Utility of B-type natriuretic peptides in the assessment of patients with systemic sclerosis-associated pulmonary hypertension in the PHAROS registry

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Received on March 1, 2016; accepted in revised form on September 28, 2016.

Clin Exp Rheumatol 2017; 35 (Suppl. 106): S106-S113.

Key words: systemic sclerosis, pulmonary hypertension, BNP, NT-proBNP

Funding: The PHAROS Registry was initially funded by Actelion, the Scleroderma Foundation and the Sibley Foundation, with ongoing funding by Gilead. However, the sponsors did not participate in the writing, study design, collection, analysis or interpretation of the data.

Competing interests: see page S112.

ABSTRACT

Objective. *To assess the utility of B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) in detecting and monitoring pulmonary hypertension (PH) in systemic sclerosis (SSc).*

Methods. *PHAROS is a multicenter prospective cohort of SSc patients at high risk for developing pulmonary arterial hypertension (SSc-AR-PAH) or with a definitive diagnosis of SSc-PH. We evaluated 1) the sensitivity and specificity of BNP≥64 and NT-proBNP≥210 pg/mL for the detection of SSc-PAH and/or SSc-PH in the SSc-AR-PAH population; 2) baseline and longitudinal BNP and NT-proBNP levels as predictors of progression to SSc-PAH and/or SSc-PH; 3) baseline BNP≥180, NT-proBNP≥553 pg/mL, and longitudinal changes in BNP and NT-proBNP as predictors of mortality in SSc-PH diagnosed patients.*

Results. *172 SSc-PH and 157 SSc-AR-PAH patients had natriuretic peptide levels available. Median BNP and NT-proBNP were significantly higher in the SSc-PH versus SSc-AR-PAH group. The sensitivity and specificity for SSc-PAH detection using baseline BNP≥64 pg/mL was 71% and 59%; and for NT-proBNP≥210 pg/mL, 73% and 78%. NT-proBNP showed stronger correlations with haemodynamic indicators of right ventricular dysfunction than BNP. Baseline creatinine, RVSP > 40 mmHg, and FVC%:DL_{CO}% ratio ≥1.8 were associated with progression from SSc-AR-PAH to SSc-PH but no association with individual or combined baseline BNP and NT-proBNP levels was observed. Baseline and follow-up BNP or NT-proBNP levels were not predictive of death, however, a composite BNP/NT-proBNP group predicted mortality (HR 3.81 (2.08-6.99), p<.0001).*

Conclusion. *NT-proBNP may be more useful than BNP in the detection and monitoring of PAH in SSc patients, but additional studies are necessary.*

Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterised by vascular damage and fibrosis that can affect multiple organ systems. Scleroderma-associated pulmonary hypertension (SSc-PH) – a frequently encountered life threatening complication of SSc – can be the result of SSc-associated pulmonary arterial hypertension (SSc-PAH, WHO Group I PH), left-sided systolic or diastolic heart dysfunction (WHO Group II PH), interstitial lung disease (WHO Group III PH), or a combination of these conditions (1).

Right heart catheterisation (RHC) confirmed PAH affects 3.7–12% of SSc patients (2-5). SSc-PAH is associated with higher mortality rates than idiopathic pulmonary arterial hypertension (IPAH) as well as non-SSc connective tissue disease-associated PAH (CTD-PAH) (5-8). Approximately 35-40% of SSc patients have clinically significant SSc associated interstitial lung disease (SSc-ILD) as diagnosed by imaging studies and/or pulmonary function tests (PFTs) with up to half of these patients having associated PH (5, 9). These patients have even worse survival rates than their SSc-PAH counterparts (39% *versus* 64% at 3 years, respectively) (10). Together, SSc-ILD and SSc-PAH account for 33% of all SSc-associated deaths (11-13).

Early diagnosis and treatment of PAH has been associated with improved sur-

vival in studies including patients with SSc-PAH (14, 15). Natriuretic peptides may be promising serum biomarkers to aid in the early detection and management of this disease (8). Recently, SSc-PAH patients have been shown to have higher natriuretic peptide levels than both IPAH and non-SSc CTD-PAH patients, correlating with their poorer survival rates (7). Brain natriuretic peptide (BNP) is released by ventricular myocytes in response to ventricular wall stress and antagonises the renin-angiotensin-aldosterone system leading to diuresis and decreased blood pressure (16). The related N-terminal peptide, NT-proBNP, formed after enzymatic cleavage in the blood from the pro-hormone of BNP, has been investigated as an alternative to BNP given its more favourable laboratory assay characteristics including enhanced stability and longer circulating half-life. As with BNP, NT-proBNP correlates with haemodynamic parameters, such as mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR), exercise capacity assessed by six-minute walk test (6MWT) (17), and estimated right-sided pressures on transthoracic echocardiography (TTE) in SSc-PAH patients (18).

Herein, we report the results of the first US, multicenter study evaluating the utility of both BNP and NT-proBNP as diagnostic and prognostic indicators for SSc-PAH and SSc-PH using the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry. More specifically, we sought to assess the utility of serum BNP and NT-proBNP levels 1) as predictors of progression to SSc-PAH and/or SSc-PH in an "at-risk" for PAH population (SSc-AR-PAH); and 2) as predictors of survival in the SSc-PH population.

Patients and methods

PHAROS is a longitudinal prospective registry involving 22 US Scleroderma Centers. Participating centers obtained institutional review board approval and all patients provided written informed consent prior to enrollment. The baseline characteristics and study design for PHAROS are described elsewhere (19). The PHAROS registry enrolls SSc patients who are: 1) at high risk for developing pulmonary hypertension (SSc-AR-PAH) or 2) have definite PH (SSc-PH) diagnosed by RHC within 6 months of enrolment. SSc-AR-PAH patients must fulfill one of the following three criteria: 1) a right ventricular systolic pressure (RVSP) on TTE ≥40 mmHg (calculated from maximum velocity of the tricuspid regurgitant jet plus the right atrium pressure); 2) a diffusion capacity of carbon monoxide (DLCO)<55% with a forced vital capacity (FVC)>70% predicted; OR 3) an %FVC/%DLCO ratio>1.8. All SSc patients at each participating center were to undergo at least annual TTE and PFTs to screen for SSc-PH at the time of registry enrolment. RHC was obtained in SSc-AR-PAH patients as clinically indicated and determined by the treating physician (31). Patients with SSc-PH had a mPAP ≥25 mmHg at rest on RHC performed within the 6 months prior to enrolment into the registry. A pulmonary capillary wedge pressure ≤15 mmHg was used to differentiate SSc-PAH (WHO Group I PAH) from WHO Group II (PH related to left heart disease). Those with moderate or severe ILD on chest imaging and FVC <60% predicted were included in WHO Group III (PH related to hypoxemia). SSc-AR-PAH patients were re-categorised as SSc-PH based on RHC over the course of the study.

The following clinical information is collected at baseline and on annual follow-up: demographics, medications, physical examination findings, New York Heart Association functional class (NYHA FC) assessment, serum autoantibodies (baseline only), BNP/NT-proBNP levels if available, serum creatinine, PFT results, TTE results, findings on HRCT, 6 minute walk distance (6MWD), haemodynamics on RHC if performed, and date and cause(s) of death. BNP or NT-proBNP levels were collected at baseline and annually if indicated as part of standard of care, with only one of the two serum biomarkers available at the majority of participating sites. Only patients who had baseline levels of BNP and/or NT-proBNP within 3 months before or after the date of enrolment were included in this analysis.

Statistical analysis

BNP and NT-proBNP levels were log-transformed as their distributions were highly skewed. Baseline characteristics and baseline natriuretic peptide levels were compared between various groups using Student's *t*-test or Wilcoxon rank sum test for continuous variables and chi-square or Fisher's exact test for categorical variables. Pearson's correlation coefficient (rho) was calculated to assess correlations between BNP or NT-proBNP and relevant variables. A rho <0.4 was considered poor correlation, between 0.4–0.7 moderate, and >0.7 excellent.

Several authors have reported various serum natriuretic peptide level cut-offs for SSc-PH screening, prediction of progression of disease, as well as survival. Thakkar *et al*. previously reported an NT-proBNP cut-off of ≥210 pg/mL as predictive of development of SSc-PAH in a prospective study screening a similar "at-risk" population (20). Cavagna *et al*. identified BNP ≥64 pg/mL as a marker for SSc-PAH (21). In contrast, Williams *et al*. found an NT-proBNP cutoff of ≥533 pg/mL was predictive of mortality in SSc-PAH patients (22). No similar studies for BNP have been reported in patients with SSc-PAH, but Nagaya et al found BNP ≥180 pg/mL to be predictive of death in IPAH patients (23). We applied univariate analyses using Cox proportional regression models to evaluate: 1) the risk of progression to SSc-PAH or SSc-PH in the SSc-AR-PAH population with baseline BNP≥64, NT-proBNP≥210 pg/mL, and other variables as predictors; and 2) the risk of mortality in the SSc-PH population with baseline BNP≥180 or NT-proBNP≥553 pg/mL as predictors. We also compared the changes in BNP and NT-proBNP levels in the SSc-PH patients who died during follow-up with those who survived using Wilcoxon rank sum test.

Results

Baseline characteristics

At the time of this analysis 389 patients were enrolled in PHAROS, and 329 had baseline natriuretic peptide levels avail-

Table I. Baseline characteristics of the PHAROS registry.

Clinical Feature	All patients (n=329)	SSc-AR-PAH (n=157)	SSc-PAH (n=114)	SSc-PH (n=172)	SSc-AR-PAH *vs*. PAH *p*-value	SSc-AR-PAH *vs*. PH *p*-value
Age, mean ± SD years (n)	58.0±11.0 (316)	57.6±10.4 (154)	60.8±10.0 (111)	58.4±11.5 (162)	0.014	0.500
Women, n (%)	264 (83.5)	132 (85.7)	95 (85.6)	132 (81.5)	0.9765	0.310
Race, n (%)	n=315	n=154	n=110	n=161	0.319	0.920
White	228 (72)	107 (69)	89 (81)	121 (75)		
African American	52 (17)	29 (19)	10 (9)	23 (14)		
Other	35 (11)	18 (12)	11 (10)	17 (11)		
Diffuse SSc, n (%)	102 (31.5)	51 (33.1)	24 (21.4)	51 (30.0)	0.037	0.546
Time from 1st symptom mean ± SD years (n)						
Raynaud's phenomenon	13.0±10.6 (302)	12.6±10.4 (145)	15.3±11.8 (107)	13.3±10.9 (157)	0.062	0.521
Non-Raynaud's phenomenon	10.6±10.2 (307)	10.8±11.7 (144)	11.4±9.7 (107)	10.4±8.7 (163)	0.534	0.859
Autoantibodies, n (%)					0.001	0.041
Anticentromere	84 (26.9)	37 (24.7)	40 (37.0)	47 (29.0)		
Anti-Scl-70	54 (17.3)	33 (22.0)	8 (7.4)	21 (13.0)		
Anti-U1 RNP	16 (5.3)	8 (5.3	4 (3.7)	8 (4.9)		
Mixed or other	73 (23.4)	41 (27.3)	18 (16.7)	32 (19.8)		
Negative	15 (4.8)	8 (5.3)	3 (2.8)	7 (4.3)		
CCB use, n (%)	119 (36.2)	55 (35.0)	40 (35.1)	64 (37.2)	0.992	0.681
Creatinine, mg/dL ± SD (n)	1.0±0.76 (321)	0.99±0.77 (151)	1.10±0.89 (111)	1.03±0.76 (170)	0.014	0.079
NYHA functional class, n (%)					<.001	<.001
I	85 (29.9)	65 (50.4)	16 (15.7)	20 (12.9)		
II	101 (35.6)	46 (35.7)	37 (36.3)	55 (35.5)		
III	91 (32.0)	18 (14.0)	45 (44.1)	73 (47.1)		
IV	7 (2.5)	0 (0)	4 (3.9)	7 (4.5)		
6MWD, mean ± SD meters (n)	358±133 (224)	406±113 (91)	326±131 (90)	326±137 (133)	<.001	<.001
Pulmonary Function Tests, mean ± SD (n)						
FVC% predicted	76.0±22.5 (285)	83.0±18.5 (135)	76.7±24.9 (96)	69.7±24.0 (150)	0.047	<.001
DL_{CO}% predicted	44.9±19.5 (275)	52.0±19.4 (134)	40.9±17.8 (90)	38.1±17.0 (141)	<.001	<.001
FVC%:DL_{CO}% ratio	2.0±0.8 (274)	1.8±0.7 (133)	2.2±1.0 (90)	2.1±0.9 (141)	<.001	<.001
Transthoracic echocardiogram						
RVSP, mean±SD mmHg (n)	49.4±21.3 (267)	38.8±13.0 (127)	63.2±23.5 (92)	58.9±22.9 (140)	<.001	<.001
Pericardial effusion, n (%)	68 (24.2)	15 (11.2)	39 (40.6)	53 (36.05)	<.001	<.001
Right-heart catheterisation, mean ± SD (n)						
mPAP, mmHg	34.7±13.0 (175)	19.2±3.7 (34)	40.0±11.4 (91)	38.4±11.6 (141)	<.001	<.001
PVR, WU	480±420 (170)	261±460 (32)	597±429 (90)	531±395 (138)	<.001	<.001
PCWP, mmHg	11.1±5.7 (174)	8.8±4.0 (33)	9.6±3.4 (91)	11.6±5.9 (141)	0.431	0.030
Cardiac output, L/min	4.9±1.6 (170)	5.1±1.1 (33)	4.7±1.6 (90)	4.9±1.7 (137)	0.167	0.310

*PHAROS: Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma; SSc-AR-PAH: Scleroderma patient's at risk for pulmonary arterial hypertension; SSc-PAH: Scleroderma associated pulmonary arterial hypertension; SSc-PH: Scleroderma associated pulmonary hypertension; CCB: calcium-channel blocker; NYHA: New York Heart Association functional class; 6MWD: six minute walk distance; FVC: forced vital capacity; DL_{CO}: diffusion capacity for carbon monoxide; RVSP: right ventricular systolic pressure (calculated); mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; WU: Wood units; PCWP: pulmonary capillary wedge pressure,

able. Within this group 157 (48%) were classified as SSc-AR-PAH and 172 (52%) as SSc-PH (114 SSc-PAH, 31 WHO Group II, 27 WHO Group III). Baseline natriuretic peptide levels were drawn a mean of -0.25±1.13 months from the date of enrolment. 59% had BNP collected (72 SSc-AR-PAH and 122 SSc-PH patients) and 41% had NT-proBNP collected (85 SSc-AR-PAH and 51 SSc-PH patients); only one patient had both serum levels available at baseline.

Baseline characteristics of the patients included in this analysis are shown in Table I. The majority of patients were female (84%), Caucasian (72%), and had limited cutaneous disease (69%). As expected, the SSc-PAH and SSc-PH group had poorer functional status, shorter 6MWD, lower FVC and DLCO, and higher RVSP on TTE than the SSc-AR-PAH group. In addition, of the 175 patients with RHC data available, the SSc-PAH and SSc-PH patients had higher mPAP and PVR compared with the SSc-AR-PAH group.

Median BNP and NT-proBNP levels were significantly higher for those with SSc-PH (135 (9-5534) and 503 (14-9999) pg/mL, respectively) compared to the SSc-AR-PAH group (43.5 (3-2560) and 82.0 (4-1223) pg/mL, respectively). WHO group II SSc-PH patients had the highest BNP levels, while SSc-PAH patients had the highest NT-proBNP levels (Table II).

Correlation between natriuretic peptides and haemodynamics in definite PH patients

In the SSc-PH group, baseline NT-proBNP levels were moderately correlated

Table II. Baseline BNP and NT-proBNP levels by pulmonary hypertension sub-type.

SSc-PH sub-type	SSc-AR-PAH	SSc-PAH WHO Group I	SSc-PH WHO Group II	SSc –PH WHO Group III	*Pairwise comparison (*p*-value)			
	0	1	2	3	0 *vs*.1-3	1 *vs*..2	1 *vs*..3	2 *vs*..3
BNP median (range, n)	43.5 (3 - 2560, 72)	138.0 (9 – 5534, 80)	326.5 (20- 3860, 22)	39.0 (16.0- 1818, 20)	<.001	0.034	0.045	0.001
NT-proBNP median (range, n)	82.0 (4.0 – 1223, 85)	679.5 (20 – 9999, 34)	454.5 (14 – 2770, 10)	123.0 (20 – 970, 7)	<.001	0.073	0.016	0.460

*Comparison performed on log transformed data and adjusted for creatinine level; SSc-PH: systemic sclerosis associated pulmonary hypertension (all subtypes); SSc-AR-PAH: Scleroderma patients at risk for pulmonary arterial hypertension; SSc-PAH: SSc associated pulmonary arterial hypertension; WHO Group II: pulmonary hypertension due to left heart disease; WHO Group III: pulmonary hypertension due to hypoxia-ILD.

with mPAP and PVR (p<0.01), while BNP levels had significant but weak correlations with these parameters (Table III). In addition, NT-pro-BNP had a moderate negative correlation with cardiac output (p<0.001). Likewise, in the SSc-PAH group, NT-pro-BNP had stronger correlations with haemodynamic indices than BNP and both natriuretic peptides had significant but weak negative correlations with 6MWD.

Predictive value of natriuretic peptides in SSc-AR-PAH patients

Of 157 SSc-AR-PAH patients at enrolment, 26 patients developed SSc-PH (16 with SSc-PAH) by RHC during a mean follow-up time of 3.5±1.7 years. Median baseline BNP and NT-proBNP levels were not significantly different in patients who developed SSc-PAH and/or SSc-PH compared to those who did not (Table IV).

We assessed whether the development of SSc-PAH and/or SSc-PH was associated with individual baseline BNP≥64 pg/mL, NT-proBNP≥210 pg/mL, combined natriuretic peptides, or other baseline variables including DLCO, RVSP, FVC/DLCO ratio, creatinine, and anti-centromere antibody status, by Cox regression analyses. We found RVSP≥40 mmHg and FVC/DLCO≥1.8 were significant predictors of developing SSc-PH, with creatinine showing a trend towards significance; for progression to SSc-PAH, RVSP≥40 mmHg and creatinine were significant predictors of progression. We did not find elevated baseline BNP or NT-proBNP to be associated with an increased risk for development of SSc-PAH and/or SSc-PH. Similarly, when combining BNP and NT-proBNP into a composite group, no significant association was observed (Table V).

Longitudinal natriuretic peptide levels were available for 61 SSc-PAH patients (38 BNP, 23 NT-proBNP) and 85 SSc-PH patients (54 BNP, 31 NT-proBNP) over a mean follow-up time of 2.6±1.5 years. Longitudinal changes in BNP or NT-proBNP were not significantly different between those who developed SSc-PH and/or SSc-PAH subgroup *versus* those that did not (Table VI).

We also determined the sensitivity and specificity of baseline BNP≥64 pg/mL and NT-pro-BNP≥210 pg/mL for the detection of PAH. While the sensitivities were quite similar between NT-pro-BNP and BNP (73% *vs*. 71%, p=0.8), there was a significant difference in the specificities (78% *vs*. 59%, p=0.002).

Mortality risk associated with natriuretic peptide levels in definite PH patients

Forty-four patients died over the follow-up period, including 14 SSc-AR-PAH and 30 SSc-PH (15 SSc-PAH) patients. We assessed whether baseline BNP≥180 pg/mL or NT-proBNP≥553 pg/mL were associated with an increased risk for death in the SSc-PH group and/or SSc-PAH subgroup. We did not find that the individual natriuretic peptides were predictive of death, however, a composite group of both BNP≥180 pg/mL and/or NT-proBNP≥553 pg/mL patients did reveal a significant association with death (44 events, HR is 3.81 (2.08–6.99), p<.0001). In the SSc-PAH cohort, a significant association between PVR and risk of death was observed (HR 2.8, 95% CI 1.1–7.0, p=0.03) and in the SSc-PH cohort, a significant association was seen between male gender (HR 2.4, 95% CI 1.0–5.5, p=0.05) and increased mortality. The median changes in longitudinal BNP and NT-proBNP levels in patients who died versus those who survived were not significantly different (Table VI).

Discussion

We evaluated serum BNP and NT-proBNP as diagnostic and prognostic markers of PAH and PH in SSc patients enrolled in PHAROS. We showed that median baseline levels of both BNP and NT-proBNP were significantly different between the SSc-AR-PAH and SSc-PH patients. Group II PH patients had the highest BNP levels, while group I PAH patients had the highest NT-proBNP levels. The sensitivity and specificity for SSc-PAH detection using baseline BNP≥64 pg/mL was 71% and 59%; and for NT-proBNP≥210 pg/mL, 73% and 78%. A composite group of both peptides showed a significant association with mortality, but individual natriuretic peptide levels did not demonstrate an association with mortality or progression to SSc-PH/PAH. The results of our study reaffirmed the correlation between serum natriuretic peptide levels and haemodynamic parameters associated with progressive right ventricular dysfunction in SSc-PAH (18, 21). In our study, NT-pro-BNP showed stronger correlations with haemodynamic indicators of right ventricular dysfunction than BNP.

To date the only comparative study of BNP and NT-proBNP for SSc-PAH

Table III. Correlations between BNP and NT-proBNP and markers of pulmonary hypertension severity.

	SSc-PAH					SSc-PH				
		BNP		NT-proBNP			BNP		NT-proBNP	
		r	*p*	r	*p*		r	*p*	r	*p*
BNP, median pg/mL (range, n)*	138.0 (9–5534, 80)	1		-		135 (9– 5534, 122)	1		-	
NT-proBNP, median pg/mL (range, n)*	679.5 (20–9999, 34)	-		1		503 (14 -9999, 51)	-		1	
mPAP, mean± SD mmHg (n)	40.0±11.5 (91)	0.32	0.01	0.52	0.005	38.4±11.6 (141)	0.45	<0.001	0.49	<.001
PVR, mean ± SD WU (n)	597±429 (90)	0.37	0.002	0.53	0.004	531±395 (138)	0.37	<.001	0.52	<.001
Cardiac output, mean ± SD L/min (n)	4.7±1.6 (90)	-0.25	0.052	-0.63	<.001	4.9±1.7 (137)	-0.29	0.005	-0.57	<.001
6MWD, mean ± SD meters (n)	326±131 (90)	-0.37	0.003	-0.16	0.40	326±137 (133)	-0.38	<.001	-0.35	0.022
NYHA functional class mean ± SD (n)	2.4±0.8(102)	1.22 (0.88-1.69)†	0.23	1.49 (0.91-2.44)†	0.11	2.4±0.8 (155)	1.28 (0.98-1.65)†	0.07	1.33 (0.93-1.89)†	0.12

*BNP and NT-proBNP were log transformed prior to logistic regression analysis; r: correlation coefficient; SSc-PAH: Scleroderma associated pulmonary arterial hypertension; SSc-PH: Scleroderma associated pulmonary hypertension; 6MWD: six minute walk distance); mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; WU: Wood units; NYHA: New York Heart Association functional class; †odds ratios of being NYHA functional classes 3-4 (*vs*. 1-2) by log natriuretic levels utilising logistic regression analysis.

screening is a single center cross-sectional study by Cavagna *et al*. on 135 SSc patients performed in Italy. This study showed sensitivities and specificities of 60% and 87% for BNP (≥64 pg/mL), and 45% and 90% for NT-proBNP (≥239.4 pg/mL) (21). A longitudinal investigation of these markers was not undertaken, nor was left heart disease or ILD associated SSc-PH included in that analysis.

Early work that suggested natriuretic peptides may be of utility in PH was performed by Nagaya *et al*. who demonstrated that serum BNP: 1) correlates with haemodynamic parameters of right ventricular dysfunction in IPAH (24), 2) predicts mortality in IPAH when an individual's BNP is greater than the median level at diagnosis (150 pg/mL) and 3-month follow-up (180 pg/mL), and 3) predicts responsiveness to treatment in IPAH (23).

Several authors have used BNP or NT-proBNP as markers or predictors of SSc-PAH and found varying levels of sensitivity and specificity, depending on the cut-off points used. The large international DETECT study incorporated NT-proBNP alongside PFTs, additional laboratory markers, and TTE, with a sensitivity of 85% and specificity of 72% for SSc-PAH screening (25). A prospective study by Thakkar *et al*. used a two-step sequential screening algorithm for SSc-PAH consisting of NT-proBNP measurement (cut-off of 209.8 pg/mL) in combination with PFTs (DLCO <70% and/or FVC/DLCO ≥1.8) to decide on further TTE screening with a sensitivity of 94% and specificity of 55% for SSc-PAH from a cohort of SSc patients deemed to be at-risk for PAH (20). Allanore *et al*. found NT-proBNP predicted SSc-PAH development in SSc patients at 29-months with 75% sensitivity and 97% specificity using a set of age- and sex-adjusted NT-proBNP cut-offs (18). Williams *et al*. found NT-proBNP levels ≥395 pg/mL have a sensitivity of 56% and specificity of 95% for diagnosing SSc-PAH. This study also found that increased baseline and longitudinal NT-proBNP levels were associated with decreased survival in SSc-PAH patients (22).

Our study did not find that baseline BNP or NT-proBNP levels, as individual subgroups or when combined in a composite group, predicted the development of SSc-PAH or SSc-PH in

Table IV. Association between baseline BNP and NT-proBNP levels and progression to SSc-PAH or SSc-PH in the SSc-AR-PAH group.

	Remained SSc-AR-PAH	Developed SSc-PAH	*p*	Developed SSc-PH	*p*
BNP, median pg/mL (range, n)	44.5 (3 – 2560, 64)	60.0 (15 – 4761, 10)	0.17* (0.15†)	50.0 (8-4761, 16)	0.20* (0.35†)
NT-proBNP, median pg/mL (range, n)	74.0 (4.0 – 1223, 77)	144.0 (58 – 234, 6)	0.29* (0.16†)	105.5 (33 – 234, 10)	0.41* (0.26†)

*t-test and † parametric test both performed on log transformed data; SSc-AR-PAH: Scleroderma patients at risk for pulmonary arterial hypertension; SSc-PAH: Scleroderma associated pulmonary arterial hypertension; SSc-PH: Scleroderma associated pulmonary hypertension.

a high-risk population after 3.51±1.70 years of follow-up. Previous work has shown that serum NT-proBNP levels fall by nearly half after several days of treatment with calcium channel blockers (CCBs) (28). In our cohort, 36% were taking CCBs at the time baseline BNP/NT-proBNP levels were obtained. However, stratification of our analyses by CCB use did not alter our results.

We found baseline creatinine to be significantly associated with the development of SSc-PAH and trended to significance for the development of SSc-PH. Previous SSc cohort studies revealed conflicting results regarding the association between baseline creatinine levels and development of PAH. One study showed creatinine levels to be an independent predictor of SSc-PAH (21) while another study showed no association (28). However, in a longitudinal study of 101 SSc patients without evidence of PAH at baseline, no significant difference in baseline creatinine levels were seen between patients who developed SSc-PAH vs those who did not at a mean follow-up of 28 months (18). In the general IPAH population, creatinine has been associated with mortality (29) however, in previously published work on the PHAROS cohort, baseline creatinine was not shown to predict mortality in SSc-PAH patients (30).

We also did not find that baseline or longitudinal changes in BNP or NT-proBNP groups predicted mortality in SSc-PAH or SSc-PH patients. However, when combined into a single composite group using each peptide's respective cutoffs, elevated natriuretic peptide levels were associated with almost a 4-fold increased risk of death. The low number of events (progression to PAH (17%, n=16) and death (13%, n=15)) in the PHAROS cohort, along with missing follow-up BNP and/or NT-proBNP levels for nearly half of these patients, may have prevented trends in individual natriuretic peptides from reaching statistical significance in our univariate analyses, and underpowered our multivariate analyses.

Our study has several limitations. PHAROS is an observational cohort and natriuretic peptide levels were obtained only if deemed indicated as standard of care. Therefore, baseline values for 14% of the cohort were missing and both BNP and NT-proBNP levels were typically not drawn from the same individual patients. In addition, BNP and NT-proBNP serum levels were often not drawn at the time of the RHC with a mean time of 1.8 months between these time-points. Patients enrolled in the PHAROS registry likely received more aggressive screening and treatment than the general SSc population possibly resulting in lead-time bias and decreased generalisability (30).

In conclusion, our study confirmed that BNP and NT-proBNP are useful in monitoring disease severity in patients with SSc-PAH and SSc-PH. NT-proBNP had stronger correlations with haemodynamic parameters than BNP in both the SSc-PAH and SSc-PH populations. Although both tests showed good sensitivity, NT-pro-BNP demonstrated superior specificity compared to BNP. Combining BNP and NT-proBNP into a composite group revealed an association with mortality but not progression to SSc-PH or SSc-PAH. Individually, neither natriuretic peptide predicted progression from SSc-AR-PAH to SSc-PAH or SSc-PH, or predicted mortality in SSc-PH patients. Further large prospective studies in which serial BNP and NT-proBNP levels are obtained

Table V. Predictors of progression to SSc-PAH and/or SSc-PH from SSc-AR-PAH using Cox regression analysis.

	SSc-PAH (9 events)		SSc-PH (13 events)	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Univariate analysis				
BNP ≥64 pg/mL	0.6 (0.1 – 5.7)	0.64	0.4 (0.1 – 3.7)	0.43
NT-proBNP ≥210 pg/mL	1.6 (0.2-14.3)	0.68	0.9 (0.1-7.2)	0.91
BNP ≥64 pg/mL and/or NT-proBNP ≥210 pg/mL	0.97 (0.2 – 4.7)	0.97	0.7 (0.1 – 3.0)	0.58
RVSP ≥40 mmHg	13.1 (1.6-109.6)	0.02	9.0 (1.9 – 42.0)	0.005
DL_{CO} < 55% predicted	1.4 (0.3-7.5)	0.66	2.3 (0.5 – 11.0)	0.29
FVC%:DL_{CO}% ratio ≥1.8	4.6 (0.9 – 24.0)	0.07	7.4 (1.6 – 34.7)	0.01
Creatinine	1.4 (1.07-1.94)	0.02	1.3 (0.99 – 1.8)	0.06
Anticentromere antibody positive	1.1 (0.2-5.7)	0.91	1.8 (0.5 – 6.6)	0.37

*HR: Hazard Ratio; SSc-AR-PAH: Scleroderma patient's at risk for pulmonary arterial hypertension; SSc-PAH: Scleroderma associated pulmonary arterial hypertension; SSc-PH: Scleroderma associated pulmonary hypertension; CCB: calcium-channel blocker; FVC: forced vital capacity; DL_{CO}: diffusion capacity for carbon monoxide; RVSP: right ventricular systolic pressure (calculated),

Table VI. Comparison of change in BNP and NT-proBNP for progression to SSc-PH and between living and deceased patients.

	Remained SSc-AR-PAH	Developed SSc-PH	*p*
change in BNP, median pg/mL (range, n)	15 (-84 – 610, 48)	36 (-20 – 1136, 12)	0.25
change in NT-proBNP, median pg/mL (range, n)	18 (-430 – 1904, 40)	421 (-5 – 1901, 19)	0.10
Follow-up in years Mean (std, n)	3.5 (1.8, 134)	2.4 (1.4, 12)	0.04
	Living	Deceased	*p*
change in BNP, median pg/mL (range, n)	0 (-1537 – 586, 42)	-78 (-727 – 8799, 12)	0.29
change in NT-proBNP, median pg/mL (range, n)	70 (-8611 – 5374, 22)	138 (-2296 – 5723, 19)	0.38
Follow-up in years Mean (std, n)	2.72 (1.61, 61)	2.17 (1.03, 18)	0.38

*Changes in BNP and NT-proBNP by death status were calculated for SSc-PH patients where longitudinal data was available; 6 patients had both BNP and NT-proBNP available for this analysis.

simultaneously will be necessary to better compare the utility of these two natriuretic peptides in clinical practice.

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Competing interests

L. Chung receives funding support from the Scleroderma Research Foundation, the Scleroderma Foundation and the Scleroderma Clinical Trials Consortium. She has served on the Advisory Board of Gilead and Actelion and as a consultant for Gilead, and serves on the Data Monitoring Committee for Reata and Cytori. She has received funding support from United Therapeutics.
D.E. Furst has received research support from AbbVie, Actelion, Amgen, BMS, NIH, Novartis, Pfizer, Roche/ Genentech and is a consultant for AbbVie, Actelion, Amgen, BMS, Cytori, Novartis, Pfizer, Roche/ Genentech.
C.T.Derk has received research grant from Gilead Pharmaceuticals.
R.T. Domsic has received consultancy and research support from Biogen-Idec and consultancy from Bayer Healthcare.
A. Fischer is a consultant for Actelion, Gilead, Genentech/Roche, Boehringer-Ingelheim and aTyr Pharmaceuticals, and has received research funds from Genentech/Roche.
M. Gomberg-Maitland and the University of Chicago have received research monies from multiple sources; however, none directly related to this manuscript.
D. Khanna has consultancy relationships with Actelion, Bayer, Bristol-Myers Squibb, ChemomAb, Corbus, Cytori, EMD Serono, genentech/Roche, Gilead, Glaxo SmithKline, MedImmune, Medac and Sanofi-Aventis/Genzyme. He has received research funding from the NIH, Astra-Zeneca, Bayer, Bristol-Myers Squibb, ChemomAb and Pfizer.
I.R. Preston provided consultancies to: Actelion, Bayer, Gilead and has served as PI for grants granted to Tufts Medical Center from Actelion, Bayer, Gilead, United Pharmaceuticals, Eiger.
R. Simms has served on the Speakers' Bureau for Gilead and has received research funding from Actelion and Novartis.
V.D. Steen has received research funding and consultation honoraria from industry, but does not feel these have any conflict of interest related to this manuscript.
R.T. Zamanian is a consultant to United Therapeutics, Bayer, Selten and Actelion. He has received research grants from NIH/NHLBI, Actelion, United Therapeutics and Vera Moulton Wall Center for PVD at Stanford.
The other co-authors have declared no competing interests.

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