ORIGINAL ARTICLE

Ambrisentan and Tadalafil Up-front Combination Therapy in Scleroderma-associated Pulmonary Arterial Hypertension

Paul M. Hassoun[1], Roham T. Zamanian[2], Rachel Damico[1], Noah Lechtzin[1], Rubina Khair[1], Todd M. Kolb[1], Ryan J. Tedford[3], Olivia L. Hulme[1], Traci Housten[1], Chiara Pisanello[3], Takahiro Sato[1], Erica H. Pullins[1], Celia P. Corona-Villalobos[4], Stefan L. Zimmerman[4], Mohamed A. Gashouta[1], Omar A. Minai[5], Fernando Torres[6], Reda E. Girgis[7], Kelly Chin[6], and Stephen C. Mathai[1]

[1]Division of Pulmonary and Critical Care Medicine and [3]Division of Cardiology, Department of Medicine, and [4]Department of Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Division of Pulmonary & Critical Care Medicine, Stanford University School of Medicine, Stanford, California; [5]Division of Pulmonary and Critical Care Medicine, The Cleveland Clinic, Cleveland, Ohio; [6]Division of Pulmonary and Critical Care Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; and [7]Division of Pulmonary Medicine, Spectrum Health/Michigan State University, Grand Rapids, Michigan

Abstract

Background: Scleroderma-associated pulmonary arterial hypertension (SSc-PAH) is a rare disease characterized by a very dismal response to therapy and poor survival. We assessed the effects of up-front combination PAH therapy in patients with SSc-PAH.

Methods: In this prospective, multicenter, open-label trial, 24 treatment-naive patients with SSc-PAH received ambrisentan 10 mg and tadalafil 40 mg daily for 36 weeks. Functional, hemodynamic, and imaging (cardiac magnetic resonance imaging and echocardiography) assessments at baseline and 36 weeks included changes in right ventricular (RV) mass and pulmonary vascular resistance as co–primary endpoints and stroke volume/pulmonary pulse pressure ratio, tricuspid annular plane systolic excursion, 6-minute walk distance, and N-terminal pro-brain natriuretic peptide as secondary endpoints.

Results: At 36 weeks, we found that treatment had resulted in significant reductions in median (interquartile range [IQR]) RV mass (28.0 g [IQR, 20.6–32.9] vs. 32.5 g [IQR, 23.2–41.4]; $P < 0.05$) and median pulmonary vascular resistance (3.1 Wood units [IQR, 2.0–5.7] vs. 6.9 Wood units [IQR, 4.0–12.9]; $P < 0.0001$) and in improvements in median stroke volume/pulmonary pulse pressure ratio (2.6 ml/mm Hg [IQR, 1.8–3.5] vs. 1.4 ml/mm Hg [IQR 8.9–2.4]; $P < 0.0001$) and mean ($\pm$ SD) tricuspid annular plane systolic excursion (2.2 $\pm$ 0.12 cm vs. 1.65 $\pm$ 0.11 cm; $P < 0.0001$), 6-minute walk distance (395 $\pm$ 99 m vs. 343 $\pm$ 131 m; $P = 0.001$), and serum N-terminal pro-brain natriuretic peptide (647 $\pm$ 1,127 pg/ml vs. 1,578 $\pm$ 2,647 pg/ml; $P < 0.05$).

Conclusions: Up-front combination therapy with ambrisentan and tadalafil significantly improved hemodynamics, RV structure and function, and functional status in treatment-naive patients with SSc-PAH and may represent a very effective therapy for this patient population. In addition, we identified novel hemodynamic and imaging biomarkers that could have potential value in future clinical trials.

Clinical trial registered with www.clinicaltrials.gov (NCT01042158).

Keywords: MRI; pulmonary arterial hypertension; therapy

(Received in original form July 17, 2015; accepted in final form September 11, 2015)

Supported by the National Institutes of Health under NHLBI awards P50 HL084946 (P.M.H.), HL114910 (P.M.H.), and K23HL90038491 (S.C.M.). Gilead Inc. and United Therapeutics Inc. provided the study drugs (ambrisentan and tadalafil, respectively) free of charge for the entire duration of the study (36 wk) and for 1 year after its completion. They had no role in the design or monitoring of the study, acquisition of clinical or imaging data, statistical analysis, interpretation of the results, or writing of the manuscript.

Author Contributions: P.M.H., R.E.G., and S.C.M.: study design; P.M.H., R.T.Z., S.C.M., R.D., T.M.K., R.J.T., T.H., E.H.P., O.A.M., F.T., and K.C.: patient recruitment, care, and follow-up; R.D., R.K., O.L.H., M.A.G., and P.M.H.: data collection, maintenance, and analysis; C.P.C.-V. and S.L.Z.: cardiac magnetic resonance imaging scan acquisition, interpretation, and analysis; C.P. and T.S.: echocardiographic interpretation and analysis; P.M.H., N.L., S.C.M., R.D., and R.K.: statistical analyses; P.M.H.: drafted the manuscript; R.T.Z., R.D., R.K., and S.C.M.: critical revision of the manuscript for important intellectual content; and P.M.H.: was principal investigator, had access to all the data in the study, and takes full responsibility for the integrity and accuracy of the data analysis.

Correspondence and requests for reprints should be addressed to Paul M. Hassoun, M.D., Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University, 1830 East Monument Street, Baltimore, MD 21205. E-mail phassoun@jhmi.edu

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 192, Iss 9, pp 1102–1110, Nov 1, 2015

Originally Published in Press as DOI: 10.1164/rccm.201507-1398OC on September 14, 2015
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Scleroderma-associated pulmonary arterial hypertension is a rare disease with a notoriously dismal response to modern pulmonary arterial hypertension therapy. In this open-label trial, we assessed the effect of up-front combined therapy on functional status, hemodynamics, and right ventricular function.

What This Study Adds to the Field: This study demonstrates that up-front combination therapy with an endothelin receptor antagonist and a phosphodiesterase inhibitor improves functional status, hemodynamics, and right ventricular structure and function in treatment-naive patients with scleroderma-associated pulmonary arterial hypertension. In addition, we identified novel hemodynamic and imaging biomarkers that could potentially be valuable endpoints in future clinical trials.

Pulmonary arterial hypertension (PAH), or group 1 of the classification of pulmonary hypertension, is defined as an elevation in mean pulmonary arterial pressure (mPAP) equal to or greater than 25 mm Hg, along with a normal wedge pressure and a pulmonary vascular resistance (PVR) greater than 3 Wood units (WU) (1). It is a progressive, debilitating disease characterized by severe remodeling of the pulmonary vasculature that results in right ventricular (RV) failure and ultimately death. However, there is significant heterogeneity in syndromes (2) as well as response to therapy within group 1. The latter is exemplified by the great disparity between response to modern therapy and survival in patients with idiopathic PAH (IPAH) compared with patients with scleroderma-associated PAH (SSc-PAH), as reported from single centers (3, 4) and large registries (5, 6). In fact, response to modern PAH-specific medical therapy (as assessed essentially by the 6-minute walk distance [6MWD]) in randomized, controlled, multicenter PAH trials has been at best modestly effective for patients with SSc-PAH compared with patients with IPAH in subgroup analyses of the various trials (7–9).

We hypothesized that targeting two distinct pathways using U.S. Food and Drug Administration–approved drugs given as up-front therapy would be beneficial in treatment-naive patients with SSc-PAH. Because survival is dependent largely on RV function (10), this clinical trial was also aimed at testing changes in novel clinical endpoints relevant to RV structure and/or function and RV–pulmonary vascular coupling. This was achieved using standard invasive hemodynamic measurements, echocardiography, and cardiac magnetic resonance (CMR) imaging performed at baseline and at the end of therapy. RV mass, which has been used previously as an endpoint in a small clinical trial of PAH therapy (11), and PVR, a strong predictor of mortality in SSc-PAH (12), were used as co–primary endpoints. Several other biomarkers of RV structure and function were also tested for their value as exploratory clinical endpoints. Some of the results of the present study have been reported previously in abstract form (13).

Methods

Full details regarding the methods are provided in the online supplement.

Study Design

This open-label, 36-week clinical trial of ambrisentan and tadalafil combination therapy in patients with SSc-PAH was approved by the institutional review boards at each of the four centers involved (Johns Hopkins University, Stanford University, University of Texas Southwestern Medical Center, and The Cleveland Clinic), and it was registered at clinicaltrials.gov (NCT01042158) before patient recruitment. Study monitoring was conducted by a National Institutes of Health/NHLBI Data and Safety Monitoring Board, followed by an Observational Study Monitoring Board at Johns Hopkins University until completion of the study.

Study Participants

Subjects older than 18 years of age who fulfilled the criteria for SSc and had PAH confirmed by right heart catheterization (RHC) with World Health Organization (WHO) functional class (FC) II or III symptoms, but who had not yet received PAH-specific therapy, were enrolled after informed consent was obtained at each center. Exclusion criteria included significant obstructive or interstitial lung disease (3, 12) or other PAH-associated diseases (*see* online supplement) and/or therapy with an endothelin receptor antagonist, a phosphodiesterase 5 inhibitor, or a prostacyclin analog.

Study Procedures

Assessments. Before initiation of study drugs, subjects underwent baseline clinical assessment, including WHO FC, complete 36-item Short Form Health Survey (SF-36), Minnesota Living with Health Failure questionnaire, 6MWD with Borg dyspnea score, and baseline blood testing (including N-terminal pro-brain natriuretic peptide [NT-proBNP]). The PAH diagnosis was made at baseline by RHC (1). Echocardiography and CMR imaging were performed at baseline within 24 hours of RHC. Clinical assessment was repeated at 16, 24, and 36 weeks. RHC and CMR imaging were repeated at 36 weeks, and echocardiography was repeated at 16 and 36 weeks.

Hemodynamic measurements. Hemodynamic measurements were obtained by RHC as detailed in the online supplement. In addition, pulmonary arterial compliance (stroke volume [SV]/pulmonary arterial pulse pressure [PP] ratio) was calculated.

Two-dimensional echocardiography and M-mode imaging. Two-dimensional echocardiography and M-mode imaging were performed. Two echocardiographers (T.S. and C.P.) blinded to the subject and study timing analyzed the data offline. Tricuspid annular plane systolic excursion (TAPSE) was measured as described elsewhere (14).

CMR imaging. Standard volumetric cine images were acquired and analyzed to assess RV mass and function. All CMR imaging studies were read at Johns Hopkins University by two investigators (C.P.C.-V. and S.L.Z.) blinded to the subject and study timing.

Therapy. Therapy was initiated with tadalafil 20 mg and ambrisentan 5 mg once daily followed by uptitration at Week 4 (ambrisentan 10 mg and tadalafil 40 mg once daily). In case of intolerable adverse events as a result of uptitration, doses were downtitrated to 20 mg of tadalafil and/or 5 mg of ambrisentan. Drugs could be held or discontinued at the investigator's discretion.

Outcome measures. Changes in PVR (as measured by RHC) and RV mass (as measured by CMR imaging) between baseline and 36 weeks were the co–primary outcome measures. Secondary outcomes included the safety of combination therapy as assessed by type and frequency of adverse events. Other outcome measures are detailed in the online supplement.

Statistical Analysis

Assuming a two-sided $\alpha = 0.05$ and a conservative estimate of within-individual correlation greater than or equal to 0.7 between repeated measurements, enrollment of 25 patients was deemed sufficient to detect a difference of 6% in RV mass (power = 87% based on RV mass of 160 g and SD of 15 g) and a difference of 3.5 WU in PVR (power = 99% based on PVR of 10 WU and SD of 5 WU). The expected effect size of change in RV mass of 6% was based on differences in RV mass measured by CMR imaging in the Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension study comparison of sildenafil with bosentan therapy in patients with both IPAH and SSc-PAH (11), whereas the expected change of 3.5 WU was based on changes in PVR observed in the Pulmonary Arterial Hypertension and Response to Tadalafil trial (15). Stata version 9 software (StataCorp, College Station, TX) was used for the power analysis. Data are presented as mean ± SD or median and interquartile range (IQR). Comparisons were made using paired *t* tests (normally distributed data) or nonparametric analysis. Paired *t* tests, Wilcoxon's signed-rank test, or χ^2 statistics were used as appropriate. $P < 0.05$ was considered significant.

Results

Study Population

Between August 25, 2011, and February 4, 2014, 42 patients who fulfilled the inclusion and exclusion criteria were screened for enrollment at the four institutions. After exclusion of 17 patients (*see* Figure E1 in the online supplement), 25 treatment-naive subjects were enrolled to receive ambrisentan 5 mg and tadalafil 20 mg once daily for a total of 4 weeks before uptitration of study medications to ambrisentan 10 mg and tadalafil 40 mg once daily. At Week 4 after enrollment, one patient was admitted to the hospital for a complicated viral infection (respiratory syncytial virus), opted for hospice care upon discharge, and was withdrawn from the study. The analysis is therefore limited to the remaining 24 patients who completed the trial. Their baseline characteristics are shown in Table 1 (*see also* Table E1). Patients were mostly female and white, were a mean age of 59 years, and had limited SSc. They had moderate functional impairment (WHO FC II/III distribution of 35%/65%) with a 6MWD of 343 ± 131 m at baseline. Pulmonary function tests revealed an isolated, moderate decrease in diffusing capacity of carbon monoxide. Comorbid conditions included systemic hypertension and diabetes mellitus. Patients had moderate to severe hemodynamic impairment, with elevated right atrial pressure of 7 ± 5 mm Hg, mPAP of 42 ± 12 mm Hg, and PVR of 8.4 ± 5.1 WU. However, they had a relatively preserved cardiac index (CI) of 2.6 ± 0.7 L/min/m^2 (Table 2).

Table 1. Baseline Demographics and Characteristics

Characteristics	Data
Age, yr	59.9 ± 10.9
Female, n (%)	22 (91.7)
Race, n (%)	
White	21 (87.5)
Black	2 (8.3)
Other	1 (4.2)
Limited scleroderma, n (%)	19 (86.4)
Systemic hypertension, n (%)	11 (45.8)
Diabetes mellitus, n (%)	4 (16.7)
WHO functional class, n (%)	
I	0
II	8 (35)
III	15 (65)
IV	0
6MWD, m	343 ± 131
Pulmonary function tests	
FEV_1, % predicted	82 ± 17
FVC, % predicted	82 ± 18
FEV_1/FVC, %	77 ± 7
TLC, % predicted	83 ± 13
D_{LCO}, % predicted	53 ± 19

Definition of abbreviations: D_{LCO} = diffusing capacity of carbon monoxide; 6MWD = 6-minute-walk distance; TLC = total lung capacity; WHO = World Health Organization.
Data are mean ± SD (n = 24 for each parameter) or count (%).
See also Table E1.
WHO functional class data were not available for one subject at baseline.

Dosing of the Treatment Drugs and Safety

At Week 4, 18 (75%) of 24 patients tolerated uptitration of ambrisentan to 10 mg, and 21 (87%) of 24 tolerated uptitration of tadalafil to 40 mg daily, as dictated by the protocol. Fluid retention was the main reason not to uptitrate ambrisentan in four patients at 4 weeks, and hypotension, headache, and nasal congestion were symptoms that prevented uptitration of tadalafil. At completion of the trial, 22 (91%) of 24 patients were on ambrisentan 10 mg daily, and the same number of patients were on tadalafil 40 mg daily. A total of 21 patients (87%) were receiving the full dosage of both ambrisentan and tadalafil. Three patients (12%) ended the trial with less than maximal dosage: one patient on ambrisentan 10 mg alone daily, another one on ambrisentan 5 mg and tadalafil 20 mg daily, and the third on tadalafil 40 mg alone daily.

The drug combination was well tolerated and safe. Side effects included fluid accumulation (29%), nasal congestion (16%), headache (29%), and gastrointestinal symptoms (Table E2). Serious adverse events were rare and limited (*see* online supplement). No patient required additional PAH-specific therapy (including prostacyclin drugs) during the study period.

Primary and Secondary Endpoints

At Week 36 of treatment, both primary endpoints were significantly improved: PVR was reduced by 55% from a median of 6.9 WU (IQR, 4.0–12.9) to 3.1 WU (IQR, 2.0–5.7) ($P < 0.01$) (Figure 1A), and RV mass was reduced by 14% from a median of 32.5 g (IQR, 23.4–41.4) to 28.0 g (IQR, 20.1–32.8) ($P < 0.05$) (Figure 1B). At Week 36, all 24 patients had a greater than 20% decrease in PVR compared with baseline, including 16 patients whose PVR decrease was greater than 50%. Fifteen patients had a 10% or greater decrease in RV mass, five were without change, and three had an increase in RV mass (Figure 1B). Of these latter three patients, two achieved a PVR of less than 3 WU on therapy at 36 weeks.

As shown in Table 2, other changes in hemodynamic parameters at 36 weeks of therapy included a significant drop in mPAP and RAP, an improvement in CI, an increase in SV/PP ratio ($P < 0.001$) (Figure 2A), and an improvement in

Table 2. Hemodynamic Data and Functional Status at Baseline and 36 Weeks

	Baseline	36 wk	*P* Value
Hemodynamics			
Heart rate, beats/min	77 ± 15	73 ± 10	NS
RAP, mm Hg	7 ± 5	5 ± 3	<0.05
mPAP, mm Hg	42 ± 12	30 ± 7	<0.01
PCWP, mm Hg	9 ± 3	11 ± 4	NS
CO, L/min	4.8 ± 1.6	5.7 ± 1.7	<0.05
CI, L/min/m^2	2.6 ± 0.7	3.3 ± 1.2	<0.01
SV, ml	63.4 ± 20.0	78.4 ± 19.7	<0.01
SVI, ml/m^2	34 ± 9	45 ± 14	<0.01
PVR, Wood units	8.4 ± 5.1	4.1 ± 3	<0.01
PP, mm Hg	44 ± 16	32 ± 10	<0.01
SV/PP, ml/mm Hg	1.8 ± 1.1	3.0 ± 1.3	<0.001
Pulmonary arterial oxygen saturation, %	65 ± 6	71 ± 4	<0.001
Functional status			
6MWD, m	343 ± 131	395 ± 99	<0.001
Borg dyspnea score	4 ± 2.5	2.8 ± 1.7	<0.02
WHO functional class I/II/III/IV, %	0/35/65/0	4/57/39/0	<0.05

Definition of abbreviations: CI = cardiac index; CO = cardiac output; mPAP = mean pulmonary arterial pressure; 6MWD = 6-minute-walk distance; NS = not significant; PCWP = pulmonary capillary wedge pressure; PP = pulmonary pulse pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SV/PP = stroke volume/pulse pressure; SV = stroke volume; SVI = stroke volume index; WHO = World Health Organization.
Data are mean ± SD (n = 24 for each parameter).
WHO functional class data were not available for one subject at baseline.

pulmonary arterial oxygen saturation (Table 2). Serum NT-proBNP decreased significantly from 1,578 ± 2,647 pg/ml at baseline to 647 ± 1,127 pg/ml at 36 weeks ($P < 0.05$).

Assessment of Functional Status and Health-related Quality of Life

As shown in Table 2, there was a significant improvement in WHO FC, with 0, 35, and 65% patients in WHO FCs I, II, and III, respectively, at baseline compared with 4, 57, and 39%, respectively, at 36 weeks. The 6MWD improved from 343 ± 131 m at baseline to 395 ± 99 m at 36 weeks ($P < 0.001$). The Borg dyspnea score improved from 4 ± 2.5 at baseline to 2.8 ± 1.7 at 36 weeks ($P < 0.02$). Improvements in health-related quality of life (HRQOL) are reported in Table E3 and the online supplement text.

Assessment of Right Ventricular Function

Aside from the changes in RV mass reported above, several improvements in ventricular size and function (Table 3) are noteworthy. Whereas there was no change in RV end-diastolic volume, there was a significant reduction in RV end-systolic volume at 36 weeks, which is consistent with a significant improvement in RV ejection fraction (RVEF) from 46 ± 10% at baseline to 57 ± 9% at Week 36 (Figure 2B). Both left ventricular (LV) end-diastolic and LV end-systolic volumes increased significantly, however, with a more substantial increase in LV end-diastolic volume, consistent with improved venous return and LVSV. Ventricular mass index decreased from 0.32 (IQR, 0.29–0.45) to 0.27 (IQR, 0.23–0.33) ($P < 0.05$). There was a trend for improvement in LV mass, consistent with improved filling of the left ventricle (Table 3).

M-mode echocardiography was not performed in 5 patients, so TAPSE was assessed in only 19 patients who had paired measurements at baseline and 36 weeks. TAPSE improved steadily from baseline to Week 16 (data not shown) and Week 36, from 1.65 ± 0.11 cm at baseline to 2.2 ± 0.12 cm at Week 36 (Figure 3) ($P < 0.0001$).

Discussion

In this open-label, multicenter trial, an up-front 36-week therapy combining an endothelin receptor antagonist (ambrisentan) with a phosphodiesterase inhibitor (tadalafil) in patients with SSc-PAH was well tolerated and resulted in significant improvement in functional status, hemodynamics, and RV remodeling and performance.

SSc-PAH, which 10–12% of patients with SSc have (16, 17), is one of the most common causes of PAH in registries in the Western world (18, 19) and is a leading cause of death in SSc (20). Despite recent advances in targeted therapies for IPAH, in large series patients with SSc-PAH are notoriously less responsive than patients with IPAH to modern PAH therapy (6, 21). Although there has been a paucity of trials targeted specifically at patients with SSc-PAH, subgroup analyses of all major PAH trials have shown discrepant results regarding therapeutic responses in comparisons of patients with IPAH with patients with SSc-PAH. For instance, whereas treatment with bosentan, the first approved oral therapy for PAH, improved WHO FC, 6MWD, time to clinical worsening, and hemodynamics in PAH, there was a nonsignificant trend toward improvement in 6MWD in patients treated with bosentan compared with placebo in a subgroup analysis of patients with SSc-PAH (7). In the Sildenafil Use in Pulmonary Arterial Hypertension trial, treatment with sildenafil, the phosphodiesterase type 5 inhibitor, demonstrated improvement in 6MWD and hemodynamics in various forms of PAH (8). In a *post hoc* analysis of the subjects with connective tissue disease–associated PAH (CTD-PAH), which included 55% of patients with SSc, there were improvements in 6MWD, WHO FC, and hemodynamics after 12 weeks of therapy with sildenafil 20 mg three times daily; however, no further improvements were noted in subjects receiving sildenafil at either 40 or 80 mg three times daily (22). Intravenous epoprostenol, arguably the most effective treatment for IPAH, results in only modest improvement in exercise and hemodynamics in SSc-PAH and is associated with poor long-term survival (23). In considering combination therapies, the Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil investigators demonstrated that adding sildenafil at 80 mg three times daily to intravenous epoprostenol improved exercise capacity, time to clinical worsening, quality of life, and hemodynamics in patients with PAH, but mainly in patients with IPAH (24). In a recent phase III clinical trial of riociguat, a

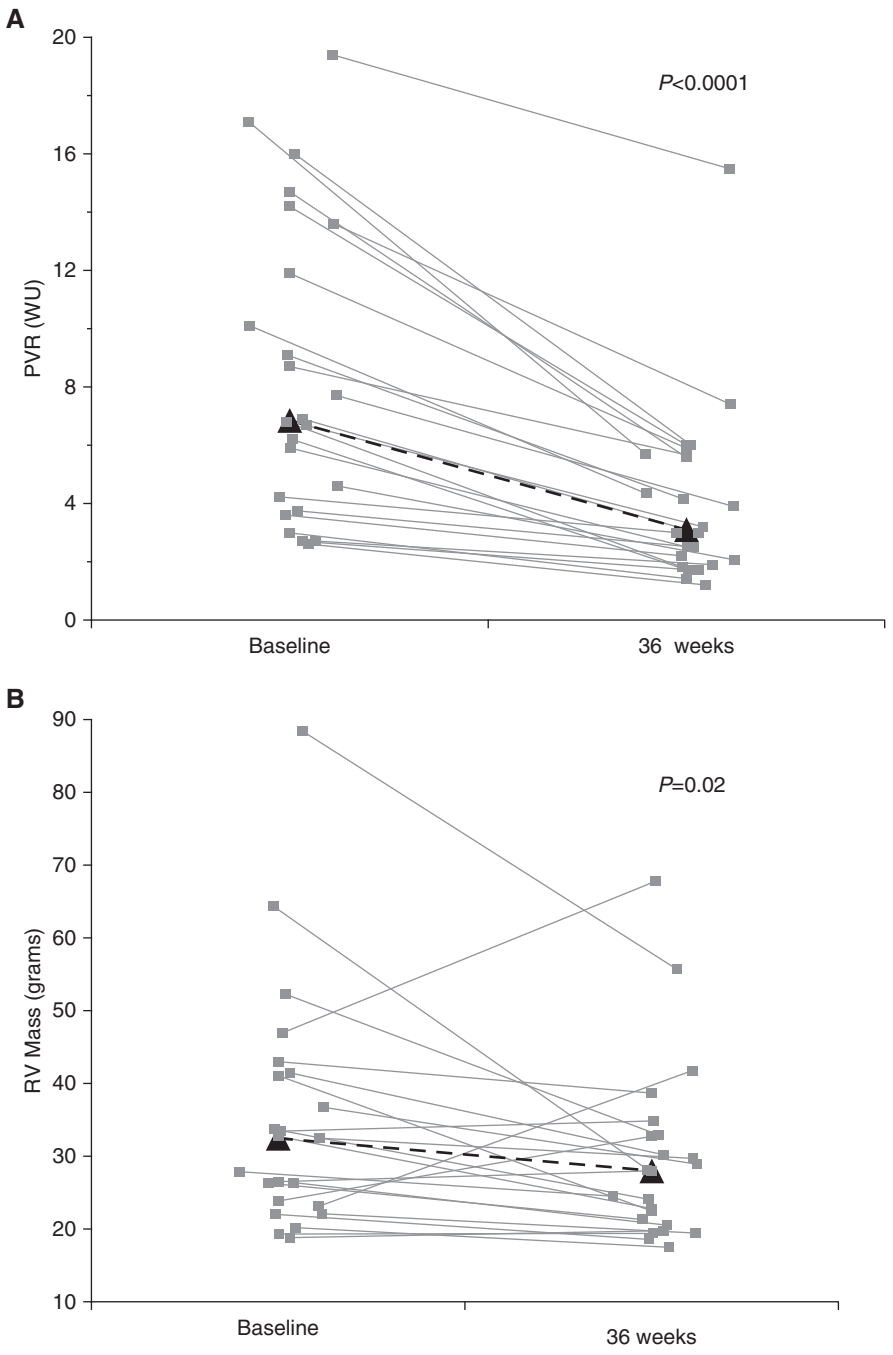

Figure 1. Effect of combination therapy on change in pulmonary vascular resistance (PVR) (*A*) and right ventricular (RV) mass (*B*) from baseline to 36 weeks. Data for 24 individual patients are shown. The *dashed line* represents the change in median values for the group. WU = Wood units.

stimulator of soluble guanylate cyclase, a key enzyme in the nitric oxide signaling pathway, the 6MWD improvement (a mean of 30 m in the 2.5-mg maximum dose group compared with a decrease of a mean of 6 m in the placebo group) in patients with PAH was consistent across several subgroups, including patients with CTD-PAH (~25% of the study population, although the proportion of patients with SSc was not reported).

The choice of primary endpoints (PVR and RV mass) over the traditional 6MWD was motivated by the fact that the 6MWD had not been specifically validated in SSc-PAH. In addition, its use has been questioned for these patients (25), considering that they are often heavily burdened with musculoskeletal impairment. Also, the minimally important difference in 6MWD, though recently defined in a large cohort of patients with PAH (treated with a phosphodiesterase 5 inhibitor) in the Pulmonary Arterial Hypertension and Response to Tadalafil trial (26), has not been validated in patients with SSc-PAH. Changes in hemodynamics between baseline and end of treatment have been used in a number of randomized clinical trials (RCTs). They may be particularly valuable because hemodynamic measurements such as RAP, CI, and PVR have significant prognostic value. In the present study, there was a 55% decrease in PVR (primary endpoint), which was accompanied by a 27% increase in CI and a 28% reduction in mPAP (both secondary endpoints). This compares very favorably with a pooled weighted analysis of 16 RCTs including a total of 2,353 patients (with the vast majority having PAH, including up to 30% patients with CTD-PAH) who were followed for 16 ± 10 weeks. Hemodynamic values, available at both baseline and follow-up, revealed a mean increase of 12 ± 6% and a mean reduction of 25 ± 8% for CI and PVR, respectively (27). In an RCT that included exclusively patients with SSc-PAH treated with continuous intravenous infusion of prostacyclin for 12 weeks, the reduction in PVR was 43% (23). In another trial of patients with CTD-PAH (SSc, lupus, and mixed CTD), who were treated with continuous subcutaneous infusion of the prostacyclin analog treprostinil, the decrease in PVR was only 20% and the increase in CI was 9% (28). Similarly, the change in mPAP in our trial was a 28% reduction, compared with an overall 7 ± 4% decrease in the metaanalysis and in contrast to 12% and 4% decreases in the studies by Badesch and coworkers (29) and Oudiz and colleagues (28), respectively. However, such comparisons should be interpreted with caution, considering the lack of a comparator control group in our study.

The SV/PP ratio, a simple hemodynamic parameter, was significantly improved after 36 weeks of therapy. It is an accepted estimate of the total arterial compliance of the pulmonary vascular tree (30) that reflects the ability of the vascular bed to dilate in response to RV contraction and then recoil during diastole.

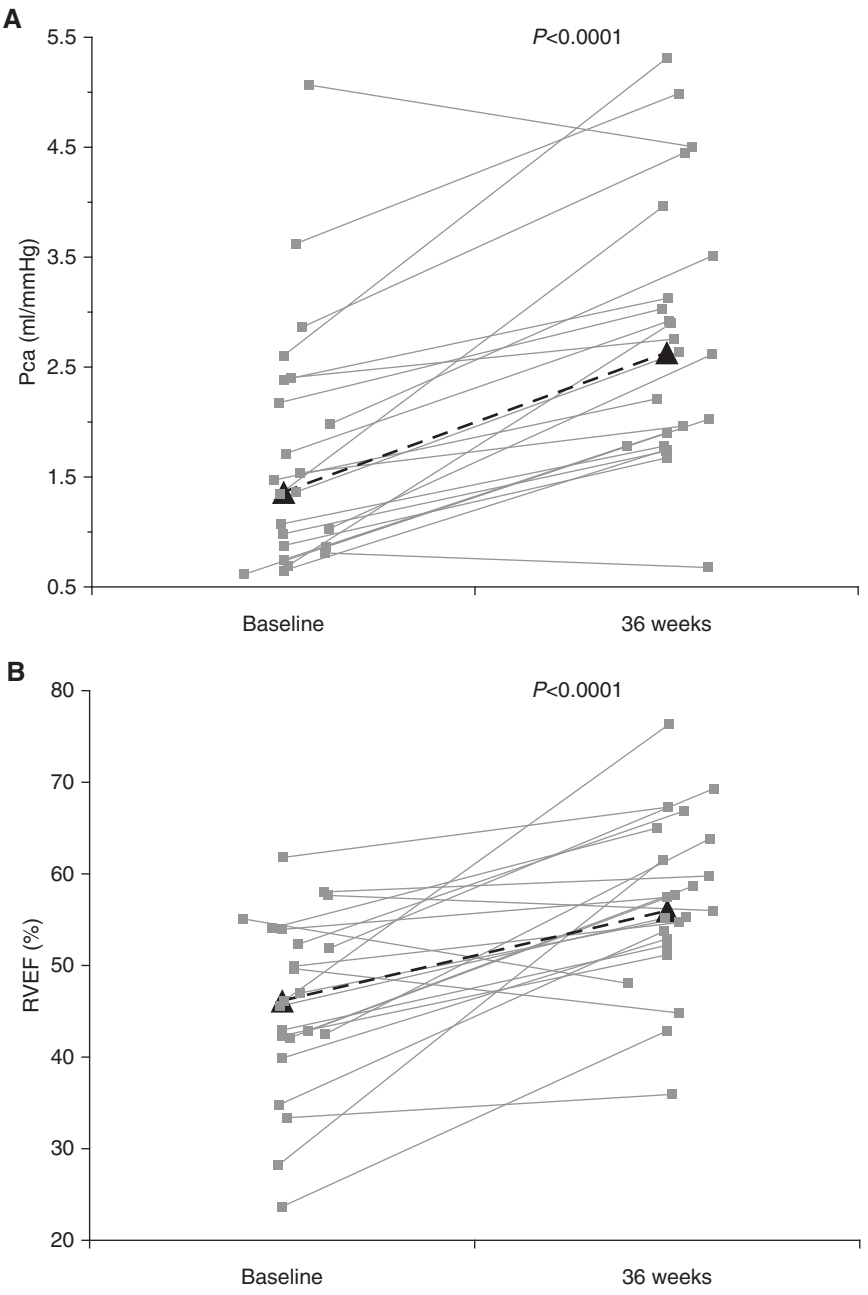

Figure 2. Effect of combination therapy on pulmonary vascular compliance (Pca) (*A*) and right ventricular ejection fraction (RVEF) (*B*) from baseline to 36 weeks. *Dashed line* represents the change in median values for the group.

Whereas PVR represents mean flow and resistance at the distal end of the pulmonary vascular tree, the SV/PP ratio is a lumped parameter that also takes into account the effects of pulsatile blood flow. The SV/PP ratio is a strong predictor of survival in both IPAH (31) and SSc-PAH (12), as well as in patients with chronic heart failure (32). It is likely that the estimation of pulmonary arterial compliance based on SV and PP is influenced by both cardiac dysfunction and increased peripheral PVR (30). Although several groups have shown that PVR and the SV/PP ratio are tightly and inversely related (33, 34), decreased pulmonary arterial compliance and distensibility may represent early pulmonary hypertensive disease (33, 35), and therefore most patients with PAH present at a stage at which their SV/PP ratio is well beyond the inflection curve of the resistance–compliance inverse relationship. In that context, it is noteworthy that SV/PP ratio improved from a mean of 1.8 ml/mm Hg at baseline to 3.0 ml/mm Hg (67% improvement) at Week 36 of therapy in the present study, an improvement that is substantially greater than that previously estimated on the basis of the results of three large PAH therapeutic trials (34).

Changes in CMR imaging values with therapy were all consistent with an improvement in pulmonary vascular load and RV function. There was a significant reduction in RV end-diastolic mass (a primary endpoint) (Figure 1B) and in RV mass index (Table 3). This was most likely secondary to a decrease in pulmonary vascular load (i.e., PVR) and subsequent de-remodeling of the RV. The Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension study was the only previous trial in which investigators used RV mass as a primary endpoint (11). In that study, sildenafil, but not bosentan, added to conventional treatment over 16 weeks reduced RV mass and improved cardiac function and exercise capacity in patients with PAH and WHO FC III symptoms. Although adaptive versus maladaptive RV hypertrophy remains a subject of controversy, the reduction in RV mass in parallel with functional and hemodynamic improvement, as well as improvement in cardiac function (by hemodynamics and CMR imaging) combined with a significant reduction in serum NT-proBNP, strongly suggests that RV de-remodeling was most likely the direct result of decreased pulmonary vascular load.

RVEF improved significantly with therapy from 46% at baseline to 57% at Week 36 (Figure 2B), which also indicates that one or several factors that affect RVEF, such as preload, afterload, contractility, and ventricular synchrony (36), improved after 36 weeks of therapy. This average 11% absolute improvement in RVEF is particularly relevant, considering an estimated meaningful treatment effect of 3–5% in cardiac CMR imaging–based RCTs (37) and in light of a recent study demonstrating that stability and/or improvement in RVEF by CMR imaging after therapy indicated better survival than decreased RVEF after therapy in a large cohort of patients with PAH (38). It is

Table 3. Changes in Cardiac Magnetic Resonance Imaging Parameters from Baseline to 36 Weeks

Variable	Baseline	36 wk	*P* Value
RVED mass, g	32.5 (23.2–41.4)	28.0 (20.6–32.9)	0.02
RV mass index, g/m^2	17.2 (13.4–27.3)	15.4 (11.7–20.3)	0.02
RVED volume, ml	151.2 (138.4–177.4)	146.4 (120.5–165.4)	0.3
RVES volume, ml	82.1 (65.6–97.7)	55.8 (49.4–79.2)	0.001
LVED volume, ml	114.0 (84.8–130.2)	135.3 (112.4–160.1)	<0.0001
LVES volume, ml	37.7 (30.1–50.2)	49.8 (41.4–60.6)	0.01
LV mass, g	88.3 (71.3–102.6)	97.2 (75.0–107.8)	0.1
LV mass/BSA, g/m^2	46.5 (42.8–58.1)	51.1 (41.7–65.9)	0.1
VMI	0.32 (0.29–0.45)	0.27 (0.23–0.33)	0.02

Definition of abbreviations: BSA = body surface area; LV = left ventricular; LVED = left ventricular end diastolic; LVES = left ventricular end systolic; RV = right ventricular; RVED = right ventricular end diastolic; RVES = right ventricular end systolic; VMI = ventricular mass index.
Paired cardiac magnetic resonance imaging data are expressed as median (interquartile range) and were obtained for 23 patients.

noteworthy that in the latter study, the average improvement in RVEF was only 3% in survivors (compared with a decrease of 9% in nonsurvivors). Other significant improvements in response to therapy in our study included a reduction in ventricular mass index, a parameter that we and others have shown to correlate with mPAP in patients with PAH (39, 40) and to predict survival in patients with SSc-PAH (40).

Although TAPSE is a parameter recognized to predict RV function and survival, its value as an endpoint susceptible to change with therapy has never been tested in prospective trials. TAPSE, a simple echocardiographic measure of global RV performance, has the advantage of being independent from the RV complex geometry, although it is dependent on load. TAPSE measurements correlated with RHC parameters and predicted survival in a general population of patients with PAH (14) and in patients with SSc-PAH (41). In the present study, there was an impressive, gradual improvement in TAPSE at 16 weeks (data not shown) and 36 weeks of therapy, from 1.6 cm at baseline to 2.2 cm at 36 weeks. There was very high interreader and intrareader agreement (0.99, respectively) for the two readers (T.S. and C.P.), who were blinded to the study timing (baseline, 16 wk, or 36 wk) and subject. Also of note is that, whereas the baseline measurement for the cohort (1.6 cm) was somewhat below the medians of 1.8 cm and 1.7 cm defined as the cutoff values predicting poor survival for PAH in general (14) and SSc-PAH (41), respectively, the post-treatment value (2.2 cm) for the group was well above these cutoff values, again suggesting general improvement in RV function consistent with the overall hemodynamic and CMR imaging improvements for the cohort.

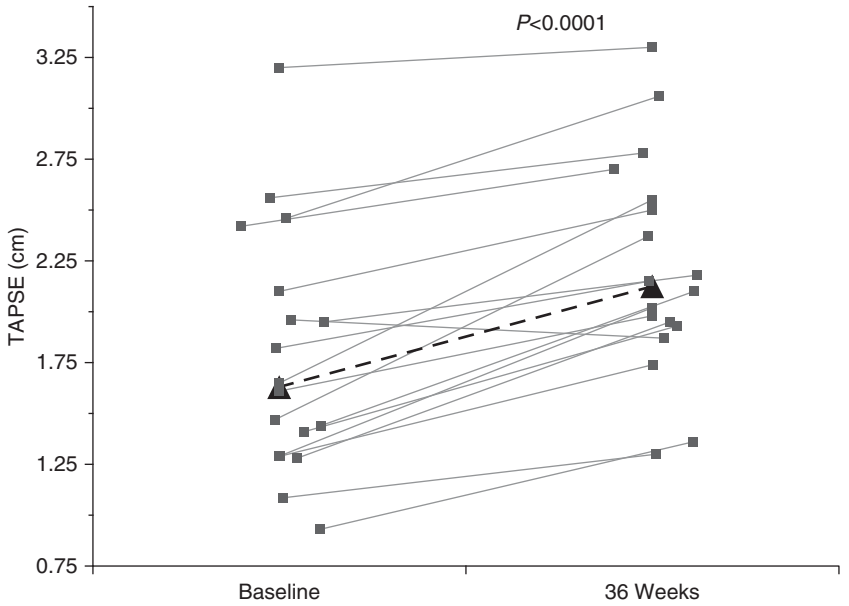

Figure 3. Effect of combination therapy on tricuspid annular plane systolic excursion (TAPSE) from baseline to 36 weeks. Data are shown for 19 patients who had paired data. *Dashed line* represents the change in mean values for the group.

Regarding HRQOL, combination therapy resulted in improvements in all domains of the SF-36, although only changes in three (physical functioning, vitality, and mental health) of the eight domains were statistically significant when we compared baseline values with those at 36-week follow-up. Importantly, changes in the SF-36 Mental Component Score and Physical Component Score were both statistically and clinically significant within this cohort. Many randomized controlled trials have included HRQOL as a secondary endpoint; however, as shown in a recent meta-analysis of HRQOL outcomes in PAH trials, few have demonstrated consistent statistically significant improvements in various HRQOL measures such as the SF-36, and none have demonstrated clinically relevant improvements (42). Thus, these findings suggest that the effect of up-front combination therapy on HRQOL may differ from initial monotherapy and may lead to clinically important improvements in HRQOL in patients with SSc-PAH.

Limitations

There are several limitations to this study. The therapeutic effect of combined therapy with ambrisentan and tadalafil for patients with SSc-PAH should be considered with caution because this was an open-label study without a placebo control group. It also involved a relatively small number of patients and thus is vulnerable to confounding natural history with treatment effects. However, there was concordance between the functional, hemodynamic, serum, and imaging biomarkers, which indicates that the therapeutic effect was real in a population that has previously shown

relatively limited response to PAH monotherapy. Importantly, the results of this study are in line with and complementary to the recently published data from a randomized, double-blind, multicenter study of first-line combination therapy (AMBrIsentan and Tadalafil in patients with pulmonary arterial hypertension [AMBITION]; registered with clinicaltrials.gov as NCT01178073), which revealed that up-front combination therapy was superior to monotherapy on the basis of the primary endpoint of time to clinical failure, including the subgroup of patients with CTD-PAH (43). The present trial is complementary to the AMBITION study, in which researchers neither included RV imaging nor assessed changes in hemodynamics. However, our data may not be extrapolated to groups other than patients with SSc-PAH.

That hemodynamic measurements were performed at four different institutions and may not have been standardized is another limitation; however, this limitation is common to most multicenter trials. In addition, although interpretation and analysis of echocardiographic and CMR imaging were centralized, acquisition of the images was performed by different operators with varied equipment.

There were very few missing data. All 24 patients underwent RHC at baseline and at 36 weeks. One patient had no baseline CMR imaging assessment, owing to claustrophobia; therefore, CMR imaging paired data were analyzed for 23 of 24 patients. Otherwise, analysis of the primary endpoints was nearly complete. Secondary endpoint data were obtained in nearly all patients. However, TAPSE measurements were limited to 19 paired measurements at baseline and 36 weeks because of technical difficulties with M-mode image capture.

In summary, this study demonstrates that up-front combination therapy with ambrisentan and tadalafil was well tolerated and effective in patients with SSc-PAH and significantly improved PAH as assessed by changes in functional status, hemodynamics, and RV structure and function at 36 weeks. Importantly, using a prospective study design, we identified hemodynamic (e.g., SV/PP ratio) and imaging (e.g., RVEF, RV mass, TAPSE) biomarkers that can potentially be used in larger future clinical trial trials to assess therapeutic effects on RV function and RV–pulmonary vascular coupling. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgments: The authors are indebted to the research coordinators at all four sites for their restless effort: Val Scotland at Stanford University, Katherine Zak of The Cleveland Clinic, and Jacqueline Quivers and Megha Sharma at the University of Texas Southwestern Medical Center. The authors also acknowledge the patients with SSc-PAH for their committed time throughout these studies; the Scleroderma Center at Johns Hopkins University; and Drs. Laura Hummers and Fredrick Wigley, who referred their patients.

References

1. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, *et al*. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013;62 (25 Suppl):D42–D50.
2. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, *et al*. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2013;62(25 Suppl):D34–D41. [Published erratum appears in *J Am Coll Cardiol* 2014;63:746.]
3. Fisher MR, Mathai SC, Champion HC, Girgis RE, Housten-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.
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. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier JF, Chabot F, *et al*. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;173:1023–1030.
6. Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, Miller DP, Nicolls MR, Zamanian RT. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest* 2010; 138:1383–1394.
7. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, *et al*. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896–903.
8. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, *et al*.; Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148–2157.
9. Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, *et al*.; Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies (ARIES) Group. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008;117: 3010–3019.
10. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, Naeije R, Newman J, Oudiz RJ, Provencher S, *et al*. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. *J Am Coll Cardiol* 2013;62(25 Suppl):D22–D33.
11. Wilkins MR, Paul GA, Strange JW, Tunariu N, Gin-Sing W, Banya WA, Westwood MA, Stefanidis A, Ng LL, Pennell DJ, *et al*. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. *Am J Respir Crit Care Med* 2005;171:1292–1297.
12. Campo A, Mathai SC, Le Pavec J, Zaiman AL, Hummers LK, Boyce D, Housten T, Champion HC, Lechtzin N, Wigley FM, *et al*. Hemodynamic predictors of survival in scleroderma-related pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2010;182:252–260.
13. Gashouta MA, Corona-Villalobos CP, Mathai SC, Damico RL, Kolb TM, Zimmerman S, Girgis RE, Minai OA, Zamanian RT, Torres F, *et al*. Impact of initial combination therapy on hemodynamics and right ventricular mass in systemic sclerosis-associated pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2014;189(Meeting Abstracts):A6678.
14. Forfia PR, Fisher MR, Mathai SC, Housten-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.
15. Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, *et al*.; Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) Study Group. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009;119:2894–2903.
16. Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, Tiev K, Cappelli S, Diot E, Vacca A, *et al*. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. *J Rheumatol* 2010;37:2290–2298.

17. Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, Kahan A, Cabane J, Francès C, Launay D, *et al*. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. *Arthritis Rheum* 2005;52:3792–3800.
18. Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, Capener D, Sephton P, Hamilton N, Armstrong IJ, *et al*. ASPIRE registry: assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre. *Eur Respir J* 2012;39:945–955.
19. Badesch DB, Raskob GE, Elliott CG, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Turner M, *et al*. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 2010;137:376–387.
20. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972–2002. *Ann Rheum Dis* 2007;66:940–944.
21. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, Vrapi 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.
22. Badesch DB, Hill NS, Burgess G, Rubin LJ, Barst RJ, Galiè N, Simonneau G; SUPER Study Group. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. *J Rheumatol* 2007;34:2417–2422.
23. Badesch DB, McGoon MD, Barst RJ, Tapson VF, Rubin LJ, Wigley FM, Kral KM, Raphiou IH, Crater GD. Longterm survival among patients with scleroderma-associated pulmonary arterial hypertension treated with intravenous epoprostenol. *J Rheumatol* 2009;36: 2244–2249.
24. Simonneau G, Rubin LJ, Galiè N, Barst RJ, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, *et al*.; PACES Study Group. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008;149:521–530.
25. Avouac J, Kowal-Bielecka O, Pittrow D, Huscher D, Behrens F, Denton CP, Foeldvari I, Humbert M, Matucci-Cerinic M, Nash P, *et al*.; EPOSS Group. Validation of the 6 min walk test according to the OMERACT filter: a systematic literature review by the EPOSS-OMERACT group. *Ann Rheum Dis* 2010;69:1360–1363.
26. Mathai SC, Puhan MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2012;186:428–433.
27. Savarese G, Musella F, D'Amore C, Losco T, Marciano C, Gargiulo P, Rengo G, Dellegrottaglie S, Bossone E, Leosco D, *et al*. Haemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension. *Eur Respir J* 2013;42:414–424.
28. Oudiz RJ, Schilz RJ, Barst RJ, Galié N, Rich S, Rubin LJ, Simonneau G; Treprostinil Study Group. Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004;126:420–427.
29. 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: a randomized, controlled trial. *Ann Intern Med* 2000;132:425–434.
30. Lankhaar JW, Westerhof N, Faes TJ, Marques KM, 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.
31. 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.
32. Pellegrini P, Rossi A, Pasotti M, Raineri C, Cicoira M, Bonapace S, Dini FL, Temporelli PL, Vassanelli C, Vanderpool R, *et al*. Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. *Chest* 2014;145:1064–1070.
33. Lankhaar JW, Westerhof N, Faes TJ, 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.
34. Tedford RJ, Hassoun PM, Mathai SC, Girgis RE, Russell SD, Thiemann DR, Cingolani OH, Mudd JO, Borlaug BA, Redfield MM, *et al*. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. *Circulation* 2012;125:289–297.
35. 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.
36. Vonk Noordegraaf A, Haddad F, Bogaard HJ, Hassoun PM. Noninvasive imaging in the assessment of the cardiopulmonary vascular unit. *Circulation* 2015;131:899–913.
37. Bradlow WM, Hughes ML, Keenan NG, Bucciarelli-Ducci C, Assomull R, Gibbs JS, Mohiaddin RH. Measuring the heart in pulmonary arterial hypertension (PAH): implications for trial study size. *J Magn Reson Imaging* 2010;31:117–124.
38. van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A, Marques KM, Westerhof N, Vonk-Noordegraaf A. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol* 2011;58:2511–2519.
39. Vogel-Claussen J, Shehata ML, Lossnitzer D, Skrok J, Singh S, Boyce D, Lechtzin N, Girgis RE, Mathai SC, Lima JA, *et al*. Increased right ventricular septomarginal trabeculation mass is a novel marker for pulmonary hypertension: comparison with ventricular mass index and right ventricular mass. *Invest Radiol* 2011;46: 567–575.
40. Hagger D, Condliffe R, Woodhouse N, Elliot CA, Armstrong IJ, Davies C, Hill C, Akil M, Wild JM, Kiely DG. Ventricular mass index correlates with pulmonary artery pressure and predicts survival in suspected systemic sclerosis-associated pulmonary arterial hypertension. *Rheumatology (Oxford)* 2009;48:1137–1142.
41. Mathai SC, Sibley CT, Forfia PR, Mudd JO, Fisher MR, Tedford RJ, Lechtzin N, Boyce D, Hummers LK, Housten T, *et al*. Tricuspid annular plane systolic excursion is a robust outcome measure in systemic sclerosis-associated pulmonary arterial hypertension. *J Rheumatol* 2011;38:2410–2418.
42. Rival G, Lacasse Y, Martin S, Bonnet S, Provencher S. Effect of pulmonary arterial hypertension-specific therapies on health-related quality of life: a systematic review. *Chest* 2014;146:686–708.
43. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery JL, Grünig E, *et al*.; AMBITION Investigators. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med* 2015;373: 834–844.