

# Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): Baseline Characteristics and Description of Study Population

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**ABSTRACT.** *Objective.* Pulmonary arterial hypertension (PAH) increases mortality in systemic sclerosis (SSc). The multicenter PHAROS registry (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma) prospectively follows subjects with SSc at high risk for or with incident pulmonary hypertension (PH). We describe the registry design and baseline characteristics of subjects enrolled during the first 18 months since the start of the study.

*Methods.* High-risk subjects are enrolled and classified as Pre-PAH if they have (1) carbon monoxide diffusing capacity (DLCO) < 55% predicted; (2) percentage of predicted forced vital capacity/DLCO ratio  $\geq$  1.6; or (3) an estimated right ventricular systolic pressure > 35 mm Hg on echocardiography. Subjects with right heart catheterization (RHC)-confirmed incident PH (mean pulmonary artery pressure  $\geq$  25 mm Hg within previous 6 months) are subclassified into PAH, pulmonary venous hypertension secondary to left-side heart disease (PVH), and PH due to interstitial lung disease (PH-ILD). Baseline and biannual demographic, clinical, and laboratory data and patient-reported health questionnaires are collected.

*Results.* There are 237 subjects enrolled in PHAROS. The majority are white (73%) and women (87%). There are 166 Pre-PAH and 71 Definite PH subjects (49 PAH, 7 PVH, and 15 PH-ILD).

*Conclusion.* PHAROS is the largest US and Canadian cohort of subjects with SSc at high risk for or with incident PAH. PAH-specific therapies are approved for 49/71 subjects with RHC-confirmed PAH. Analyses of PHAROS registry data will permit identification of risk factors for development of PAH among SSc patients at high risk for PAH and enhance understanding of the course of SSc-PAH. (First Release Aug 15 2011; J Rheumatol 2011;38:2172-9; doi:10.3899/jrheum.101243)

## Key Indexing Terms:

SYSTEMIC SCLERODERMA  
REGISTRY

PULMONARY HYPERTENSION  
PULMONARY ARTERIAL HYPERTENSION

Systemic sclerosis (scleroderma, SSc) is a multisystem connective tissue disease characterized by immune disturbance, abnormal vasculature, and organ fibrosis and dysfunction. Pulmonary complications of SSc, including interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), are well established as the leading causes of SSc-related deaths<sup>1</sup>.

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The prevalence of PAH confirmed by right heart catheterization (RHC) in SSc is estimated to be between 7.5% and 12%<sup>2,3</sup>. Prior to the availability of PAH-specific therapies, the 5-year survival rate was 10% for persons with SSc with PAH compared to 80% for SSc without PAH<sup>4</sup>.

As more effective PAH-specific therapies have become available, it is increasingly important to accurately predict which SSc patients are most likely to develop SSc-PAH. The vascular changes in SSc likely occur throughout the disease course and identifying those with the earliest clinical signs of pulmonary vascular disease should lead to an earlier diagnosis of PAH. Earlier detection should promote earlier initiation of PAH-specific therapies to improve cardiac hemodynamics, pulmonary function, quality of life measures, and possibly survival.

The most recent clinical classification of pulmonary hypertension (PH) separates patients into 5 specific groups<sup>5,6</sup>. Patients with SSc are at risk for the development of PH Groups 1-3 (Table 1). This includes the primary pulmonary arterial vasculopathy of PAH (Group 1), pulmonary venous hypertension associated with left-side heart disease (PVH; Group 2), and PH secondary to chronic lung disease such as ILD (Group 3). We emphasize that these classification dis-

Table 1. Types of pulmonary hypertension (PH) affecting patients with systemic sclerosis. Adapted from the Dana Point 2009 criteria for PH<sup>5</sup>.

Group	Pulmonary Hypertension	Abbreviation
1	Pulmonary arterial hypertension associated with connective tissue diseases	PAH
2	Pulmonary venous hypertension associated with left heart disease (e.g., diastolic dysfunction)	PVH
3	Pulmonary hypertension associated with respiratory disease (e.g., pulmonary fibrosis)	PH-ILD

tions require an RHC and that PAH-specific therapies are approved only for patients with Group 1 disease.

The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) study was established in 2006 to prospectively follow SSc subjects at high risk for developing or with incident SSc-associated PAH (SSc-PAH) within 6 months of RHC-based diagnosis. The goals of PHAROS are to (1) determine the rate of evolution to PAH in a high-risk SSc population; (2) identify which risk factors are most predictive for development of SSc-PAH; (3) characterize the types and features of PH that occur in SSc; and (4) determine the effectiveness of PAH-specific therapies. Studies utilizing PHAROS registry data will enable the development of rational treatment strategies for SSc-PAH. In this study, we describe the design of the PHAROS registry and report baseline characteristics including the PH classification of PHAROS registry subjects for the first 18 months since the study began.

## MATERIALS AND METHODS

PHAROS is a multicenter study in compliance with the US Health Insurance Portability and Accountability Act (HIPAA) conducted at 18 US and Canadian sites. Each participating center's institutional review board approved the study protocol. Although funded by commercial support, the sponsoring companies had no role in study design, data analysis, or preparation of this report.

The PHAROS registry includes 2 subgroups of subjects: (1) those at increased risk for developing SSc-PAH, who are classified as "Pre-PAH"; and (2) those with incident PH enrolled within 6 months of RHC-confirmed diagnosis according to the 2009 Dana Point criteria for PH [mean pulmonary artery pressure (mPAP)  $\geq$  25 mm Hg at rest]<sup>5</sup>. We defined a classification listing of "Pre-PAH" based on the presence of any 1 of these 3 criteria on study entry: (1) diffusing capacity for carbon monoxide (DLCO)  $<$  55% predicted without severe ILD [as defined by forced vital capacity (FVC)  $<$  65% predicted and/or a thoracic high-resolution computed tomography (HRCT) scan that showed moderate to severe ILD according to the local radiologist<sup>7</sup>]; or (2) FVC %predicted/DLCO %predicted ratio  $\geq$  1.6; or (3) estimated right ventricular systolic pressure (RVSP)  $>$  35 mm Hg on Doppler echocardiography.

Inclusion criteria were age  $>$  18 years and fulfillment of American College of Rheumatology criteria for SSc<sup>8</sup> or the LeRoy definitions of limited cutaneous or diffuse cutaneous SSc<sup>9</sup>. Patients with PH were excluded if they were receiving PAH-specific treatment at the time of the initial RHC or had a left ventricular ejection fraction  $<$  50% on echocardiography or signs or symptoms of systolic heart failure at the baseline clinical examination. An additional exclusion criterion included PH attributed to other diseases included in the current PH classification system (e.g., congenital systemic-to-pulmonary shunt, HIV infection, cardiopulmonary disease attributed to drugs and toxins, sarcoidosis, histiocytosis X, lymphangiomyomatosis, etc.)<sup>5</sup>.

The investigator entering data for each subject confirmed the PH group according to the 2009 Dana Point classification criteria for PH<sup>5</sup> prior to this analysis, as follows.

Group 1: PAH: on RHC an mPAP  $\geq$  25 mm Hg at rest with a pulmonary

capillary wedge pressure (PCWP)  $\leq$  15 mm Hg without significant ILD as defined by an FVC  $\geq$  65% predicted; and mild, if any, ILD by HRCT according to the local radiologist<sup>7</sup>.

Group 2: PVH: an RHC mPAP  $\geq$  25 mm Hg at rest with a PCWP  $>$  15 mm Hg.

Group 3: Pulmonary hypertension secondary to chronic lung disease (PVH): these patients had mPAP  $\geq$  25 mm Hg with PCWP  $\leq$  15 mm Hg but also had significant ILD with FVC  $<$  65% predicted and/or a thoracic HRCT scan that showed moderate to severe ILD with or without honeycombing. Fibrosis was graded as normal (no fibrosis), mild, moderate, or severe by the local radiologist interpreting the study<sup>7</sup>.

Other information collected included baseline demographics: age at diagnosis of SSc and PH, clinical history, SSc subtype, disease duration, medication, and smoking history. Subjects completed questionnaires including the Scleroderma Health Assessment Questionnaire<sup>10</sup>, the University of California at San Diego Dyspnea Index<sup>11</sup>, and the 36-item Short-Form health survey (SF-36)<sup>12</sup> that were administered by study personnel in person, by telephone, or by mailing or faxing forms to participating subjects every 6 months. Physical examination findings of SSc and PH features were recorded. Each participating center performed baseline laboratory testing including autoantibody profiles and brain natriuretic peptide (BNP) or N-terminal pro-BNP. Autoantibody profiles consisted of anticentromere (ACA), antitopoisomerase, an isolated antinuclear pattern on antinuclear antibody (ANA; without other SSc-specific antibodies), anti-U1-RNP, anti-RNA polymerase III, other, or none. A subject without an SSc-specific antibody who had multiple ANA patterns was characterized as "other."

High-resolution thoracic CT scans, RHC, pulmonary function tests (PFT), Doppler echocardiography, and 6-minute walk distance tests (6MWD) were performed as clinically indicated as determined by the clinician investigator. As part of the standard of care, baseline studies were repeated and recorded yearly along with the medical history, hospitalizations, medication information, and outcome events. Outcome events comprised the development of PH as defined above, hospitalization for PH, or the need for PAH-specific therapy. PAH-specific therapy was initiated at the discretion of the treating clinician.

All data were collected using paper case report forms and manually entered into a central computerized database by site-specific research coordinators. Vital status was reported for study subjects by each participating site prior to analyses.

Continuous variables were summarized by mean  $\pm$  SD and compared using t tests (or nonparametric equivalent when appropriate). Categorical variables were compared using the chi-square statistic (or Fisher's exact test when appropriate). For all analyses, a 2-sided p value  $<$  0.05 was considered statistically significant. For analyses comparing the 3 PH groups, subjects in Groups 2 and 3 were collapsed into one group due to the small number of subjects in these groups. SAS version 9.2 (SAS, Cary, NC, USA) was used for all statistical analyses.

## RESULTS

Two hundred thirty-seven subjects met PHAROS echocardiography or PFT criteria and were enrolled in the registry. Of these, 87 underwent RHC at the discretion of the clinical investigator. Seventy-one had Definite PH based on the Dana Point criteria. Sixteen had normal mPAP and were classified as Pre-PAH (Figure 1).

*The Pre-PAH cohort.* There were 166 subjects who were classified as Pre-PAH at entry; Table 2 summarizes the clinical features of these patients. There were no significant differences in demographic data or autoantibodies between the Pre-PAH and Definite PH subjects. The mean age at enrollment into PHAROS was 57 years (range 35 to 79), 87% were women, 75% white, 16% African American, 6% Hispanic, and 2% Asian. The mean time from first non-Raynaud's symptom to study entry was 9 years, whereas the mean time from the appearance of Raynaud's phenomenon to study entry was 13 years. Fifty-three percent had SSc-specific autoantibodies (68/127); of these, 42% (28/68) had anticentromere

antibodies, 32% (23/68) had antitopoisomerase antibodies, and 25% (17/68) had an isolated nucleolar antibody pattern without other specificity. The remainder had a mixed ANA, negative ANA, or no autoantibody information available. Pre-PAH patients with different SSc-specific autoantibodies had similar pulmonary physiologic features based on PFT (Table 3). The mean New York Heart Association (NYHA) classification for those with Pre-PAH was 1.3 (SD 1.0), although 36 were not classified due to lack of dyspnea. Figure 2 depicts the entry criteria of the Pre-PAH cohort.

At baseline, 16 (10%) subjects of the Pre-PAH group had symptoms, an elevated RVSP (mean 38 mm Hg  $\pm$  SD 10,

Table 2. Demographic, clinical, and laboratory features of patients with Pre-PAH and Definite PH.

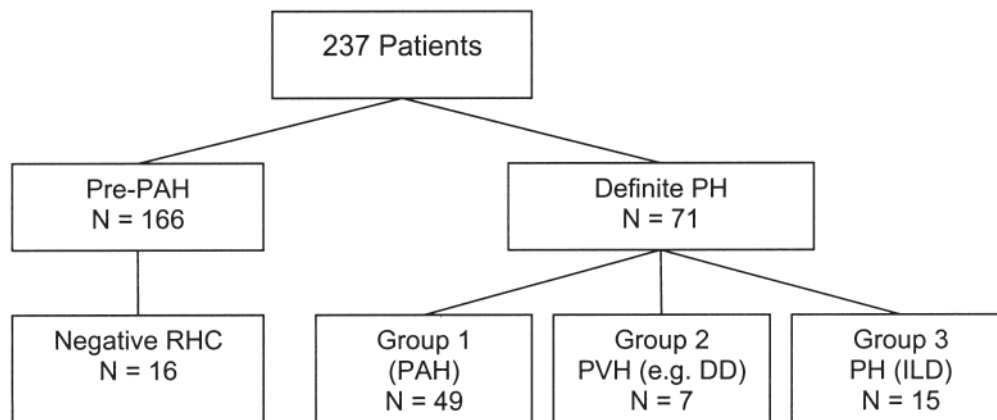
Feature	Pre-PAH, n = 166	Definite PH, n = 71
Female, n (%)	138 (87)	55 (87)
Ethnicity, n (%)		
White	116 (75)	42 (67)
African American	25 (16)	14 (22)
Hispanic	9 (6)	2 (3)
Asian	3 (2)	4 (6)
Age at SSc diagnosis, yrs, mean (SD)	46 (13)	45 (14)
Age at PHAROS enrollment, yrs, mean (SD) (range 35-79)	57 (11)	57 (10)
Time from first non-Raynaud's until study entry, yrs, mean (SD)	9 (8)	9 (7)
Time from first Raynaud's until study entry, yrs, mean (SD)	13 (10)	13 (10)
Limited SSc, n (%)	58 (63)	20 (57)
Autoantibodies, n (%)	n = 127	n = 50
Anticentromere	28 (22)	19 (38)
Antitopoisomerase	23 (18)	8 (16)
Isolated nucleolar ANA	17 (13)	19 (38)
BNP, pg/ml, mean (SD)	35 (15)	94 (70)
Entry criteria		
DLCO < 55% predicted	91 (55)	58 (79)
FVC/DLCO > 1.6	88 (53)	51 (70)
Estimated RVSP on echo > 35 mm Hg	50 (30)	47 (64)
Cardiopulmonary		
Echo RVSP, mm Hg, mean (SD)*	38 (10)	57 (17)
Right heart catheterization, normal ranges <sup>31</sup> , mean (SD)		n = 16
mPAP (< 25 mm Hg)*		20 (4)
PVR (20–120 dyn $\times$ s/cm <sup>5</sup> )*		180 (94)
Cardiac output (4–8 l/min)		5.4 (1.3)
PCWP (6–12 mm Hg)		8.2 (3.3)
BORG Dyspnea Index, mean (SD)*	1.9 (1.8)	3.2 (2.3)
6MWD, m, mean (SD)	393 (134)	337 (135)
NYHA functional class, n (%)*		
Unclassified (no dyspnea)	36 (23)	5 (7)
1	51 (33)	10 (15)
2	42 (27)	29 (44)
3	25 (16)	17 (25)
4	1 (1)	6 (9)

\* Denotes statistically significant difference ( $p < 0.05$ ). Autoantibody percentages calculated using the number of patients with an autoantibody present as the denominator (n = 112 for Pre-PAH, n = 50 for Definite PH). BNP: brain natriuretic peptide; FVC: % predicted forced vital capacity; DLCO: % predicted diffusing lung capacity for carbon monoxide; RVSP: estimated right ventricular systolic pressure on 2-dimensional Doppler echocardiography. Right heart catheterization (RHC) values with normal values in parentheses; mPAP: mean systolic pulmonary artery pressure; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure. Functional class values; NYHA: New York Heart Association; 6MWD: 6-minute walk distance. The Pre-PAH cohort includes 16 patients who underwent an RHC that revealed a normal mPAP.

**Table 3.** Scleroderma-specific antibodies and pulmonary function and echocardiography values in patients with Pre-PAH. Autoantibody data were available for 127/166 Pre-PAH patients. Pre-PAH patients were divided according to the 3 most commonly present autoantibodies to determine the association between scleroderma-specific antibodies and clinical PAH markers. The other patients did not have detectable autoantibodies or had an anti-U1-RNP, anti-RNA polymerase III, other, or no autoantibody information was available. A patient without an SSc-specific antibody who had multiple ANA patterns was characterized as “other.” There were no statistically significant differences between groups.

Mean (SD)	ACA, n = 28	Scl-70, n = 23	Nucleolar, n = 17
FVC, % predicted	95 (16)	79 (15)	79 (16)
DLCO, % predicted	56 (22)	46 (16)	51 (22)
FVC/DLCO	1.78 (0.46)	1.85 (0.52)	1.74 (0.60)
RVSP, mm Hg	37 (7)	41 (10)	39 (9)

ACA: anticentromere, Scl-70: antitopoisomerase antibodies; ANA: antinuclear antibodies.



**Figure 1.** Classification of PHAROS patients. Of 237 patients enrolled since the inception of the study, 166 were classified as pre-pulmonary artery hypertension (Pre-PAH) and 71 had incident pulmonary hypertension (PH) confirmed by right heart catheterization (RHC). Sixteen patients underwent RHC for suspected PH and mean pulmonary artery pressure was normal (< 25 mm Hg). Of the 71 patients with Definite PH, 49, 7, and 15 were classified into Groups 1, 2, and 3, respectively<sup>32</sup>. DD: diastolic dysfunction; ILD: interstitial lung disease; PVH: pulmonary venous hypertension.

range 19–62 mm Hg), or PFT abnormalities that led individual investigators to perform an RHC that revealed a normal mPAP. Four of these had an estimated RVSP on echocardiogram > 40 mm Hg; the mean %predicted DLCO in this group was markedly reduced (38% ± 16%) and the mean PCWP was 8 mm Hg. Ten RHC-negative subjects had undergone thoracic HRCT that revealed no (n = 5), mild (n = 3), moderate (n = 1), or severe (n = 1) fibrosis.

**Definite PH cohort.** There were 71 subjects who were classified as Definite PH confirmed by RHC. These subjects were classified according to 2009 Dana Point criteria for PH: 49 (69%) met criteria for Group I PAH, with resting mPAP ≥ 25 mm Hg and PCWP ≤ 15 mm Hg; 7 (10%) had mPAP ≥ 25 mm Hg and PCWP > 15 mm Hg, fulfilling the Group 2 PH criteria (PVH); 15 (21%) patients had mPAP ≥ 25 mm Hg and significant ILD (as defined above) and were classified as Group 3 (PH-ILD). Table 4 describes the demographic data of this cohort by PH group.

Cardiopulmonary features are presented in Table 4. The mPAP on RHC was remarkably similar in all 3 groups: 36, 35, and 34 mm Hg, respectively. The mean RVSP on echocardiogram was also similar in the 3 groups: 57, 45, and 52 mm Hg, respectively. As expected, the PFT measurements revealed no significant restriction in Group 1 (mean FVC 86%), whereas both the PVH and PH-ILD patients had significant reductions in FVC (62% and 56%, respectively; p < 0.0001). DLCO was significantly lower in Groups 2 and 3 compared to Group 1 (p = 0.04), while FVC/DLCO ratio was higher in Group 1, although not significantly (p = 0.29). Group 1 subjects had a trend of more dyspnea, shorter 6MWD, and higher NYHA functional class compared to Group 2 and 3 subjects combined (not statistically significant).

Group 1 PAH subjects were the most likely to have a positive anticentromere antibody result: 45% in Group 1, 25% in Group 2, 10% in Group 3 (p = 0.053). Although an isolated antinucleolar antibody is not a common antibody in SSc<sup>1</sup>, it

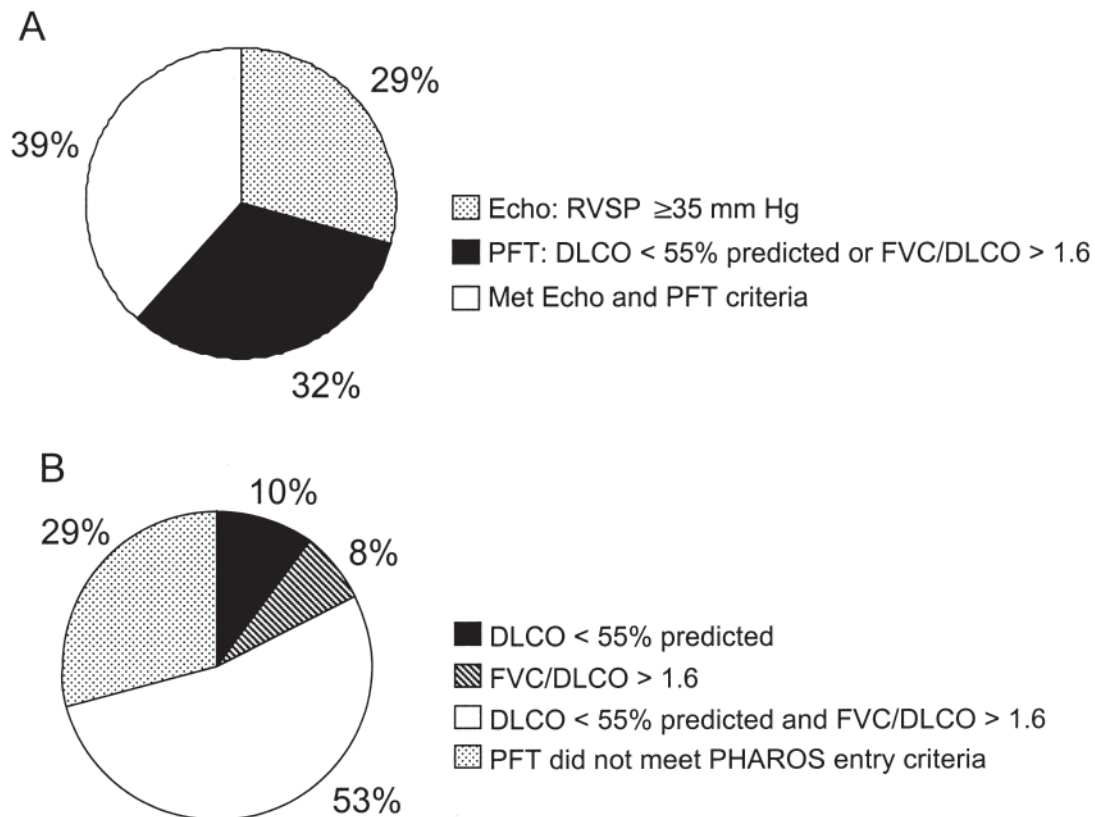


Figure 2. Classification of patients meeting the PHAROS eligibility criteria. A. PHAROS entry criteria at baseline (n = 157). B. Pulmonary function test (PFT) entry criteria at baseline (n = 157). Echo: echocardiography; FVC: forced vital capacity; RVSP: right ventricular systolic pressure.

was prevalent in relatively high numbers in all 3 PH groups: in 40% with PAH, 40% with PVH, and 30% with PH-ILD (p = 0.75). Twenty-one subjects were receiving endothelin I receptor antagonists and 24 subjects were receiving phosphodiesterase inhibitors.

## DISCUSSION

In this study, we describe the PHAROS registry study design as well as the baseline characteristics and initial clinical data using information collected during the first 18 months from the start of the study. PH is a leading cause of death in persons with SSc; some of the goals of the PHAROS registry are identifying the factors that predict the development of PAH among SSc patients at high risk for PAH and the response to various PAH-specific therapies.

PH is defined as an mPAP  $\geq$  25 mm Hg on resting RHC. Several disease entities can cause elevations in pulmonary artery pressures in SSc, but the most common causes are intrinsic pulmonary arterial vasculopathy (Group 1, PAH), left-side heart disease (Group 2, PVH), and ILD (Group 3, PH-ILD; Table 1). We found that one-third (22/71) of subjects thought to be at high risk for PAH according to our 3 criteria had PVH or PH-ILD. Thus, it is imperative that clinicians

treating patients with SSc understand that RHC is necessary to accurately establish the diagnosis of PAH. Further, PAH-specific therapies are approved only for patients with Group 1 disease (PAH). The use of PAH-specific therapies in SSc patients with PVH and PH-ILD has not been studied and should only be done with great caution because increased vasodilatation in the pulmonary vasculature of these patients may increase ventilation-perfusion mismatch and worsen symptoms.

There were significant differences between subjects with Pre-PAH and Definite RHC-confirmed incident PH. Patients with RHC-confirmed incident PH had higher mean estimated RVSP on echocardiogram, mean pulmonary vascular resistance, and BORG Dyspnea Index scores, and lower NYHA functional class. Six-minute walk test results did not vary significantly between those with Pre-PAH and Definite PH, which may be due to insufficient power to detect significant differences secondary to small numbers of subjects.

Of the 127/166 Pre-PAH subjects for whom autoantibody data were available, the majority had positive SSc-specific antibodies (anticentromere, antitopoisomerase, and nucleolar ANA). It has recently been shown that patients with diffuse cutaneous SSc with U3-RNP, a specific nucleolar antibody,

Table 4. Demographic, clinical, and laboratory features of patients with Definite PH.

Characteristic	PH Group		
	Group 1, PAH, n = 49	Group 2, PVH, n = 7	Group 3, PH-ILD, n = 15
Female, n (%)	40 (91)	5 (83)	12 (80)
Age at SSc diagnosis, yrs, mean (SD)	44 (18)	40 (21)	44 (10)
Age at PHAROS enrollment, yrs, mean (SD)	59 (12)	54 (13)	54 (8)
Race, n (% white)*	31 (76)	1 (20)	8 (57)
Limited SSc, n (%)*	33 (72)	3 (50)	5 (36)
Time from first non-Raynaud's, yrs, mean (SD)	10 (6)	10 (7)	9 (7)
Time from first Raynaud's, yrs, mean (SD)	13 (9)	15 (12)	11 (9)
RHC, mean (SD)			
mPAP (< 25 mm Hg)	36 (12)	35 (8)	34 (9)
PCWP (5–15 mm Hg)*	11 (3)	20 (4)	11 (4)
Cardiac output (3–4 l/min)	5.2 (1.5)	6.6 (0.6)	5.4 (1.1)
PVR (150–250 dyn×s/cm <sup>5</sup> )	400 (240)	297 (255)	287 (115)
Autoantibodies, n (%)			
Anticentromere	15 (45)	1 (25)	1 (10)
Scl-70*	1 (3)	0	6 (50)
Nucleolar	12 (40)	2 (40)	3 (30)
Pulmonary function tests, mean % predicted (SD)			
FVC*	86 (28)	62 (26)	56 (12)
DLCO*	43 (18)	34 (7)	30 (10)
FVC/DLCO	2.30 (1.1)	2.06 (0.6)	2.08 (0.6)
Echocardiography			
RVSP (mm Hg), mean (SD)	57 (21)	45 (15)	52 (16)
6MWD, m, mean (SD)	337 (133)	420 (116)	292 (132)
NYHA functional class, n (%)			
Unclassified (no dyspnea)	2 (4)	2 (33)	1 (8)
1	9 (19)	1 (17)	0
2	20 (42)	2 (33)	7 (54)
3	13 (27)	1 (17)	3 (23)
4	4 (8)	0	2 (15)

\* Denotes a statistically significant difference ( $p < 0.05$ ). SSc: systemic sclerosis. SSc disease duration: time from onset of first non-Raynaud's symptom to the date of first visit; FVC: % predicted forced vital capacity; DLCO: % predicted diffusing lung capacity for carbon monoxide; RVSP: estimated right ventricular pressure on 2-dimensional Doppler echocardiography. Right heart catheterization (RHC) values ( $n = 16$ ) with normal values in parentheses; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure. Functional class values; NYHA: New York Heart Association; 6MWD: 6-minute walk distance.

have increased prevalence of PAH<sup>13</sup>. We found high prevalence of antinucleolar antibodies especially among African American subjects with PAH. This is particularly important because many commercial laboratories are no longer performing immunofluorescent ANA testing, and thus the ANA pattern is not reported. We emphasize that determination of ANA pattern is very useful in the clinical care of patients with SSc, and care providers should ensure that ANA patterns are part of the autoantibody assessments for these patients.

Among patients with Definite PH, the majority, 69% (49), had PAH (Group 1 disease). These subjects tended to be white, with limited cutaneous SSc without a positive anti-topoisomerase antibody compared to subjects with PVH and PH-ILD. As expected, we found significantly lower FVC and DLCO in those with PVH and PH-ILD compared to those with PAH. DLCO was very low in all groups. Only 14% of those with PH had DLCO > 55% of predicted levels.

Interestingly, the mean DLCO was lowest in Groups 2 and 3, showing that low DLCO itself does not necessarily predict PAH compared to PVH and PH-ILD. However, the mean %predicted FVC was significantly lower in the non-PAH groups, and importantly the mean FVC%/DLCO% ratio was highest in those with PAH. Eighty-two percent of those with PAH, 70% with PVH, and only 25% with PH-ILD had a FVC/DLCO ratio > 1.6. Thus, the high ratio may be a useful indicator as part of the determination whether an SSc-PH patient has PAH compared to other causes of PH.

The mPAP in the 3 Definite PH groups was lower compared to findings in other clinical trials that have included subjects with SSc, and we believe this likely reflects ascertainment bias. PHAROS investigators are rheumatologists with dedicated SSc programs who specifically identify high-risk and incident cases of PAH. We are hopeful that the longitudinal study of the PHAROS cohort will show whether earlier

detection of SSc-PAH will prompt earlier initiation of PAH-specific therapies and lead to improved survival.

Currently available PAH-specific medications target 1 of 3 pathophysiological pathways<sup>14</sup>. The dual endothelin receptor antagonist bosentan appears to improve exercise tolerance and hemodynamics in SSc-PAH in the short term, although it is unclear whether treatment with bosentan imparts long-term functional and survival benefits<sup>15,16,17,18,19</sup>. The prostacyclin analogs epoprostenol and treprostinil appear to improve exercise tolerance and hemodynamics in SSc-PAH<sup>20,21,22</sup>. And sildenafil and tadalafil, phosphodiesterase type-5 inhibitors that improve production of nitric oxide, may be useful in SSc-PAH as well<sup>23,24</sup>.

Before the newer PAH-specific therapies were available, few patients with SSc-PAH lived longer than 5 years from the time of diagnosis of PAH<sup>25</sup>. With the new treatments, survival may be improving, although patients with SSc-PAH continue to fare worse than patients with idiopathic PAH. Additionally, SSc patients with PH-ILD have a worse prognosis than patients with SSc-PAH, with 3-year survival of 39% compared with 64% ( $p < 0.01$ )<sup>26</sup>. There are several reasons why patients with SSc-PAH may have increased mortality rates compared with other forms of PAH, including concomitant ILD, pulmonary veno-occlusive disease<sup>27</sup>, myocardial disease<sup>28</sup>, and diastolic dysfunction, or a combination of these<sup>26,29</sup>. A unique phenotype consisting of both ILD and PAH that imparts an increased burden on a straining right ventricle may account for worse disease. Chang and colleagues reported 18% of 618 patients with SSc had evidence for combined PAH and PH-ILD<sup>30</sup>. Overbeek and colleagues found evidence of small vessel intimal fibrosis in both arterioles (8/8) and venules (7/8) in 8 subjects with SSc-PAH, but in only 3/11 subjects with idiopathic PAH<sup>27</sup>. Additionally, left ventricular diastolic dysfunction is common in SSc and causes PVH and increased pulmonary arterial pressures. Consequently, PH in SSc is likely multifactorial and the interaction of several disease entities may contribute to decreased survival. We anticipate that the PHAROS registry will allow exploration of outcomes of subjects in the Pre-PAH and Definite PH groups and determine which factors influence survival.

Because the PH in an individual patient with SSc may be multifactorial and include varying degrees of PAH, PVH, and PH-ILD, longitudinal analyses of PHAROS data from patients with multifactorial PH will be needed to determine whether the institution of PAH-specific therapies is beneficial or harmful.

The PHAROS registry was designed to collect data on SSc subjects thought to be at increased risk for PAH as defined by 3 inclusion criteria or with newly established PH identified by RHC. There are a number of limitations to the conclusions that can be drawn from this study population. First, we have no means of assessing what percentage of patients with SSc are seen at PHAROS participating centers, and what percent-

age of eligible SSc patients seen at each center are actually enrolled in PHAROS. Second, as noted there were no standardized protocols for laboratory, echocardiographic, or PFT or RHC testing. All tests and clinical assessments were performed at the discretion of the individual clinician investigator according to practices at each participating center, thus there is the potential for bias due to unequal duration in followup. However, one of the strengths of the PHAROS registry is that it provides for longitudinal collection of a large amount of data from a large, multicenter group of subjects with SSc by rheumatologists specializing in SSc rather than based in PH centers.

We believe the subjects in PHAROS, both Pre-PAH and those newly diagnosed with Definite PH, are going to be an important population to follow over time. Monitoring the time course between Pre-PAH and Definite PH in SSc will assist the design of future prevention trials to assess the influence of therapies. Determining risk factors for SSc-PAH will enhance development of practical screening programs to closely monitor patients at highest risk and avoid unnecessary invasive testing for low-risk patients. We hope data from the PHAROS registry will also lead to better care for patients and contribute to interventions that reduce SSc-PAH-associated morbidity and mortality.

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#### APPENDIX

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