arthritis; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; RHC = right-sided heart catheterization; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; TLC = total lung capacity; WHO = World Health Organization

Pulmonary arterial hypertension (PAH) is a frequent complication of patients with connective tissue diseases (CTD), particularly affecting patients with systemic sclerosis (SSc), systemic lupus

erythematosus (SLE), and mixed CTD (MCTD). PAH affects approximately 3% to 13% of patients with CTD¹⁻³ and is a major cause of death in these patients.⁴

Historically, patients with CTD-associated PAH (CTD-APAH) have been characterized as having the most severe disease with the highest mortality rates of all PAH subgroups.⁵⁻⁷ Although patients with CTD-APAH have experienced improvements in survival with the introduction of prostacyclins, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors,^{8,9} their prognosis continues to be worse than patients with idiopathic PAH (IPAH).^{10,11}

Few PAH studies have compared clinical features and outcomes of patients with various types of CTD. A recent study demonstrated that patients with SLE-APAH have a similar hemodynamic profile but better survival than patients with SSc-APAH.¹² However, a complete characterization of the patient cohorts was not provided, and the SLE-APAH group only consisted of 28 patients. This study also included small subgroups of patients with MCTD-APAH (n = 28) and rheumatoid arthritis (RA)-APAH (n = 12), but the groups were too small to demonstrate significant survival differences from patients with SSc-APAH.

REVEAL (the Registry to Evaluate Early and Long-term PAH Disease Management) is a multicenter, observational, US-based registry that includes information about current demographics and treatment practices for patients with PAH.¹³ We sought to use the REVEAL registry, the largest US cohort of patients with PAH confirmed by right-sided heart catheterization (RHC), to characterize the clinical features and outcomes of patients with CTD-APAH currently under care at PAH centers. We selected the IPAH subgroup, the largest and most homogeneous PAH population in REVEAL, for the control group. We sought to determine whether differences in disease severity and current-day management impact

short-term hospitalization and survival. Finally, we aimed to characterize and compare the SSc-APAH group to patients with other CTDs, including SLE-, MCTD-, and RA-APAH, using the largest populations of these groups described to date.

MATERIALS AND METHODS

REVEAL Registry

REVEAL is a longitudinal registry involving 54 US pulmonary hypertension centers. Each participating center obtained institutional review board approval prior to patient enrollment. The design and objectives of REVEAL are described elsewhere.¹³ All patients provided informed consent prior to enrollment, and "enrollment" was defined as the date consent was given. "Diagnosis" was defined as the date of diagnostic RHC occurring at or before the date of enrollment. Newly diagnosed patients were defined as those whose diagnostic RHC occurred within 90 days of enrollment. All consecutive patients who, in the opinion of the enrolling investigator, had a clinical diagnosis of World Health Organization (WHO) group 1¹⁴ PAH and met the following inclusion criteria were eligible for enrollment: (1) mean pulmonary artery pressure of > 25 mm Hg at rest or 30 mm Hg with exercise, (2) mean pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure of ≤ 18 mm Hg, (3) pulmonary vascular resistance of ≥ 240 dynes × s × cm⁻⁵ (divide by 80 for Wood units), and (4) ≥ 3 months of age.

Data Collection

Data were collected using electronic data capture (EDC), beginning with the initial screening visit. Data collected retrospectively included time of diagnosis and symptom onset, specialty of evaluating physicians, tests used to diagnose PAH, WHO group 1 classification, and use of PAH-specific medications. After meeting enrollment criteria, no tests or study visits were required, but data were collected prospectively every 90 days, including PAH treatments, concomitant treatments, diagnostic procedures, and outcomes, including information regarding hospitalizations, deaths, causes of death, and progression of disease requiring transplantation or atrial septostomy. Patients in open-label clinical trials had data collected; however, data collection was temporarily suspended for patients in blinded trials until completing the blinded portion of the study. The EDC system prompted quarterly updates with an option to indicate that the patient was not seen since the last update. Potential data inconsistencies were identified primarily by the EDC system at the point of entry. Additional queries were generated by the data coordinating center. Approximately 20% of sites each year were monitored on site for adherence to the protocol and resolution of data queries. For all sites, 100% of queries involving key variables, such as the hemodynamic parameters associated with inclusion criteria, were resolved.

The first 2,967 consecutive patients were enrolled from March 1, 2006 through September 30, 2007. The database was locked on August 10, 2009 for the present analyses. We developed an algorithm (Fig 1) to exclude patients with PCWP > 15 mm Hg, who have been shown to differ in many respects from those meeting the traditional hemodynamic definition of PAH,¹⁵ and those with evidence of significant interstitial lung disease (ILD), to focus our analyses on patients with pulmonary arteriopathy. Patients with evidence of "severe" fibrosis on high-resolution CT (HRCT) scan of the chest were excluded; those with "moderate" fibrosis

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were excluded if pulmonary function testing revealed a total lung capacity (TLC) of <60% predicted.

Statistical Analysis

Cross-sectional bivariate analyses were performed comparing patients with IPAH to those with CTD-APAH, and SSc-APAH to SLE-, MCTD-, and RA-APAH. Comparisons were also performed between patients with SSc-APAH and patients without SSc-APAH, including those with SLE-APAH, MCTD-APAH, and RA-APAH. The following variables were selected a priori as clinically important: age, sex, BMI, race, smoking history, presence of Raynaud phenomenon, presence of renal insufficiency (investigator clinical judgment based on clinical parameters and biochemistry values), New York Heart Association (NYHA) functional class, hemodynamic parameters on diagnostic RHC, echocardiographic findings, 6-min walk distance (6MWD), B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) levels, pulmonary function testing results, presence of ILD on HRCT, percentage using PAH-specific medications or combination therapy (at least two PAH-specific therapies), and percentage using immunosuppressive medications. All comparisons were performed on data at the time of enrollment, with the exception of hemodynamic parameters, which used information obtained at the diagnostic RHC. Mean and standard deviations were used to describe parametric data. Student *t* test or Wilcoxon test was used to compare continuous variables and χ^2 or Fisher exact test to compare categorical variables. Because BNP and NT-proBNP levels were highly skewed, the variables were log-transformed for comparison as continuous variables. No imputation was performed for missing data. No correction for multiple comparisons was performed, because all variables were selected a priori, and a *P* value < .05 was considered statistically significant. Cumulative probabilities of survival and freedom from hospitalization for any reason at 1 year were calculated using the Kaplan-Meier estimator and compared using the log-rank test. Follow-up time was calculated from the date of enrollment. Sensitivity analyses were performed including only newly diagnosed patients with PAH to extend the generalizability of key results to incident patients. SAS, version 9.1 (SAS Institute; Cary, NC) statistical software was used for all analyses.

RESULTS

Poorer Outcomes in CTD-APAH Compared With IPAH

Of the 1,892 patients included in these analyses, 1,251 patients were diagnosed with IPAH and 641 with CTD-APAH. Fourteen percent of patients with IPAH and 15% of patients with CTD-APAH had a new diagnosis of PAH at enrollment (*P* = .45). Compared with patients with IPAH, patients with CTD-APAH were older, more predominantly female, less obese, and more likely African American (Table 1). More patients with CTD-APAH suffered from Raynaud phenomenon (26.5% vs 1.4%, *P* < .0001) and renal insufficiency (6.9% vs 3.9%, *P* = .005); however, mean creatinine values did not differ significantly between the groups.

Patients with CTD-APAH had a better overall hemodynamic profile on diagnostic RHC, with lower mean right atrial pressure, pulmonary artery pressure, and pulmonary vascular resistance, and higher cardiac output than patients with IPAH (Table 2). The time between diagnostic RHC and enrollment was longer in the IPAH group (41.1 ± 44.1 vs 27.2 ± 29.9 months, *P* < .0001). Despite the shorter time between diagnosis and enrollment in the patients with CTD-APAH, the groups did not differ with respect to NYHA functional class, and the CTD-APAH group was less likely to have right ventricular enlargement or reduced right ventricular systolic function on echocardiogram at the time of enrollment. However, the patients with CTD-APAH were much more likely to have a pericardial effusion and had lower mean 6MWD (300.5 ± 118.0 vs 329.4 ± 134.7 m, *P* = .01) and higher mean BNP levels (432.8 ± 789.1 vs 245.6 ± 427.2 pg/mL, *P* < .0001). After excluding patients with significant ILD (Fig 1), a higher proportion of patients with CTD-APAH had evidence of mild ILD on HRCT (52.6% vs 30.7%, *P* < .0001). The mean forced vital capacity (FVC) and TLC were only mildly decreased in both groups at the time of enrollment but were statistically significantly lower in the CTD-APAH group. In contrast, the mean diffusing capacity of carbon monoxide (DLCO) was markedly lower ($44.9\% \pm 18.0\%$ vs $63.6\% \pm 22.1\%$ predicted, *P* < .0001) and the FVC/DLCO ratio was higher (1.9 ± 0.9 vs 1.5 ± 1.0 , *P* < .0001) in the CTD-APAH group compared with the IPAH group. Sensitivity analyses showed similar differences in newly diagnosed patients, although differences of the same magnitude were not statistically significant for all variables because of smaller sample sizes (not shown).

At the time of enrollment, patients with CTD-APAH were less likely to be on prostacyclin (36.3% vs 46.9%, *P* < .0001) and combination PAH therapy (39.5% vs 45.0%, *P* = .03) than those with IPAH (Table 3). More

FIGURE 1. Enrollment algorithm, designed to ensure that all of the patients included in our analysis met the strict criteria of World Health Organization group 1 PAH. CTD-APAH = connective tissue disease-associated pulmonary arterial hypertension; HRCT = high-resolution CT; ILD = interstitial lung disease; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; TLC = total lung capacity determined by pulmonary function testing.

Table 1—Demographic Features of Patients With Connective Tissue Disease-Associated Pulmonary Arterial Hypertension, Idiopathic Pulmonary Arterial Hypertension, Systemic Sclerosis-Associated Pulmonary Arterial Hypertension, and Systemic Lupus Erythematosus-Associated Pulmonary Arterial Hypertension

Demographic Feature	Etiology		P Value, CTD-APAH vs IPAH	Etiology		P Value, SSc-APAH vs SLE-APAH	P Value, SSc-APAH vs Non-SSc-APAH
	CTD-APAH (n = 641)	IPAH (n = 1,251)		SSc-APAH (n = 399)	SLE-APAH (n = 110)		
Age, y	57.1 ± 13.7	50.1 ± 17.5	< .0001	61.8 ± 11.1	45.5 ± 11.9	< .0001	< .0001
Sex, No. (%)			< .0001			.06	.18
Male	63 (9.8)	264 (21.1)		46 (11.5)	6 (5.5)		
Female	578 (90.2)	987 (78.9)		353 (88.5)	104 (94.5)		
BMI, kg/m ²	27.4 ± 6.8	29.7 ± 7.3	< .0001	27.4 ± 6.9	27.9 ± 7.2	.55	.54
Race, No. (%)			.03			< .0001	< .0001
White	448 (71.8)	924 (74.8)		324 (83.9)	40 (37.4)		
African American	103 (16.5)	144 (11.7)		42 (10.9)	34 (31.8)		
Hispanic	47 (7.5)	102 (8.3)		14 (3.6)	19 (17.8)		
Others	26 (4.2)	65 (5.2)		6 (1.6)	14 (13.1)		
Smoking history, No. (%)			.1			.1	.05
Never	385 (63.1)	685 (58.1)		229 (60.4)	72 (68.6)		
Past	201 (33.0)	448 (38.0)		137 (36.1)	27 (25.7)		
Current	24 (3.9)	47 (4.0)		13 (3.4)	6 (5.7)		
Raynaud phenomenon, No. (%)	170 (26.5)	18 (1.4)	< .0001	130 (32.6)	15 (13.6)	< .0001	.0001
Renal insufficiency, No. (%)	43 (6.9)	47 (3.9)	.005	34 (8.7)	5 (4.6)	.15	.01
Creatinine, mg/dL (No.)	1.1 ± 0.78 (488)	1.1 ± 0.9 (883)	.37	1.2 ± 0.7 (305)	1.0 ± 0.3 (84)	.0095	.0002

Values are mean ± SD unless otherwise noted. Non-SSc-APAH patients include SLE-APAH, mixed connective tissue disease-APAH, and rheumatoid arthritis-APAH. CTD-APAH = connective tissue disease-associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; SLE-APAH = systemic lupus erythematosus-associated pulmonary arterial hypertension; SSc-APAH = systemic sclerosis-associated pulmonary arterial hypertension.

patients with CTD-APAH were treated with concomitant immunosuppression (11.9% vs 1.3%, $P < .0001$).

One-year survival rates from the time of enrollment were 86% in the CTD-APAH group and 93% in the IPAH group ($P < .0001$) (Fig 2A). Freedom from hospitalization at 1 year was also lower in patients with CTD-APAH (73% vs 67%, $P = .03$) (Fig 2B). Among the incident population, survival in the CTD-APAH group remained significantly lower than in the IPAH group (78% vs 91%, $P < .0001$).

SSc-APAH Displays a Unique Phenotype Compared With Other CTD

Of the 641 patients with CTD-APAH, 589 patients had a known diagnosis: SSc (399), SLE (110), MCTD (52), and RA (28). Two hundred fifty-one patients (63%) with SSc had limited cutaneous disease, 77 (19%) had diffuse cutaneous involvement, and 71 (18%) were unclassified. Sixteen percent of patients with SSc had newly diagnosed PAH at enrollment, which was not significantly different from the 14% of patients with SLE ($P = .5$), 8% of patients with MCTD ($P = .11$), and 18% of patients with RA ($P = .83$) who were newly diagnosed. Patients with SSc-APAH were significantly older than patients with other CTDs with a mean age of 61.8 ± 11.1 years vs 45.5 ± 11.9 years for patients with

SLE-APAH ($P < .0001$) (Table 1), 49.4 ± 16.1 years for patients with MCTD-APAH ($P < .0001$), and 54.0 ± 15.8 years for patients with RA-APAH ($P = .0005$) (e-Table 1). All groups were predominantly female and did not differ with respect to BMI. A higher percentage of patients with SSc-APAH were former smokers. The groups were significantly different with respect to race. The majority of patients with SSc-APAH were white (84%); in contrast, only 37% of patients with lupus were white, 32% were African American, 18% were Hispanic, and 13% were of another racial background. A higher percentage of patients with MCTD-APAH were of Hispanic background compared with patients with SSc-APAH (12% vs 3.6%). Approximately one-third of patients with SSc-APAH and MCTD-APAH were reported to suffer from Raynaud phenomenon compared with 14% of patients with SLE-APAH ($P < .0001$) and 3.6% of patients with RA-APAH ($P = .001$). The prevalence of renal insufficiency was highest in the SSc-APAH group ($P = .01$ for SSc vs non-SSc), and these patients also had significantly higher creatinine levels compared with the other CTD-APAH subgroups.

The time between diagnostic RHC and enrollment was shorter in the patients with SSc-APAH compared with other CTDs (24.2 ± 24.1 vs 34.4 ± 39.1 months,

Table 2—Disease Characteristics of Patients With CTD-APAH, IPAH, SSc-APAH, and SLE-APAH

Characteristic	Etiology		P Value, CTD-APAH vs IPAH	Etiology		P Value, SSc-APAH vs SLE-APAH	P Value, SSc-APAH vs Non-SSc-APAH
	CTD-APAH (n = 641)	IPAH (n = 1,251)		SSc-APAH (n = 399)	SLE-APAH (n = 110)		
NYHA/WHO functional class, No. (%)			.45			.06	.04
I	11 (2.4)	30 (3.3)		7 (2.4)	1 (1.2)		
II	111 (24.1)	207 (22.7)		65 (22.7)	25 (29.1)		
III	286 (62.0)	549 (60.1)		171 (59.8)	56 (65.1)		
IV	53 (11.5)	127 (13.9)		43 (15.0)	4 (4.7)		
Hemodynamics ^a							
Mean right atrial pressure, mm Hg (No.)	8.8 ± 5.6 (583)	9.6 ± 5.6 (1130)	.003	9.1 ± 5.9 (363)	8.1 ± 4.9 (101)	.11	.05
Mean pulmonary artery pressure, mm Hg (No.)	45.0 ± 11.2 (641)	52.6 ± 13.8 (1251)	<.0001	44.6 ± 11.8 (399)	46.6 ± 9.2 (110)	.1	.17
Mean pulmonary capillary wedge pressure, mm Hg (No.)	8.9 ± 3.5 (641)	9.2 ± 3.5 (1249)	.08	9.1 ± 3.5 (399)	8.1 ± 3.3 (110)	.01	.06
Cardiac output, L/min (No.)	4.4 ± 1.4 (641)	4.2 ± 1.5 (1251)	.003	4.4 ± 1.5 (399)	4.3 ± 1.5 (110)	.34	.18
Cardiac index (Fick or thermodilution), L/min × m ² (No.)	2.5 ± 0.7 (494)	2.3 ± 0.9 (906)	.0004	2.5 ± 0.7 (307)	2.4 ± 0.8 (78)	.26	.22
Pulmonary vascular resistance, WU (No.)	9.8 ± 5.3 (641)	12.5 ± 7.6 (1249)	<.0001	9.6 ± 5.3 (399)	10.7 ± 5.6 (110)	.056	.13
Pulmonary vascular resistance index, WU × m ² (No.)	17.0 ± 9.1 (494)	22.7 ± 12.2 (908)	<.0001	16.7 ± 9.1 (307)	18.8 ± 9.3 (78)	.07	.24
Echocardiography							
Right ventricular systolic pressure, mm Hg (No.)	72.7 ± 25.5 (441)	75.2 ± 35.4 (809)	.18	73.1 ± 25.7 (275)	73.2 ± 25.3 (77)	.98	.93
Right ventricular enlargement, No. (%)			<.0001			.0006	.003
None	136 (24.6)	151 (14.4)		94 (27.2)	12 (12.2)		
Mild/moderate	281 (50.8)	555 (53.1)		160 (46.4)	66 (67.3)		
Severe	136 (24.6)	339 (32.4)		91 (26.4)	20 (20.4)	.38	.25
Right ventricular systolic dysfunction, No. (%)			<.0001				
None	213 (42.4)	275 (29.0)		137 (42.7)	32 (38.1)		
Mild/moderate	194 (38.6)	450 (47.4)		119 (37.1)	38 (45.2)		
Severe	95 (18.9)	224 (23.6)		65 (20.2)	14 (16.7)	.003	.01
Left ventricular systolic dysfunction, No. (%)			.88				
None	490 (92.5)	920 (92.4)		308 (93.9)	86 (87.8)		
Mild/moderate	36 (6.8)	66 (6.6)		20 (6.1)	9 (9.2)		
Severe	4 (0.8)	10 (1.0)		0 (0.0)	3 (3.1)	.03	.02
Pericardial effusion, No. (%)			<.0001				
None	312 (61.7)	728 (76.9)		181 (57.3)	66 (71.0)		
Mild/moderate	186 (36.8)	213 (22.5)		127 (40.2)	27 (29.0)		
Severe	8 (1.6)	6 (0.6)		8 (2.5)	0 (0.0)		
6-Min walk distance, m (No.)	300.5 ± 118.0 (208)	329.4 ± 134.7 (354)	.01	288.0 ± 115.1 (132)	324.3 ± 121.3 (32)	.12	.08
BNP, pg/mL (No.)	432.8 ± 789.1 (311)	245.6 ± 427.2 (614)	<.0001	552.2 ± 977.8 (179)	263.8 ± 338.8 (59)	.0004	<.0001
NT-proBNP, pg/mL (No.)	2,312.7 ± 4,203 (62)	1,262.9 ± 3,304 (95)	.0005	2,898.3 ± 4,760 (45)	740.4 ± 1,333 (11)	.01	.005
Pulmonary parenchymal profile							
Mild interstitial lung disease on HRCT scan, No. (%)			<.0001			.16	.39

(Continued)

Table 2—Continued

Characteristic	Etiology		P Value, CTD-APAH vs IPAH	Etiology		P Value, SSc-APAH vs SLE-APAH	P Value, SSc-APAH vs Non-SSc-APAH
	CTD-APAH (n = 641)	IPAH (n = 1,251)		SSc-APAH (n = 399)	SLE-APAH (n = 110)		
Yes	205 (52.6)	168 (30.7)		139 (54.1)	24 (43.6)		
No	185 (47.4)	379 (69.3)		118 (45.9)	31 (56.4)		
Pulmonary function tests							
FEV ₁ , % predicted (No.)	73.7 ± 18.8 (385)	78.3 ± 18.1 (680)	<.0001	73.4 ± 18.4 (254)	73.0 ± 18.8 (56)	.9	.4
FVC, % predicted (No.)	76.0 ± 19.2 (388)	82.1 ± 17.7 (682)	<.0001	75.3 ± 18.6 (255)	77.8 ± 20.1 (57)	.37	.13
FEV ₁ /FVC ratio (No.)	0.8 ± 0.1 (457)	0.8 ± 0.1 (810)	.41	0.8 ± 0.09 (300)	0.8 ± 0.1 (71)	.15	.16
TLC, % predicted (No.)	82.7 ± 16.8 (431)	92.0 ± 30.3 (730)	<.0001	82.7 ± 16.4 (274)	82.1 ± 16.6 (67)	.78	.83
DLCO, % predicted (No.)	44.9 ± 18.0 (420)	63.6 ± 22.1 (691)	<.0001	41.2 ± 16.3 (272)	53.3 ± 19.5 (62)	<.0001	<.0001
DLCO ≤ 32% predicted, No. (%)	109 (26.0)	65 (9.4)	<.0001	83 (30.5)	9 (14.5)	.01	.001
FVC/DLCO ratio (No.)	1.9 ± 0.9 (329)	1.5 ± 1.0 (548)	<.0001	2.0 ± 0.9 (214)	1.7 ± 0.8 (48)	.051	.02

Values are mean ± SD unless otherwise noted. Fick cardiac index is used unless missing, in which case thermodilution is used. Non-SSc-APAH includes patients with SLE-APAH, mixed connective tissue disease-APAH and rheumatoid arthritis-APAH. BNP = B-type natriuretic peptide; DLCO = diffusing capacity of carbon monoxide; HRCT = high-resolution computed tomography; NT-proBNP = N-terminal-pro B-type natriuretic peptide; NYHA/WHO = New York Heart Association/World Health Organization; TLC = total lung capacity; WU = Wood units. See Table 1 legend for expansion of other abbreviations.

*Reported hemodynamics are from time of diagnosis.

$P = .0001$). Hemodynamics at diagnostic RHC did not differ between the patients with SSc-APAH and other CTDs, except that the right atrial pressure was higher (9.1 ± 5.9 vs 8.1 ± 5.0 mm Hg, $P = .05$). At enrollment, a higher percentage of patients with SSc-APAH were functional class IV compared with the other CTD ($P = .04$), but the 6MWD was not significantly different (Table 2, e-Table 2). Echocardiographic features at the time of enrollment were significantly better in the patients with SSc-APAH compared with the other CTDs, in that a lower percentage of patients with SSc-APAH had evidence of right ventricular enlargement and left ventricular systolic dysfunction. However, a higher percentage of patients with SSc-APAH had evidence of a pericardial effusion. BNP levels at enrollment were highest in the patients with SSc-APAH with a mean value of 552.2 ± 977.8 pg/mL compared with 263.8 ± 338.8 in patients with SLE-APAH ($P = .0004$), 268.5 ± 342.6 in patients with MCTD-APAH ($P = .006$), and 181.6 ± 220.5 in patients with RA-APAH ($P = .03$). Similar findings were observed for NT-proBNP levels. The proportion of patients with mild ILD on HRCT at enrollment was not significantly different in the SSc-APAH group compared with the other CTD, and the groups did not differ with respect to lung volumes. However, the DLCO was significantly lower in the SSc-APAH group with a mean value of $41.2\% \pm 16.3\%$ predicted compared with $53.3\% \pm 19.5\%$ predicted in patients with SLE-APAH ($P < .0001$), $52.0\% \pm 19.6\%$ predicted in patients with MCTD-APAH ($P = .0005$), and $49.8\% \pm 13.8\%$ predicted in patients with RA-APAH ($P = .03$). The FVC/DLCO ratio was highest in the SSc-APAH group compared with the other CTDs (2.0 ± 0.9 vs 1.8 ± 0.8 , $P = .02$).

The groups did not differ with regard to the proportion of patients receiving various PAH-specific therapies except that patients with lupus were less likely to receive endothelin receptor antagonists than patients with SSc-APAH (Table 3, e-Table 3). A significantly higher proportion of patients with SLE-APAH, MCTD-APAH, and RA-APAH were receiving concomitant immunosuppressive agents compared with patients with SSc-APAH (22%, 26%, and 18%, respectively, vs 6.8%, $P < .0001$ for patients with SSc vs patients without SSc). However, five patients with SSc-APAH were receiving cyclophosphamide and none of the other patients with CTD were.

At 1 year from the time of enrollment, 82% of the patients with SSc-APAH were alive, compared with 94% of the patients with SLE-APAH ($P = .0009$), 88% of the patients with MCTD-APAH ($P = .5$), and 96% of the patients with RA-APAH ($P = .01$) (Fig 3). Freedom from hospitalizations at 1 year did not differ between patients with SSc-APAH and any of the other CTDs (data not shown).

Table 3—Pulmonary Arterial Hypertension-Specific and Immunosuppressive Therapies in Patients With CTD-APAH, IPAH, SSc-APAH, and SLE-APAH

Therapy	Etiology		P Value, CTD-APAH vs IPAH	Etiology		P Value, SSc-APAH vs SLE-APAH	P Value, SSc-APAH vs Non-SSc-APAH
	CTD-APAH (n = 620)	IPAH (n = 1,196)		SSc-APAH (n = 385)	SLE-APAH (n = 107)		
Prostacyclin	225 (36.3)	561 (46.9)	< .0001	141 (36.6)	37 (34.6)	.7	.73
Endothelin-1 antagonists	310 (50.0)	563 (47.1)	.24	201 (52.2)	44 (41.1)	.04	.43
Phosphodiesterase inhibitors	312 (50.3)	597 (49.9)	.87	196 (50.9)	60 (56.1)	.34	.73
Combination therapy ^a	245 (39.5)	538 (45.0)	.03	159 (41.3)	40 (37.4)	.47	.59
Calcium channel blockers for PAH	58 (9.4)	140 (11.7)	.13	34 (8.8)	12 (11.2)	.45	.45
Immunosuppressants	74 (11.9)	15 (1.3)	< .0001	26 (6.8)	24 (22.4)	< .0001	< .0001
Cyclophosphamide	6 (1.0)	2 (0.2)	.01	5 (1.3)	0 (0.0)	.24	.12
Prednisone	10 (1.6)	5 (0.4)	.008	2 (0.5)	6 (5.6)	.0002	.001
Azathioprine	24 (3.9)	3 (0.3)	< .0001	12 (3.1)	6 (5.6)	.22	.18
Mycophenolate mofetil	25 (4.0)	2 (0.2)	< .0001	6 (1.6)	10 (9.3)	< .0001	< .0001
Methotrexate	10 (1.6)	4 (0.3)	.003	2 (0.5)	2 (1.9)	.17	.003

Values are No. (%). Non-SSc-APAH includes SLE-APAH, mixed connective tissue disease-APAH, and rheumatoid arthritis-APAH. PAH = pulmonary arterial hypertension. See Table 1 legend for expansion of other abbreviations.

^aAt least two PAH-specific medications, including prostacyclin, endothelin-1 antagonists, and phosphodiesterase inhibitors.

DISCUSSION

We report the most comprehensive characterization of patients with CTD-APAH using the largest cohort of patients with RHC-confirmed PAH ever described. We compared the entire CTD-APAH group to patients with IPAH, and also compared patients with SSc-APAH to those with SLE-APAH, MCTD-APAH, and RA-APAH. We found that patients with SSc-APAH have a unique phenotype characterized by markedly elevated BNP levels, reduced DLCO, and poor short-term survival rates. In comparing the CTD-APAH and IPAH cohorts, we observed that despite seemingly better hemodynamics on diagnostic RHC, patients

with CTD-APAH were more likely to exhibit markers of poor prognosis, including lower 6MWD, the presence of pericardial effusion, and elevated BNP levels.^{9,11,16-19} Our findings validate the results of previous smaller studies comparing SSc-APAH to IPAH.^{6,11,20} The lower 6MWD observed in the CTD-APAH group may in part be related to concomitant musculoskeletal problems, and the higher prevalence of pericardial effusions may be a manifestation of inflammatory serositis in some patients. However, patients with CTD-APAH also had poorer 1-year survival and freedom from hospitalization rates than patients with IPAH.

Our study is the first, to our knowledge, to compare clinical and echocardiographic features in patients

FIGURE 2. Kaplan-Meier curves of 12-month survival and freedom from all-cause hospitalization in IPAH vs CTD-APAH cohorts. A, Patients with CTD-APAH had a worse survival (86% vs 93%, $P < .0001$). B, Lower freedom from hospitalization rate (67% vs 73%, $P = .03$). See Figure 1 legend for expansion of abbreviations.

FIGURE 3. Kaplan-Meier curves of 12-month survival in SSc-APAH, SLE-APAH, MCTD-APAH, and RA-APAH. Patients with SSc-APAH had a worse 12-month survival compared with A and C. A, Patients with SLE-APAH (82% vs 94%, $P = .0009$). C, Patients with RA-APAH (82% vs 96%, $P = .01$). B, However, patients with SSc-APAH and MCTD-APAH displayed similar 12-month survival outcomes (82% vs 88%, $P = .53$). MCTD-APAH = mixed connective tissue disease-associated PAH; RA-APAH = rheumatoid arthritis-associated PAH; SLE-APAH = systemic lupus erythematosus-associated PAH; SSc-APAH = systemic sclerosis-associated PAH. See Figure 1 legend for expansion of other abbreviations.

with SSc-APAH vs PAH associated with other CTDs. Studies have shown that traditional measures of right ventricular function by echocardiography may be inaccurate.²¹ Although all echocardiograms were reported by pulmonary hypertension centers, there was not a centralized interpretation of these studies, and not all centers were able to provide data using Tei-index or tricuspid annular plane systolic excursion. With the limitations of echocardiography in mind, nonetheless, we showed that despite better echocardiographic features, essentially similar hemodynam-

ics on diagnostic RHC, and similar 6MWD, patients with SSc-APAH were more likely to be in functional class IV and have evidence of pericardial effusions. Most notably, patients with SSc-APAH had the lowest DLCO and the highest BNP levels compared with patients with the other CTD-APAH. One-year survival rates were lowest in patients with SSc-APAH, but did not differ significantly from patients with MCTD-APAH.

Potential explanations for the poorer outcomes in patients with CTD-APAH, and SSc-APAH in particular, may be rooted in the underlying biology leading to dramatically reduced DLCO and increased BNP values in this cohort. Using percent metabolism and hydrolysis of an angiotensin-converting enzyme substrate as markers for endothelial function, Langleben et al²² have recently shown that patients with CTD-APAH have significantly reduced endothelial metabolic function. Moreover, they showed that for a given cardiac index, patients with CTD-APAH have a lower functional capillary surface area than an IPAH cohort. Such reduction in functional capillary surface area directly correlated with the degree of DLCO reduction. These findings suggest that the reduction in DLCO in patients with CTD-APAH reflects diminishing vascular area with reduced metabolic activity.²² Another possible explanation for the poorer outcomes in patients with CTD-APAH in our cohort is that they received less-aggressive PAH treatment than patients with IPAH, with a lower percentage receiving prostacyclin and combination therapies. Patients with SSc-APAH did not receive significantly different PAH-specific therapy compared with patients with other CTDs (Table 3, e-Table 3). Despite the poor prognostic indicators observed in patients with CTD-APAH, and SSc-APAH in particular, physicians may be hesitant to initiate intravenous or aggressive therapies because of concern for increased risk of infection, drug side effects, or perceived risk of pulmonary edema related to diastolic dysfunction or the relatively higher prevalence of pulmonary venoocclusive disease in these patients.²³⁻²⁵ In addition, physicians may be concerned about poor fine-motor dexterity in patients with sclerodactyly, digital ulcers, arthritis, and/or significant deformities, which could make the handling of their drug delivery system more difficult. Although patients with CTD-APAH were more likely to receive concomitant immunosuppressive therapies than patients with IPAH, only 12% of the patients with CTD were reported to be receiving immunosuppression at the time of enrollment. Likewise, only 22% of patients with SLE-APAH and 26% of patients with MCTD-APAH were receiving immunosuppressive therapies, none of whom were being treated with cyclophosphamide. This contrasts with a recent UK study, which found that 86% of patients with SLE-APAH were receiving immunosuppression, highlighting the difference in

practice styles in the United States compared with the United Kingdom.¹² Limited data suggest that patients with SLE- and MCTD-APAH may experience clinical improvement with first-line immunosuppressive therapy or in combination with vasodilators.^{26,27} These reports also indicate that patients with SSc-APAH are unlikely to respond to immunosuppression alone.²⁶ These studies are based on retrospective uncontrolled data, and therefore the usefulness of concomitant immunosuppressive therapies for the treatment of CTD-APAH awaits further evaluation in randomized controlled clinical trials.

We found that marked elevations in BNP and NT-proBNP levels are specific to patients with SSc-APAH (Table 2, e-Table 2). This is consistent with a smaller study showing that patients with SSc-APAH had substantially higher NT-proBNP levels compared with patients with IPAH, which correlated with severity of PAH in the patients with SSc-APAH.²⁰ Although the mechanisms responsible for the disproportionate elevation of natriuretic peptide levels in patients with SSc-APAH await elucidation, we speculate that the high prevalence of myocardial fibrosis, reported in up to 50% to 80% of patients with SSc, may be a contributing factor.²⁸ Unfortunately, we were unable to assess the presence of myocardial fibrosis in our cohort, because cardiac magnetic resonance imaging, which is currently the best way to evaluate cardiac structure, was not possible at all centers. The prevalence of renal insufficiency, which can affect serum levels of natriuretic peptides, was higher in the CTD-APAH group than the IPAH group, and was highest in the patients with SSc-APAH compared with the other CTD. However, an analysis of covariance controlling for renal insufficiency still showed significantly higher BNP levels in the CTD-APAH ($P < .001$ compared with IPAH) and SSc-APAH groups ($P < .001$ compared with non-SSc) (data not shown). We also showed that severely reduced DLCO is specific to SSc-APAH. Previous studies have shown that a decreasing DLCO is predictive of the development of PAH in patients with both limited and diffuse cutaneous SSc.^{29,30} Our study is the first to show that a markedly low DLCO differentiates patients with SSc-APAH from those with SLE-APAH, MCTD-APAH, and RA-APAH. In our study, the proportion of patients with mild ILD did not differ between the SSc and non-SSc groups; therefore, we believe that the substantial reduction in DLCO reflects the underlying systemic vasculopathy in patients with SSc.³¹ Similar to the study by Hachulla et al,³² we found that patients with SSc-APAH who had a DLCO of $\leq 32\%$ predicted experienced significantly poorer survival than those with higher DLCO values ($P = .007$) (not shown). Overall, our results are consistent with the findings of a recent smaller study indicating that the combination of ele-

vated natriuretic peptide levels and decreased DLCO is highly predictive of the development of PAH in SSc.³³

One-year survival rates were 93% for patients with IPAH and 86% for patients with CTD-APAH. These estimates are comparable to previous studies including prevalent or incident patients conducted in the current era of PAH management (89% to 95% for IPAH and 81% to 87% for SSc-APAH on active PAH treatment).^{8-11,34,35} We also showed for the first time that hospitalization rates were significantly higher in patients with CTD-APAH compared with patients with IPAH. It is possible that a proportion of these deaths and hospitalizations were related to flares or complications of their underlying CTD, such as coronary artery disease, infections, cancer, or other complications related to immunosuppression, rather than PAH. Unlike the recent UK study by Condliffe et al,¹² we found that short-term survival was significantly worse in patients with SSc-APAH than those with SLE-APAH and RA-APAH, with 1-year survival rates of 82% vs 94% and 96%, respectively. One-year survival rates were lower for all groups in the UK study (78% for SSc-APAH and SLE-APAH, 83% for RA-APAH), but survival in patients with SSc-APAH was substantially worse by 3 years (47% in SSc-APAH, 74% in SLE-APAH, and 66% in RA-APAH). Similar to the Condliffe study, we found that 1-year survival did not differ between patients with SSc- and MCTD-APAH, presumably because these patients often display prominent features of SSc. The overall lower short-term survival rates in the Condliffe et al¹² study may be attributed in large part to the fact that all patients had incident PAH. Our study shows that survival in patients with PAH with predominantly prevalent disease may improve after the initial high-risk period following PAH diagnosis; however, patients with CTD-APAH, and SSc-APAH specifically, experience poorer short-term survival rates in both incident and prevalent analyses.

An interesting finding in our cohort was the low prevalence of Raynaud phenomenon in the patients with CTD. The prevalence of Raynaud phenomenon in SSc and SLE has been estimated to be as high as 90% and 45%, respectively.³⁶ Raynaud phenomenon was likely underreported in our study because rheumatologists are not involved in data collection and entry in the REVEAL database. However, 86% of patients with CTD-APAH were enrolled at sites that routinely involve a rheumatologist in the diagnosis and care of patients with CTD-APAH.

Given the design of our study, some missing data were unavoidable. We had limited information on important variables, including autoantibody status, the presence of antiphospholipid antibodies, and the timing of CTD onset and duration. These variables have all been shown to be important in predicting

the development and severity of PAH in patients with SSC.^{30,37,38} Similar to other pulmonary hypertension registries, our cohort includes prevalent and incident cases. This enables the collection of a large sample size, at the expense of homogeneity with regard to PAH disease duration. However, our results agree with another study that included only incident cases, which showed better hemodynamics, but poorer survival, in SSC-APAH compared with IPAH.¹¹ In addition, the inclusion of prevalent cases renders our results more generalizable to patients seen routinely in clinical practice. Finally, results of a sensitivity analysis on the incident cases showed consistent trends with those observed for the entire cohort (data not shown). Because of the substantial lag time between symptom onset and diagnosis in PAH,¹⁵ it may not be feasible to study the natural history of PAH in a truly incident cohort. Nonetheless, the fact that surviving patients with CTD-APAH differ so substantially from surviving patients with IPAH suggests that there are either large baseline differences, that the disease progresses much more rapidly in CTD-APAH, or possibly both. Other important confounders that we plan to adjust for in future analyses include age, sex, race, and smoking history. Mortality rates in patients with IPAH increase with advancing age and are highest in African American women³⁹; therefore, it will be important to adjust for these confounders in future multivariate longitudinal and long-term survival analyses.

In conclusion, we have characterized the largest US-based, multicenter cohort of patients with CTD-APAH described to date. Our study verifies that patients with SSC-APAH display a unique phenotype with the worst short-term prognosis. SSC-APAH is further differentiated by the highest BNP levels and lowest DLCO, highlighting the systemic effects of the disease beyond the pulmonary vasculature. Further research is necessary to determine the mechanisms by which these markers develop.

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Additional information: The e-Tables can be found in the Online Supplement at <http://chestjournal.chestpubs.org/content/138/6/1383/suppl/DC1>.

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