Hemodynamic Predictors of Survival in Scleroderma-related Pulmonary Arterial Hypertension

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Rationale: Pulmonary arterial hypertension (PAH) related to systemic sclerosis (SSc) has a poorer prognosis compared with other forms of PAH for reasons that remain unexplained.

Objectives: To identify risk factors of mortality in a well-characterized cohort of patients with PAH related to systemic sclerosis (SSc-PAH).

Methods: Seventy-six consecutive patients with SSc (64 women and 12 men; mean age 61 ± 11 yr) were diagnosed with PAH by heart catheterization in a single center, starting in January 2000, and followed over time. Kaplan-Meier estimates were calculated and mortality risk factors were analyzed.

Measurements and Main Results: Forty (53%) patients were in World Health Organization functional class III or IV. Mean pulmonary artery pressure was 41 ± 11 mm Hg, pulmonary vascular resistance (PVR) was 8.6 ± 5.6 Wood units, and cardiac index was 2.4 ± 0.7 L/min/m². Median follow-up time was 36 months, with 42 deaths observed. Survival estimates were 85%, 72%, 67%, 50%, and 36% at 1, 2, 3, 4, and 5 years, respectively. Multivariate analysis identified PVR (hazard ratio [HR], 1.10; 95% confidence interval [CI], 1.03–1.18; $P < 0.01$), stroke volume index (HR, 0.94; 95% CI, 0.89–0.99; $P = 0.02$), and pulmonary arterial capacitance (HR, 0.43; 95% CI, 0.20–0.91; $P = 0.03$) as strong predictors of survival. An estimated glomerular filtration rate less than 60 ml/min/1.73 m² portended a threefold risk of mortality.

Conclusions: Our results suggest that specific components of right ventricular dysfunction and renal impairment contribute to increased mortality in SSc-PAH. Understanding the mechanisms of right ventricular dysfunction in response to increased afterload should lead to improved targeted therapy in these patients.

Pulmonary arterial hypertension (PAH) is a dreadful complication of systemic sclerosis (SSc) and one of the leading causes of morbidity and mortality in this syndrome (1). Several studies have suggested a significant improvement in overall survival rates from 50% at 1 year in earlier studies (2–4) to up to 80% and 50% at 1 and 3 years, respectively, in more recent studies (5–8). However, when compared with other types of PAH, such as idiopathic PAH (IPAH) (4, 6, 7), SSc-related pulmonary arterial hypertension (SSc-PAH) continues to have a less favorable response to modern therapy and worse survival for reasons that remain largely unexplained.

Factors such as age and other comorbidities do not fully account for this difference in outcomes (7). Studies comparing hemodynamic parameters and survival of patients with IPAH

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Scleroderma-related pulmonary arterial hypertension (SSc-PAH) carries a poor prognosis compared with other forms of PAH for reasons that remain unexplained.

What This Study Adds to the Field

This is the largest single-center study exploring predictors of mortality in SSc-PAH. Our data suggests that stroke volume index, pulmonary arterial capacitance, and estimated glomerular filtration rate are strong predictors of mortality, emphasizing the importance of cardiac adaptation to pulmonary vascular disease in patients with SSc-PAH.

and SSc-PAH suggest that increased myocardial dysfunction from failure to adapt to increased pulmonary vascular load might contribute to the poorer prognosis in SSc-PAH (7). However, in a large British registry of patients with PAH related to connective tissue diseases, including SSc-PAH, traditional hemodynamic measurements, such as right atrial pressure (RAP), cardiac index, and pulmonary vascular resistance (PVR) failed to demonstrate prognostic value after adjustment for functional class and other variables (6), suggesting that these standard hemodynamic measures may be inadequate predictors of survival in SSc-PAH. Furthermore, renal dysfunction, recently recognized as an important cofactor for mortality in PAH, has not been evaluated in studies looking at survival of patients with SSc-PAH (9, 10).

Therefore, we sought to evaluate our experience with SSc-PAH and identify predictors of survival in this patient cohort. We hypothesized that traditional hemodynamic parameters would not be significant predictors of survival in SSc-PAH and further surmised that more specific measurements of right ventricular (RV) function and RV load derived from routine right heart catheterization (RHC) would be stronger predictors of survival in SSc-PAH. We also analyzed the impact of renal dysfunction on survival. Some of the results of these studies have been previously reported in abstract form (11, 12).

METHODS

Full methodological details are provided in the online supplement.

Patient Population

The Johns Hopkins University Institutional Review Board approved this study. Consecutive patients with SSc diagnosed with PAH by RHC and evaluated at the Johns Hopkins Pulmonary Hypertension (PH) Program between January 1, 2000 and March 31, 2009 were included. The diagnosis of SSc was based on specific criteria as previously reported (7) and all diagnoses were confirmed by rheumatologists with

(Received in original form December 7, 2009; accepted in final form March 25, 2010)

Supported by National Heart, Lung and Blood Institute grants K23 HL092297 (S.C.M.) and P50 HL084946 (P.M.H.).

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 182, pp 252–260, 2010

Originally Published in Press as DOI: 10.1164/rccm.200912-1820OC on March 25, 2010
Internet address: www.atsjournals.org

expertise in SSc (F.M.W. and L.K.H.). Date of onset of scleroderma was defined as the date of first non-Raynaud symptom attributable to scleroderma.

The selection process is summarized in Figure 1. Out of the 242 patients with SSc referred to the PH Clinic for suspected PH, 210 patients underwent RHC. A diagnosis of PH (defined as a resting mean pulmonary artery pressure [mPAP] ≥ 25 mm Hg) (13) was confirmed in 185 patients. Twenty-eight patients were excluded due to the presence of high pulmonary capillary wedge pressure (>15 mm Hg) indicating pulmonary venous hypertension. Patients with other potential causes of PH, including significant chronic obstructive pulmonary disease and interstitial lung disease (ILD), were excluded. The criteria for significant chronic obstructive pulmonary disease or ILD were indicated in previous studies (7, 10, 14) and are detailed in the online supplement. Patients were also excluded if they had been previously treated with active drugs for PAH.

Hemodynamic measurements also included stroke volume index (SVI), pulmonary arterial capacitance (SV/PP) calculated from stroke volume (SV) divided by the pulmonary artery pulse pressure, and right ventricle stroke work index as calculated by $SVI \times (mPAP - RAP) \times 0.0136$ (15).

Echocardiogram reports, serum autoantibodies, pulmonary function tests results, computerized tomography, and World Health Organization functional classification (WHO FC), were obtained from clinical records. Renal function was assessed by the estimated glomerular filtration rate (eGFR) using the Modified Diet in Renal Disease equation (16). Renal dysfunction was defined as eGFR less than 60 ml/min/1.73 m².

Survival time was considered starting on the date of diagnosis of PAH by RHC. Death was determined from the clinical and hospital records as well as the Social Security Death Index. All causes of death were considered for survival analysis.

Treatment was established in accordance with the standards of practice of the Johns Hopkins PH Program and based on the availability of different treatments across the years. The effect of period-specific treatment on overall outcomes was analyzed.

Statistical Analysis

Continuous variables are shown as mean $\pm$ standard deviation (SD) or median (quartile [Q]1–Q3 range). Group comparisons were made using Student *t* test or Wilcoxon rank test as appropriate for continuous variables, and χ^2 statistics or Fisher exact test, as appropriate for categorical variables. A *P* value less than 0.05 was considered significant.

Survival analysis was performed using the Kaplan-Meier method. Comparisons between groups were assessed by log-rank test. Univariable Cox and multivariable proportional hazards modeling were performed to determine the variables associated with mortality. All computations were performed using Stata statistical software (version 10.1; Stata, College Station, TX).

RESULTS

Study Population

As described in METHODS and Figure 1, 185 out of 210 patients with SSc who underwent RHC had PH. Thirty-three patients were excluded based on the presence of significant ILD as defined by a TLC $<60\%$ or TLC between 60 and 70% with the presence of significant radiological abnormalities as detailed in the online supplement.

Baseline characteristics are shown in Table 1. Most patients were white (86.8%) and women (84.2%). The median time of duration of SSc at diagnosis was 10.8 years (range, 0–37 yr), whereas symptoms of Raynaud phenomenon preceded the diagnosis of PAH for a median time of 15 years (range, 0.2–49 yr). The diagnoses of SSc and PAH were established in the same year in 17 patients.

SSc-related autoantibodies were found in 57 out of 63 patients who had completed studies, including detection of

Figure 1. Algorithm of selection of patients. Highlighted box indicates patients included. Patients with overlap syndrome (*n* = 15) included 6 with polymyositis/dermatomyositis, 3 with systemic lupus erythematosus, 1 with rheumatoid arthritis, 1 with Sjögren syndrome, 3 with mixed connective tissue disease, and 1 with combined rheumatoid arthritis and Sjögren syndrome. Patients excluded with other overlapping diagnoses (*n* = 3) included one patient with acute pulmonary embolism, one with sarcoidosis, and one with severe restrictive disease due to obesity. * Refers to patients already on pulmonary arterial hypertension (PAH)-specific therapy before diagnostic catheterization. COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVH = pulmonary venous hypertension; PVR = pulmonary vascular resistance; SSc = systemic sclerosis.

antinuclear, anticentromere, and antitopoisomerase antibodies. Anticentromere autoantibodies were present in 33 patients, 32 of them with limited disease, and were the predominant antibodies in female compared with male patients (57.4% vs. 22.2%; *P* = 0.07). Antitopoisomerase antibodies were present in four patients, all women, all with limited disease. Antinuclear antibodies were present in 15 (23.8%) patients and were the predominant antibodies in African Americans compared with whites (50% vs. 19%; *P* = 0.07). There were also three patients with antiRNP antibodies, one patient with antiRNA polymerase III, one patient with both anticentromere and antinuclear antibodies, and six patients with positive undefined antinuclear antibodies.

Echocardiographic and hemodynamic data are shown in Table 2. Results from baseline echocardiography were available in 65 patients (85%). Forty-four patients (71%) had evidence of RV dilation, and 23 (35%) had evidence of pericardial effusion.

TABLE 1. BASELINE CHARACTERISTICS

	No.	Mean $\pm$ SD
Age, yr	76	60.7 $\pm$ 10.7
BMI, kg/m ²	76	26.9 $\pm$ 5.9
Women, %	76	64 (84.2)
Race, n (%)	76	
White		66 (86.8)
African American		8 (10.5)
Asian		1 (1.3)
Other		1 (1.3)
Smoking, n (%)	76	
Never		40 (52.6)
Former		33 (43.4)
Current		3 (3.9)
Limited scleroderma, n (%)	75	65 (86.7)
Median duration of non-Raynaud symptoms, yr (Q ₁ ; Q ₃)	64	10.8 (3.2; 19.2)
Median duration of Raynaud, yr (Q ₁ ; Q ₃)	61	15.5 (7.4; 26.4)
Raynaud severity score	44	1.61 $\pm$ 1.0
Skin severity score	44	5.9 $\pm$ 7.8
Gastrointestinal severity score	64	1.0 $\pm$ 0.6
Autoantibodies, n (%)	63	
Anticentromere		33 (52.4)
Antitopoisomerase		4 (6.3)
Antinuclear		15 (23.8)
Anticentromere + antinuclear		1 (1.6)
AntiRNP		3 (4.8)
Anti-POL III		1 (1.6)
Undefined antinuclear (ANA)		6 (9.5)
Creatinine, mg/dl	68	1.02 $\pm$ 0.4
eGFR, ml/min/1.73 m ²	68	71 $\pm$ 28
eGFR < 60 ml/min/1.73 m ²	68	31 (45.6)
WHO functional class, n (%)	76	
I		4 (5.3)
II		32 (42.1)
III		37 (48.7)
IV		3 (3.9)
Systemic hypertension, n (%)	76	26 (34.2)
Diabetes mellitus, n (%)	76	6 (7.9)
FEV ₁ , % predicted	73	82 $\pm$ 15
FVC, % predicted	75	83.8 $\pm$ 15.4
TLC, % predicted	76	89.1 $\pm$ 13.9
D _{CO} , % predicted	74	48.6 $\pm$ 17.6
Median follow-up, yr (Q ₁ ; Q ₃)	76	3.8 (1; 4.1)
Deaths, n (%)	76	42 (55.3)

Definition of abbreviations: AntiPOL III = antipolimerase III; AntiRNP = antiribonucleoprotein; BMI = body mass index; D_{CO} = diffusing capacity of carbon monoxide; eGFR = estimated glomerular filtration rate; WHO = World Health Organization.

Baseline characteristics are expressed as n (%) or mean $\pm$ SD, unless the median value (Q₁; Q₃) is specifically indicated.

Fifteen out of 50 patients (30%) had evidence of nonsystolic dysfunction of the left ventricle. Estimated left ventricular systolic function was normal (mean left ventricular ejection fraction, 60 $\pm$ 6%). Traditional hemodynamic measurements indicated moderate-to-severe PAH (mean RAP, 8 $\pm$ 4 mm Hg; mPAP, 42 $\pm$ 11 mm Hg; cardiac index, 2.4 $\pm$ 0.7 L/min/m²; and PVR, 8.6 $\pm$ 5.6 Wood units). Mean stroke volume index (31 $\pm$ 10 ml/m²) and SV/PP (1.47 $\pm$ 0.84 ml/mm Hg) were similarly depressed.

WHO FC was I or II for 36 patients (47.4%) and III or IV for 40 patients (52.6%) at time of diagnosis (Table 1). The proportion of patients diagnosed in early stages of PAH varied over the years (Table 3). The proportion of patients in WHO FC I or II at diagnosis was 5.6%, 55.6%, and 38.9% during the years 2000–2002, 2003–2005, and 2006–2009, respectively (P = 0.02).

Renal Function

Serum creatinine levels within 3 months of RHC were available in 68 patients. Based on eGFR, 31 (45.6%) patients had renal

TABLE 2. ECHOCARDIOGRAPHIC CHARACTERISTICS AND HEMODYNAMICS

	Mean $\pm$ SD
Echocardiography (n = 65)	
LA diameter, cm	3.8 $\pm$ 0.7
LVEF, %	60 $\pm$ 6
Estimated RVSP, mm Hg	67 $\pm$ 21
Diastolic dysfunction, n (%)	15 (30)
RV dilation, n (%)	
None	18 (29)
Mild	27 (43.6)
Moderate	9 (14.5)
Severe	8 (12.9)
Pericardial effusion, n (%)	
None	42 (64.6)
Small	18 (27.7)
Moderate	4 (6.2)
Severe	1 (1.5)
Hemodynamics (n = 76)	
RAP, mm Hg	8 $\pm$ 4
sPAP, mm Hg	68 $\pm$ 19
dPAP, mm Hg	26 $\pm$ 9
mPAP, mm Hg	42 $\pm$ 11
PCWP, mm Hg	10 $\pm$ 3
Cardiac index, L/min/m ²	2.4 $\pm$ 0.7
Cardiac output, L/min	4.3 $\pm$ 1.5
Heart rate, bpm	80 $\pm$ 14
SV, ml	54 $\pm$ 19
SVI, ml/m ²	31 $\pm$ 10
PVR, Wood units	8.6 $\pm$ 5.6
PP, mm Hg	43 $\pm$ 13
SV/PP, ml/mmHg	1.47 $\pm$ 0.84
RVSWI, g · m/m ²	13.3 $\pm$ 5
Pulmonary artery oxygen saturation, %	65 $\pm$ 9

Definition of abbreviations: dPAP = diastolic pulmonary artery pressure; LA = left atrial; LVEF = left ventricle ejection fraction; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PP = pressure pulse; PVR = pulmonary vascular resistance; RV = right ventricle; RVSP = right ventricle systolic pressure; RVSWI = right ventricle stroke work index; sPAP = systolic pulmonary artery pressure; SV = stroke volume; SVI = stroke volume index; SV/PP = pulmonary artery capacitance.

Echocardiographic characteristics and hemodynamic are expressed as n (%) or mean $\pm$ SD.

dysfunction at the time of diagnosis. Patients with renal dysfunction were older compared with those with normal renal function (64.6 vs. 58.9 yr; P = 0.03) and tended to have diffuse SSc subtype (19.3% vs. 8.1%; P = 0.28) and systemic hypertension (45.2 vs. 24.3%; P = 0.08). Only 2 of the 31 patients with renal dysfunction (6.5%) had a documented previous history of renal crisis. The eGFR was significantly but weakly associated with several baseline hemodynamic parameters, with the following Spearman correlations: PVR, -0.27 ; P = 0.02; cardiac index, 0.28 ; P = 0.02; SVI, 0.39 ; P < 0.01; SV/PP, 0.33 ; P < 0.01; and mixed venous blood oxygen saturation (SvO₂), 0.40 ; P < 0.01. The correlations with RAP and mPAP were not significant. The proportion of renal dysfunction was higher in patients with WHO FC III to IV (58 vs. 31.2%; P = 0.02). The proportion of patients taking diuretics at the time of the analysis was 62.1 and 44.4% for patients with and without renal dysfunction, respectively (P = 0.16).

Treatment

Thirty-eight (64.4%) patients were already receiving or were started on calcium channel blockers at low doses (i.e., < 60 mg of nifedipine daily) during follow-up due to different conditions: systemic hypertension, cardiac arrhythmia, or Raynaud symptoms. At least 60 patients (88.2%) received diuretics during follow-up.

TABLE 3. WORLD HEALTH ORGANIZATION FUNCTIONAL CLASS, HEMODYNAMIC VARIABLES, AND FIRST TREATMENT BY YEAR OF DIAGNOSIS

	Year of Diagnosis			Total (n = 76)	P Value
	2000–2002 (n = 14)	2003–2005 (n = 37)	2006–2009 (n = 25)		
WHO FC I–II, n (%)	2 (5.6)	20 (55.6)	14 (38.9)	36 (47.4)	0.02
mPAP, mm Hg	47 ± 9	42 ± 12	38 ± 10		0.04
Cardiac index, L/min/m ²	2.3 ± 0.7	2.4 ± 0.7	2.7 ± 0.7		0.14
SVI, ml	27 ± 10	29 ± 11	34 ± 9		0.13
PVR, Wood units	11 ± 7	9 ± 6	7 ± 4		0.08
SV/PP, ml/mm Hg	1.19 ± 0.6	1.37 ± 0.7	1.71 ± 1.04		0.15
First treatment					<0.01
Prostacyclin, n (%)	6 (46.2)	2 (6.1)	0	8 (11.6)	
ERA,* n (%)	6 (46.2)	19 (57.6)	32 (4.4)	26 (37.7)	
PDE5-I,† n (%)	0	12 (36.4)	22 (95.6)	34 (49.3)	
Calcium blockers, n (%)	1 (7.8)	0	0	1 (1.4)	

Definition of abbreviations: ERA = endothelin receptor antagonists; mPAP = mean pulmonary artery pressure; PDE5-I = phosphodiesterase 5 inhibitors; PVR = pulmonary vascular resistances; SVI = stroke volume index; SV/PP = pulmonary artery capacitance; WHO FC = World Health Organization functional class.

Values are expressed as n (%) or mean ± SD.

* Includes bosentan, ambrisentan or sitaxsentan.

† Includes sildenafil or tadalafil.

Sixty-nine (90.8%) patients received PAH-specific therapy after RHC. Initial treatment consisted of intravenous prostacyclin in 8 patients (11.6%), endothelin receptor antagonists in 26 (37.7%), phosphodiesterase 5 inhibitors (PDE5-I) in 34 (49.3%), and calcium channel blockers at high dose in 1 (1.4%), all as monotherapy. As shown in Table 3, initial therapy varied across the years ($P < 0.01$). At the end of follow-up, 5 patients were on prostanoids alone (7.2%), 10 were on endothelin receptor antagonists alone (14.5%), 19 on PDE5-I alone (27.5%), and 35 patients were receiving combined therapy (50.7%).

Survival and Predictors of Mortality

The median follow-up time was 36 months (3 yr), with a maximum follow-up of 9.4 years. The overall median survival time was 4.02 years and there were 42 deaths observed. Four patients were lost to follow-up. The cause of death could be determined in 33 patients and included right heart failure (24 patients), sudden cardiac death (1), lung cancer (2), sepsis/multisystem failure (2), postoperative complications of bowel obstruction (1), motor vehicle accident (2), and lower gastrointestinal bleeding (1). There were no deaths in the group of patients with WHO FC I.

The Kaplan-Meier survival curves are shown in Figure 2. Overall survival was 85%, 72%, 67%, 50%, and 36% at 1, 2, 3, 4, and 5 years from diagnosis, respectively. As expected, survival was worse in patients with WHO FC III to IV compared with I to II (log rank test: $P = 0.02$), as shown in Figure 2. The median survival time varied by WHO FC, with a median survival for FC IV patients shorter than 10 months.

Univariable and multivariable analysis were performed using the first 5 years of follow-up (with 36 deaths observed during that period), as survival curves show a relatively small group of patients at risk after that period. Hazard ratios (HRs) for the univariable analyses are shown in Table 4. WHO FC, cardiac index, PVR, SVI, SV/PP, pulmonary artery oxygen saturation, and eGFR were significant predictors in the univariable analysis. Neither the year of diagnosis nor the duration of scleroderma before PAH diagnosis was a significant predictor for mortality.

Several multivariable analysis models were built using a single hemodynamic parameter in each model and adjusting for age, WHO FC, and eGFR. These variables were included

because they have been shown to be significant predictors of survival in other studies. Initial treatment was not included as this did not necessarily reflect the treatment received during the

Figure 2. Survival curves for all patients and by World Health Organization functional class (WHO FC).

TABLE 4. UNIVARIATE ANALYSIS FOR SURVIVAL PREDICTORS

Variable	Unadjusted HR (95% CI)	P Value
Age, per yr	1.02 (0.99–1.05)	0.15
BMI, per kg/m ²	1.01 (0.95–1.06)	0.84
Sex, male	0.89 (0.35–2.27)	0.80
SSc type, diffuse	0.9 (0.27–2.97)	0.87
Time since SSc, per yr	0.99 (0.95–1.03)	0.60
eGFR < 60, per ml/min/1.73 m ²	2.63 (1.29–5.37)	<0.01
WHO FC (III–IV vs. I–II)	2.23 (1.12–4.42)	0.02
%FVC, per unit %	1.01 (0.99–1.03)	0.30
%D _{CO} , per unit %	0.99 (0.97–1.01)	0.20
RV dilation		
None–mild	Reference	
Moderate–severe	1.65 (0.81–3.35)	0.17
Pericardial effusion		
None	Reference	
Mild–moderate–severe	1.69 (0.9–3.32)	0.13
RAP, per mm Hg	1.03 (0.95–1.12)	0.44
mPAP, per mm Hg	1.02 (1.00–1.05)	0.08
PCWP, per mm Hg	0.99 (0.90–1.09)	0.88
Cardiac index, per L/min/m ²	0.55 (0.33–0.93)	0.02
SVI, per ml	0.94 (0.91–0.98)	<0.01
PVR, per Wood unit	1.07 (1.02–1.12)	<0.01
SV/PP, per ml/min/mm Hg	0.42 (0.23–0.76)	<0.01
Pulmonary artery oxygen saturation, per unit%	0.96 (0.93–0.99)	0.03
Year of diagnosis		0.97
2000–2002	Reference	
2003–2005	1.01 (0.46–2.19)	0.99
2006–2009	1.02 (0.36–2.85)	0.97

Definition of abbreviations: BMI = body mass index; CI = confidence interval; D_{CO} = diffusing capacity of carbon monoxide; ERA = endothelin receptor antagonists; mPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; PDE5-I = phosphodiesterase 5 inhibitors; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RV = right ventricle; SSc = systemic sclerosis; SVI = stroke volume index; SvO₂ = mixed venous blood oxygen saturation; SV/PP = pulmonary artery capacitance; WHO FC = World Health Organization Functional Class.

follow-up period. Echocardiographic measurements were not introduced in multivariate analysis due to statistical limitations with the sample size and number of missing values. Multivariable analysis models are shown in Table 5. Although PVR, SVI, SV/PP, and pulmonary artery oxygen saturation were significant predictors in the adjusted models, cardiac index, RAP, and mPAP were not. eGFR was a strong predictor across all the models. Neither WHO FC nor age was significant in the multivariable models, and the addition of these adjusting variables did not result in a higher prediction value after comparing the various models by the likelihood ratio test. A posterior comparison between the different models was performed using

the Akaike Information Criterion. The models including SVI, PVR, or SV/PP had a better prediction.

Although PVR and SV/PP did not follow a normal distribution, the analysis using log-transformed variables did not change the significance of the results. The proportional hazards assumption was confirmed for each of the models. The survival curves for SVI, PVR, and SV/PP, dichotomized using the respective median values, are shown in Figure 3 along with the corresponding HRs and significance. The dichotomization by median values shows the following HRs for mortality: HR, 3.13 (95% CI, 1.50–6.52; $P < 0.01$) for PVR greater than 7.2 Wood units; HR, 2.34 (95% CI, 1.11–4.96; $P = 0.03$) for SVI less than 30 ml; and HR, 3.06 (95% CI, 1.41–6.65; $P < 0.01$) for SV/PP less than 1.25 ml/min/mm Hg.

DISCUSSION

To our knowledge, our study reports clinical characteristics and predictors of survival for the largest single-center cohort of patients with SSc-PAH. We found improved overall survival in SSc-PAH compared with historical series (2–4), with a median survival of 4 years. Although WHO FC was predictive of survival in univariate analysis, traditional hemodynamic parameters, such as RAP, mPAP, and cardiac index, were not after adjusting for WHO FC. However, SVI, SV/PP, and PVR were independent predictors of survival, suggesting that these measures may be more relevant indices of cardiovascular dysfunction in patients with SSc-PAH.

SVI was a strong predictor of survival in this cohort, with a twofold increased risk of death for patients with SVI less than 30 ml/m². Although the prognostic value of SVI has been demonstrated in IPAH (17, 18), there are few studies examining its relevance in SSc-PAH. Studies comparing SSc-PAH and IPAH have shown a greater degree of RV dysfunction in SSc-PAH at similar levels of pulmonary artery pressure (7). A recent study by Overbeek and colleagues compared the relationship between mean ventricular pressure and stroke volume in a limited number of patients with SSc-PAH and IPAH. Although both groups of patients had similar RAP and cardiac index, patients with SSc-PAH demonstrated lower stroke volumes for any given mean RV pressure, suggesting impaired RV contractility (19). The values of RV stroke work index, a surrogate of RV contractility, were lower in our cohort of patients with SSc-PAH compared with values reported in IPAH (18, 20), suggesting a significant maladaptive response with decreased RV contractility in response to pulmonary vascular load. Furthermore, SVI identified patients at high risk of death, suggesting that RV dysfunction may not be adequately assessed by simple measurements of cardiac index. The most plausible

TABLE 5. MULTIVARIATE ANALYSIS

Variables Included in the Model	Model A (cardiac index)		Model B (PVR)		Model C (SVI)		Model D (SV/PP)	
	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value	Coefficient (95% CI)	P Value
Age	1 (0.97–1.04)	0.71	1.01 (0.98–1.05)	0.46	1.01 (0.97–1.05)	0.61	1 (0.97–1.04)	0.93
WHO FC	1.43 (0.60–3.42)	0.42	1.20 (0.49–2.92)	0.69	1.12 (0.46–2.77)	0.80	1.19 (0.48–2.94)	0.71
eGFR < 60	2.94 (1.30–6.64)	<0.01	3.41 (1.52–7.67)	<0.01	2.56 (1.10–5.96)	0.03	2.95 (1.29–6.79)	<0.01
Cardiac index	0.51 (0.24–1.10)	0.09						
PVR			1.10 (1.03–1.18)	<0.01				
SVI					0.94 (0.89–0.99)	0.02		
SV/PP							0.43 (0.20–0.91)	0.03
LL	96.807		94.487		95.209		95.096	
AIC	201.614		196.974		198.417		198.192	

Definition of abbreviations: AIC = Akaike information criteria; CI = confidence interval; eGFR = estimated glomerular filtration rate; LL = log likelihood; PVR = pulmonary vascular resistance; SVI = stroke volume index; SV/PP = pulmonary artery capacitance; WHO FC = World Health Organization Functional Class.

Figure 3. Survival curves by median values of pulmonary vascular resistance (PVR), stroke volume index (SVI), and pulmonary artery capacitance (SV/PP).

explanation for this discrepancy is the presence of a compensatory increase in heart rate mediated by a sympathetic response to an increased afterload (21), thus maintaining cardiac index within normal values despite a decline in stroke volume. This is consistent with our recent report of a significantly higher resting heart rate and higher N-terminal prohormone brain natriuretic

peptide serum levels in patients with SSc-PAH compared with those with IPAH, both abnormalities suggesting neurohormonal activation in these patients (10). A recent report has also indicated that high resting heart rate and subsequent increase during follow-up is associated with increased risk of death in IPAH (22).

The reasons for impaired RV contractility in SSc-PAH are likely multifactorial. Age-related changes in cardiac responses to high pressure loads (20) may explain some of the apparent differences in RV contractility between IPAH and SSc-PAH, but direct myocardial involvement from SSc due to microvascular disease or fibrosis may also be a contributing factor. A high prevalence of early RV dysfunction has been observed in patients with SSc without PAH as determined by endomyocardial biopsy (23), magnetic resonance imaging (24–27), and tissue-Doppler echocardiography (28–32), although the presence of PH induced by exercise was evidenced in one of the studies (29).

PVR and pulmonary artery capacitance (SV/PP) were also independent predictors for survival, after adjusting for other variables. PVR has been demonstrated as an independent predictor of survival in SSc-PAH (5) and IPAH (33), although not consistently (6). We recently demonstrated, in a cohort of patients with PH-SSc with and without ILD, that PVR was a significant predictor of survival in multivariate analysis (34). SV/PP is believed to be an estimate of the compliance of the pulmonary vascular tree, reflecting the ability of the vascular bed to dilate in response to RV contraction and then recoil during diastole. Thus, although SV/PP reflects pulsatile flow in the proximal pulmonary vasculature, PVR represents mean flow and resistance at the distal end of the pulmonary vascular tree. SV/PP has been shown as a strong predictor of survival in a large cohort of patients with IPAH (18, 35). However, no studies to date have evaluated its prognostic value in SSc-PAH. In the present study, SV/PP was a significant predictor of survival, with a threefold risk of death when dichotomized by median value of 1.25 ml/mm Hg. Although the estimation of pulmonary artery capacitance from SV and PP may be influenced by cardiac dysfunction and also by increased peripheral PVR (36), proximal pulmonary artery distensibility estimated by magnetic resonance imaging has been associated with mortality (37). These findings support the hypothesis that factors other than PVR also account for increased afterload in PAH. It is noteworthy that decreased pulmonary artery capacitance and distensibility might be present in early stages of the disease (38, 39).

RAP was not a significant predictor of mortality in our cohort. Although RAP is classically associated with mortality in IPAH (33), two studies, including our smaller previous cohort, showed no association between RAP and mortality in patients with SSc-PAH (7, 47). This lack of correlation further emphasizes the fact that mere increases in cardiopulmonary pressures (e.g., RAP and mPAP) do not correlate with survival, and traditional hemodynamic parameters used in IPAH to predict survival cannot be applied to SSc-PAH.

The proportion of patients with renal dysfunction was remarkably high in our cohort, with 46% of patients having an eGFR less than 60 ml/min/m², which was in fact associated with an almost threefold risk of death. This prevalence of renal dysfunction contrasts with that described in patients with SSc (10–16% [40–42]), and in patients with various other forms of PAH (12%) (9). Renal dysfunction constitutes a significant risk for mortality in both patients with PAH (9) and patients with SSc (40, 43). The concurrence of chronic renal dysfunction in patients with left heart failure also leads to poorer outcomes (44). It is plausible that the combination of SSc, PAH, and right

heart failure may increase the probability of developing renal dysfunction with further fluid retention and neuroendocrine activation. The lack of data regarding the presence of proteinuria or renal biopsies precludes further elucidation of pathophysiological mechanisms. Likewise, the influence of drug therapy may alter the measures of renal function. Nonetheless, it is remarkable that the deterioration of renal function portends such a high risk for mortality in these patients.

Survival continues to be poor in patients with WHO FC III to IV, with rates of 76% and 53% at 1 and 3 years, respectively. However, prognosis was also notably reduced in patients in early stages, with a median survival of 4.2 years for patients with FC II. Therefore, despite an increase in patients referred at an early stage of the disease (FC I and II, see Table 3), survival remains unacceptably low for these patients compared with patients with IPAH, for whom survival rates are currently around 87%, 71%, and 63% at 1, 3, and 5 years, respectively (45, 46).

A number of limitations must be noted. First, although subjects were included in our registry and followed prospectively, some data were collected retrospectively resulting in missing values, which might influence survival analysis. Second, because our data indicate that patients referred in more recent years had better functional status compared with earlier years (Table 3), it is possible that this may have accounted for an overall better prognosis. However, there were no significant differences in survival among the three different eras (Table 4). Third, we could not assess the impact of treatment on survival, and interestingly, a recent study in 49 patients with SSc-PAH has shown that hemodynamic predictors after treatment can be better predictors of survival than baseline parameters (47). Finally, although patients with significant ILD at the time of PAH diagnosis were excluded from our cohort (as the pathogenesis, hemodynamics, and outcomes of PH for these patients can be quite different from patients with PAH), we cannot exclude subclinical ILD and its effects on outcomes.

We were not able to evaluate the prognostic value of the 6-minute walk test because few subjects completed this test during the first years of enrollment. Although the 6-minute walk test has been routinely used as the main outcome measure in randomized clinical trials assessing PAH therapy (48), there are many potential confounding factors in patients with SSc (49) that make it less attractive in this disease. In addition, this test has not been specifically validated in SSc or in early stages of PAH (50). Nevertheless, the lack of systematic assessment of functional capacity in this cohort remains a limitation of our study.

Conclusion

In summary, we have shown that measures of RV function (SVI), pulmonary vascular compliance (SV/PP), and pulmonary vascular resistance (PVR), rather than traditional hemodynamic measures commonly used in PAH (e.g., cardiac index, mPAP, and RAP), were independently associated with survival in this cohort of patients with SSc-PAH. These findings suggesting that the pathophysiology of PAH and RV response in SSc may differ from that of other forms of PAH should be confirmed in larger prospective studies.

Furthermore, survival remains unacceptably poor, with 1-, 3-, and 5-year rates of 85%, 67%, and 36%, respectively, despite the use of PAH-specific therapy. Future studies should focus on identifying mechanisms of RV dysfunction to increasing afterload in SSc and on possible direct effects of SSc on the heart and pulmonary vasculature.

Conflict of Interest Statement: A.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.C.M. has received industry-sponsored grants from Gilead Sciences (\$50,001–\$100,000); he has received sponsored grants from NIH (more than \$100,000); his spouse has received sponsored grants from NIH (more than \$100,000). J.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.L.Z. has received industry-sponsored grants from Actelion (\$50,001–\$100,000); he has received sponsored grants from NIH (more than \$100,000) and ATS (\$50,001–\$100,000). L.K.H. has received lecture fees from Actelion Pharmaceuticals (\$1001–\$5000); she has received industry-sponsored grants from Novartis, Actelion, and United Therapeutics (each for more than \$100,000); she has received a sponsored grant from NIH/NIAMS (more than \$100,000); she has received two sponsored grants from NIH/NHLBI (\$100,000). D.B. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.C.C. has received advisory board fees from Actelion, Pfizer, United Therapeutics, and Gilead (each for \$1001–\$5000); he has received expert witness fees from Diet Drug Litigation (more than \$100,000); he has received sponsored grants from NIH (more than \$100,000), and American Heart Association (more than \$100,000). N.L. has received consultancy fees from Respironics and Transave (both up to \$1,000); he has received lecture fees from Hill-Rom (up to \$1,000); he has received expert witness fees from Honeywell (\$5,001–\$10,000); he has received industry-sponsored grants from Transave (\$1,001–\$5,000); he has received sponsored grants from NIH (\$50,001–\$100,000). F.M.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. R.E.G. has received advisory board fees from Gilead, Actelion, and United Therapeutics (each for \$1,001–\$5,000); he has received industry-sponsored grants from Pfizer, United Therapeutics, and Lilly (each for \$50,001–\$100,000), and Actelion (\$10,001–\$50,000); he has received sponsored grants from NIH (more than \$100,000). P.M.H. has received advisory board fees from Novartis (\$1,001–\$5,000); he has received lecture fees from ABComm (\$1,001–\$5,000); he has received industry-sponsored grants from Actelion/United Therapeutics (\$100,000).

References

1. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis* 2007;66:940–944.
2. Stupi AM, Steen VD, Owens GR, Barnes EL, Rodnan GP, Medsger TA. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum* 1986;29:515–524.
3. Koh ET, Lee P, Gladman DD, Abu-Shakra M. Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. *Br J Rheumatol* 1996; 35:989–993.
4. Kawut SM, Taichman DB, Archer-Chicko CL, Palevsky HI, Kimmel SE. Hemodynamics and survival in patients with pulmonary arterial hypertension related to systemic sclerosis. *Chest* 2003; 123:344–350.
5. Williams MH, Das C, Handler CE, Akram MR, Davar J, Denton CP, Smith CJ, Black CM, Coghlan JG. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. *Heart* 2006;92:926–932.
6. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs SR, Vrapai F, Das C, Elliot CA, Johnson M, DeSoyza J, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* 2009;179:151–157.
7. Fisher MR, Mathai SC, Champion HC, Girgis RE, Houston-Harris T, Hummers L, Krishnan JA, Wigley F, Hassoun PM. Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. *Arthritis Rheum* 2006;54:3043–3050.
8. Badesch DB, McGoon MD, Barst RJ, Tapson VF, Rubin LJ, Wigley FM, Kral KM, Rappioui IH, Crater GD. Longterm survival among patients with scleroderma-associated pulmonary arterial hypertension treated with intravenous epoprostenol. *J Rheumatol* 2009;36:2244–2249.
9. Shah SJ, Thenappan T, Rich S, Tian L, Archer SL, Gombert-Maitland M. Association of serum creatinine with abnormal hemodynamics and mortality in pulmonary arterial hypertension. *Circulation* 2008;117: 2475–2483.
10. Mathai SC, Bueso M, Hummers LK, Boyce D, Lechtzin N, Le Pavec J, Campo A, Champion HC, Houston T, Forfia PR, et al. Disproportionate elevation of NT-proBNP in scleroderma-related pulmonary hypertension. *Eur Respir J* 2010;35:95–104.
11. Campo A, Mathai SC, Zaiman A, Champion HC, Houston T, Boyce DM, Lechtzin N, Hummers L, Wigley F, Girgis RE, et al. Survival of pulmonary arterial hypertension related to systemic sclerosis: a single center longitudinal study. *Am J Respir Crit Care Med* 2009;179: A2657.

12. Campo A, Mathai SC, Girgis RE, Zaiman AL, Hummers L, Wigley F, Hassoun PM. Hemodynamic predictors of survival in scleroderma related pulmonary hypertension: a single center study. Presented at the annual international meeting for the European Respiratory Society. September 12–16, 2009, Vienna, Austria.
13. Simonneau G, Galiè N, Rubin LJ, Langleben D, Seeger W, Domenighetti G, Gibbs S, Lebrech D, Speich R, Beghetti M, et al. Clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2004;43: 5S–12S.
14. Girgis RE, Frost AE, Hill NS, Horn EM, Langleben D, McLaughlin VV, Oudiz RJ, Robbins IM, Seibold JR, Shapiro S, et al. Selective endothelin A receptor antagonism with sitaxsentan for pulmonary arterial hypertension associated with connective tissue disease. *Ann Rheum Dis* 2007;66:1467–1472.
15. Her C. Right ventricular stroke-work. An index of distribution of pulmonary perfusion in acute respiratory failure. *Chest* 1983;84: 719–724.
16. Levey AS, Greene T, Kusek J, Beck GJ, Group MS. A simplified equation to predict glomerular filtration rate from serum creatinine [abstract]. *J Am Soc Nephrol* 2000;11:A0828.
17. Van Wolferen SA, Marcus JT, Boonstra A, Marques KM, Bronzwaer JG, Spreeuwenberg MD, Postmus PE, Vonk-Noordegraaf A. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. *Eur Heart J* 2007;28: 1250–1257.
18. Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. *J Am Coll Cardiol* 2006;47:799–803.
19. Overbeek MJ, Lankhaar JW, Westerhof N, Voskuyl AE, Boonstra A, Bronzwaer JG, Marques KM, Smit EF, Dijkmans BA, Vonk-Noordegraaf A. Right ventricular contractility in systemic sclerosis-associated and idiopathic pulmonary arterial hypertension. *Eur Respir J* 2008;31:1160–1166.
20. Kawut SM, Al-Naamani N, Agestrand C, Rosenzweig EB, Rowan C, Barst RJ, Bergmann S, Horn EM. Determinants of right ventricular ejection fraction in pulmonary arterial hypertension. *Chest* 2009;135: 752–759.
21. Velez-Roa S, Ciarka A, Najem B, Vachiery JL, Naeije R, van de Borne P. Increased sympathetic nerve activity in pulmonary artery hypertension. *Circulation* 2004;110:1308–1312.
22. Henkens I, Van Wolferen S, Gan C, Boonstra A, Swenne C, Twisk J, Kamp O, van der Wall E, Schaliij M, Vonk-Noordegraaf A. Relationship of resting heart rate to prognosis in patients with idiopathic pulmonary arterial hypertension. *Am J Cardiol* 2009; 103:1451–1456.
23. Fernandes F, Alvarez Ramires FJ, Arteaga E, Ianni BM, Oliveira Bonfá ESD, Mady C. Cardiac remodeling in patients with systemic sclerosis with no signs or symptoms of heart failure: an endomyocardial biopsy study. *J Card Fail* 2003;9:311–317.
24. Allanore Y, Meune C, Vignaux O, Weber S, Legmann P, Kahan A. Bosentan increases myocardial perfusion and function in systemic sclerosis: a magnetic resonance imaging and tissue-Doppler echography study. *J Rheumatol* 2006;33:2464–2469.
25. Tzelepis GE, Kelekis NL, Plastiras SC, Mitseas P, Economopoulos N, Kampolis C, Gialafos EJ, Moyssakis I, Moutsopoulos HM. Pattern and distribution of myocardial fibrosis in systemic sclerosis. *Arthritis Rheum* 2007;56:3827–3836.
26. Bezante GP, Rollando D, Sessarego M, Panico N, Setti M, Filaci G, Molinari G, Balbi M, Cutolo M, Barsotti A, et al. Cardiac magnetic resonance imaging detects subclinical right ventricular impairment in systemic sclerosis. *J Rheumatol* 2007;34:2431–2437.
27. Hachulla AL, Launay D, Gaxotte V, de Groote P, Lamblin N, Devos P, Hatron PY, Beregi JP, Hachulla E. Cardiac magnetic resonance imaging in systemic sclerosis: a cross-sectional observational study of 52 patients. *Ann Rheum Dis* 2009;68:1878–1884.
28. Forfia PR, Fisher MR, Mathai SC, Houston-Harris T, Hemnes AR, Borlaug BA, Chamera E, Corretti MC, Champion HC, Abraham TP, et al. Tricuspid annular displacement predicts survival in pulmonary hypertension. *Am J Respir Crit Care Med* 2006;174: 1034–1041.
29. Huez S, Roufosse F, Vachiery JL, Pavelescu A, Derumeaux G, Wautrecht JC, Cogan E, Naeije R. Isolated right ventricular dysfunction in systemic sclerosis: latent pulmonary hypertension? *Eur Respir J* 2007;30:928–936.
30. Meune C, Allanore Y, Pascal O, Devaux JY, Dessault O, Duboc D, Weber S, Kahan A. Myocardial contractility is early affected in systemic sclerosis: a tissue Doppler echocardiography study. *Eur J Echocardiogr* 2005;6:351–357.
31. Lindqvist P, Caidahl K, Neuman-Andersen G, Ozolins C, Rantapää-Dahlqvist S, Waldenström A, Kazzam E. Disturbed right ventricular diastolic function in patients with systemic sclerosis. A Doppler tissue imaging study. *Chest* 2005;128:755–763.
32. Meune C, Avouac J, Wahbi K, Cabanes L, Wipff J, Mouthon L, Guillemin L, Kahan A, Allanore Y. Cardiac involvement in systemic sclerosis assessed by tissue-Doppler echocardiography during routine care. A controlled study of 100 consecutive patients. *Arthritis Rheum* 2008;58:1803–1809.
33. McLaughlin VV, Presberg KW, Doyle RL, Abman SH, McCrory DC, Fortin T, Ahearn G. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126:78–92.
34. Mathai SC, Hummers LK, Champion HC, Wigley FM, Zaiman A, Hassoun PM, Girgis RE. Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. *Arthritis Rheum* 2009;60:569–577.
35. Mahapatra S, Nishimura RA, Oh JK, McGoon MD. The prognostic value of pulmonary vascular capacitance determined by Doppler echocardiography in patients with pulmonary arterial hypertension. *J Am Soc Echocardiogr* 2006;19:1045–1050.
36. Lankhaar JW, Westerhof N, Faes TJC, Marques KMJ, Marcus JT, Postmus PE, Vonk-Noordegraaf A. Quantification of right ventricular afterload in patients with and without pulmonary hypertension. *Am J Physiol Heart Circ Physiol* 2006;291:H1731–H1737.
37. Gan CTJ, Lankhaar JW, Westerhof N, Marcus JT, Becker A, Twisk JWR, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Noninvasively assessed pulmonary artery stiffness predicts mortality in pulmonary arterial hypertension. *Chest* 2007;132:1906–1912.
38. Lankhaar J-W, Westerhof N, Faes TJC, Gan CT, Marques KM, Boonstra A, van den Berg FG, Postmus PE, Vonk-Noordegraaf A. Pulmonary vascular resistance and compliance stay inversely related during treatment of pulmonary hypertension. *Eur Heart J* 2008;29: 1688–1695.
39. Sanz J, Kariisa M, Dellegrottaglie S, Prat-González S, Garcia MJ, Fuster V, Rajagopalan S. Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2009;2:286–295.
40. Ioannidis JPA, Vlachoyannopoulos PG, Haidich AB, Medsger TA, Lucas M, Michet CJ, Kuwana M, Yasuoka H, van den Hoogen F, te Boome L, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. *Am J Med* 2005;118: 2–10.
41. Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, Moinsadeh P, Müller-Ladner U, Pfeiffer C, Riemekasten G, et al. The registry of the German Network for systemic sclerosis: frequency of disease subsets and patterns of organ involvement. *Rheumatology* 2008;47:1185–1192.
42. Scheja A, Bartosik I, Wuttge DM, Hesselstrand R. Renal function is mostly preserved in patients with systemic sclerosis. *Scand J Rheumatol* 2009;38:295–298.
43. Mayes MD, Lacey JV, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, Schottenfeld D. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. *Arthritis Rheum* 2003;48:2246–2255.
44. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol* 2006; 47:1987–1996.
45. Ruiz-Cano MJ, Escribano P, Alonso R, Delgado J, Carreira P, Velázquez T, Sánchez MA, Sáenz de la Calzada C. Comparison of baseline characteristics and survival between patients with idiopathic and connective tissue disease-related pulmonary arterial hypertension. *J Heart Lung Transplant* 2009;28:621–627.
46. McLaughlin VV, Shillington A, Rich S. Survival in primary pulmonary hypertension: the impact of epoprostenol therapy. *Circulation* 2002; 106:1477–1482.
47. Launay D, Sitbon O, Le Pavec J, Savale L, Tcherakian C, Yaici A, Achouh L, Parent F, Jais X, Simonneau G, et al. Long-term outcome of systemic sclerosis associated pulmonary arterial hypertension treated with bosentan as first-line monotherapy followed or not by

- the addition of prostanoids or sildenafil. *Rheumatology* 2010;49:490–500.
48. Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, Rich S, Barst RJ, Barrett PS, Kral KM, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. *Ann Intern Med* 2000;132:425–434.
49. Garin MC, Highland KB, Silver RM, Strange C. Limitations to the 6-minute walk test in interstitial lung disease and pulmonary hypertension in scleroderma. *J Rheumatol* 2009;36:330–336.
50. Hoeper MM, Oudiz RJ, Peacock A, Tapson VF, Haworth SG, Frost AE, Torbicki A. End points and clinical trial designs in pulmonary hypertension. Clinical and regulatory perspectives. *J Am Coll Cardiol* 2004; 43(12 suppl S):48S–55S.