

Pulmonary Arterial Hypertension In Systemic Sclerosis: Challenges In Diagnosis, Screening And Treatment

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Abstract: Systemic sclerosis (SSc) is a chronic, multisystem autoimmune disease characterized by vasculopathy, fibrosis and immune system activation. Pulmonary hypertension and interstitial lung disease account for majority of SSc-related deaths. Diagnosis of SSc-PAH can be challenging due to nonspecific clinical presentation which can lead to delayed diagnosis. Many screening algorithms have been developed to detect SSc-associated pulmonary arterial hypertension (SSc-PAH) in early stages. Currently used PAH-specific medications are largely extrapolated from IPAH studies due to smaller number of patients with SSc-PAH. In this review, we discuss the current state of knowledge in epidemiology and risk factors for development of SSc-PAH, and challenges and potential solutions in the diagnosis, screening and management of SSc-PAH.

Keywords: scleroderma, pulmonary hypertension, screening

Introduction

Systemic sclerosis (SSc) is a chronic, multisystem autoimmune disease characterized by vasculopathy, fibrosis and immune system activation. SSc is clinically classified into two subsets based on the extent of skin involvement: 1) limited cutaneous SSc (lcSSc) with skin involvement restricted to distal limbs below elbow and knees with or without facial involvement and 2) diffuse cutaneous SSc (dcSSc) occurring proximally to the elbows and knees. The natural history of these two cutaneous subtypes differs, with diffuse SSc being characterized by more rapid onset of skin and internal organ involvement. Systemic manifestations of SSc includes the hallmark of puffy fingers or skin thickening, as well as myopathy, joint involvement and contractures, interstitial lung disease, gastrointestinal dysmotility and cardiac involvement. Vascular manifestations of SSc include Raynaud's phenomenon, digital ulcers, scleroderma renal crisis and pulmonary hypertension.

Systemic sclerosis has the highest case-specific mortality of the autoimmune diseases.¹ In modern day studies, pulmonary hypertension and interstitial lung disease account for majority of SSc-related deaths. In this review, we discuss the current state of knowledge in epidemiology and risk factors for development of SSc-associated pulmonary arterial hypertension (SSc-PAH), and challenges and potential solutions in the diagnosis, screening and management of SSc-PAH.

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Pulmonary Hypertension (PH) In SSc

Pulmonary hypertension (PH) is classified according to the 6th World Symposium on Pulmonary Hypertension, Nice, 2018² (Table 1). In SSc, PH can occur secondary to pulmonary vascular disease (WHO Group 1), SSc-interstitial lung disease (WHO Group 2) and cardiac involvement (WHO Group 3). This review will concentrate on SSc-PAH, or WHO Group 1 disease, as it is by far the most frequent PH manifestation in SSc. Until very recently, and pertaining to most of the literature presented in this review, SSc-PAH was considered as isolated pulmonary arterial hypertension defined as mean pulmonary artery pressure (mPAP) >25 mmHg on right heart

Table 1 Updated Clinical Classification of Pulmonary Hypertension in 6th World Symposium on Pulmonary Hypertension, Nice, 2018

<p>1. Pulmonary arterial hypertension (PAH)</p> <p>1.1 Idiopathic PAH</p> <p>1.2 Heritable PAH</p> <p>1.3 Drug- and toxin-induced PAH</p> <p>1.4 PAH associated with:</p> <p> 1.4.1 Connective tissue disease</p> <p> 1.4.2 HIV infection</p> <p> 1.4.3 Portal hypertension</p> <p> 1.4.4 Congenital heart disease</p> <p> 1.4.5 Schistosomiasis</p> <p>1.5 PAH long-term responders to calcium channel blockers</p> <p>1.6 PAH with overt features of venous/capillaries (PVOD/PCH)</p> <p>1.7 Persistent PH of the newborn syndrome</p>
<p>2. PH due to left heart disease</p> <p>2.1 PH due to left heart disease</p> <p>2.2 PH due to heart failure with reduced LVEF</p> <p>2.3 Valvular heart disease</p> <p>2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH</p>
<p>3. PH due to lung diseases and/or hypoxia</p> <p>3.1 Obstructive lung disease</p> <p>3.2 Restrictive lung disease</p> <p>3.3 Other lung disease with mixed restrictive/obstructive pattern</p> <p>3.4 Hypoxia without lung disease</p> <p>3.5 Developmental lung disorders</p>
<p>4. PH due to pulmonary artery obstructions</p> <p>4.1 Chronic thromboembolic PH</p> <p>4.2 Other pulmonary artery obstructions</p>
<p>5. PH with unclear and/or multifactorial mechanisms</p> <p>5.1 Hematological disorders</p> <p>5.2 Systemic and metabolic disorders</p> <p>5.3 Others</p> <p>5.4 Complex congenital heart disease</p>

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catheterization (RHC) and pulmonary capillary wedge pressure ≤ 15 mmHg without evidence of significant pulmonary parenchymal disease. The 6th World Symposium on Pulmonary Hypertension recently updated the definition of PAH to be mPAP >20 mmHg and included PVR ≥ 3 Woods based on recent data from normal subjects.²

Survival in SSc-PAH Lags Behind Other Causes of PAH

Survival in SSc-PAH remains below that of idiopathic PAH (IPAH) or PAH from other causes. Kawut et al called attention to this in 2003 when they published a 55% one-year survival in SSc-PAH patients compared to 84% one-year survival in other PAH patients.³ Today, with more therapy options available, survival has improved, but SSc-PAH survival continues to lag behind. Three-year survival of SSc-PAH in more recent publications reports 56–75%.^{4,5} In a recent US-based multicenter observational study of SSc-PAH patients, long-term survival (eight years) was 49%.⁵

Current PAH medications have been mainly studied in IPAH despite overall worse outcome with trifold higher risk of death and less response to PAH therapy in patients with SSc-PAH and potential differences in pathophysiology of these diseases. It is only in the last few years that multicenter clinical trials to evaluate medications in targeted SSc populations have been performed; with no results published at the time of this review article. These trials have faced challenges in enrollment due to the low frequency of SSc-PAH, and the need for stable PAH-related therapy at the time of trial initiation (Table 2).

Epidemiology of Systemic Sclerosis Associated Pulmonary Arterial Hypertension

In the literature, prevalence of SSc-PAH varies depending on the population studied, criteria used to define PAH and the method of choice for diagnosis: Right heart catheterization (RHC) vs echocardiography (ECHO). Prevalence of SSc-PAH was reported to range between 13 and 35% with ECHO and 8 and 12% with RHC.^{6–9} This difference could be explained by poor reliability of ECHO in estimating pulmonary arterial pressures. Importantly, the recent change in definition of PAH previously mentioned to mPAP >20 based on recent data from normal subjects, will assuredly increase the prevalence of SSc-PAH.¹⁰

In a French prospective multicenter cohort using the older criteria, the incidence of SSc-PAH was estimated as

Table 2 Ongoing Clinical Trials in Systemic Sclerosis-Related Pulmonary Arterial Hypertension and Pulmonary Arterial Hypertension with Planned Enrollment of Connective Tissue Disease-Related Pulmonary Arterial Hypertension as of August 2019

Trial ID	Trial Phase	Study Design	Intervention	Estimated Enrollment	Study Start Date
NCT02981082 ⁶⁵	1	Double-blind Placebo-controlled	Dimethyl fumarate	34	12/2016
NCT01086540 ⁶⁶	2	Double-blind Placebo-controlled	Rituximab	58	06/2011
NCT02682511 ⁶⁷	2	Double-blind Placebo-controlled	Ifetroban	34	01/2017
NCT03726398 ⁶⁸	2 and 3	Open label	Macitentan	26	09/2018
NCT03630211 ⁶⁹	2	Open label	Autologous stem cell transplant	8	07/2018
NCT02657356 ⁷⁰	3	Double-blind Placebo-controlled	Bordoxolonemethyl	200	10/2016
NCT03626688 ⁷¹	3	Double-blind Placebo-controlled	Ralinepag	700	08/2018
NCT03449524 ⁷²	2	Double-blind Placebo-controlled	CXA-10	96	08/2018

0.61 cases per 100 patient-years after an average follow-up of 41 months of SSc patients.⁴ Incidence was 1.25 cases per 100 patient-years in diffuse and 0.4 cases per 100 patient-years in limited subgroups.⁴

The Rationale for Screening in SSc-PAH

PAH occurs at a markedly higher rate in SSc compared to the general population. Prevalence estimates for PAH in SSc are 8–15%, depending on the series.^{6–9} In striking contrast, the prevalence of PAH is 15–52 cases per million, or 0.00005% in the general population.¹¹ Initial clinical manifestations of SSc-PAH are mostly nonspecific and include dyspnea, fatigue, and exercise intolerance. Historically, the majority of SSc-PAH patients presented at advanced stage, with diagnosis often delayed for more than two years from symptom onset,¹² likely related to the nonspecific nature of initial symptoms. It is well recognized that patients who have less severe disease at the time of diagnosis have a better survival rate both in SSc¹³ and idiopathic PAH. Studies have demonstrated that early PH-specific treatment may improve long-term outcomes in these patients.¹⁴ The combination of high prevalence, nonspecific early symptoms making diagnosis difficult, combined with proven benefit of early diagnosis and therapy provides strong rationale for a screening approach for PAH/PH in SSc patients. A small, but nicely reported study in France demonstrated the benefit of improved SSc-PAH-related survival when patients were diagnosed during a systematic PAH detection program compared to those diagnosed on symptoms alone.⁷ In summary, the above highlights the importance for rheumatologists to maintain a high index of suspicion to timely and appropriately screen SSc patients for this life-threatening complication.

Risk Factors for Developing PAH in SSc

Given the dismal prognosis of SSc-PAH and reported survival benefit with early treatment, early recognition, diagnosis and therapy intervention is key. Identification of risk factors could help clinicians to appropriately stratify the patients and closely monitor at-risk groups. To date, several clinical characteristics and serological markers have been proposed as risk factors associated with development of PAH in patients with SSc.

Clinical risk factors can be categorized as patient- and disease-specific factors. Older age at the time of SSc diagnosis and male gender are patient-specific factors that have been associated with higher risk of PAH development.^{15–17} Disease-specific risk factors include presence of calcinosis, gastroesophageal reflux disease, and digital ulcers, more severe Raynaud's phenomenon, increased number of telangiectasias, and decreased nailfold capillary density.^{16,18–20} Although it is promising that most of these disease-specific risk factors are microvascular complications of SSc as spectrum of a systemic progressive vasculopathy; they had inconsistent results between studies in literature and would benefit from validation in large cohorts.

Serological markers have long been investigated as markers of PAH development in SSc, and four primary SSc-related antibodies have been associated with increased risk of PAH. These antibodies include anti-centromere, anti-Th/To, anti-U1 ribonucleoprotein (RNP), and anti-U3 RNP.^{16,18} Anti-U3RNP and anti-Th/To antibodies can be difficult to obtain accurately through commercial testing, but both are associated with nucleolar staining on antinuclear antibody (ANA) test by indirect immunofluorescence. Therefore, it is reasonable to state that patients with one of these four antibodies or nucleolar pattern ANA

result should be carefully monitored for signs and symptoms of PAH, and undergo routine clinical screening.

Besides the proposed clinical and serological risk factors, there are two established predictors of SSc-PAH that were incorporated into clinical practice as screening strategies. First, a decline in diffusing capacity of lung for carbon monoxide (DL_{CO}) and a high forced vital capacity (FVC)/ DL_{CO} ratio ($FVC/DL_{CO} > 1.6$) have been shown to be strong predictors of PAH development.^{16,21} Second, the N-terminal pro-B-type natriuretic peptide (NT-proBNP) measure that is released from cardiac myocytes as a response to wall stress. Studies have shown that plasma NT-proBNP levels are higher in patients with PAH, correlate strongly with hemodynamic parameters and WHO class, and have a high positive predictive value of PAH.^{21–23} Screening strategies using DL_{CO} and NT-proBNP will be discussed in the screening section below.

Diagnosis Of Pulmonary Hypertension In SSc: Challenges And Solutions

Diagnosis of SSc-PAH is challenging for clinicians for several reasons. First, the patients with SSc-PAH present with nonspecific symptoms such as fatigue, exercise intolerance, and dyspnea, which could be from multiple potential causes in these patients. These etiologies include ILD, musculoskeletal involvement, cardiac involvement and deconditioning. PH in SSc could also be due to SSc-unrelated etiologies (such as, chronic hypoxic lung disease, chronic thromboembolic hypertension), which is critical to distinguish given the differences in prognosis and treatment. Therefore, it is important to have a high index of suspicion especially in at-risk populations and perform appropriate diagnostic work-up to accurately rule out other causes. Furthermore, SSc patients can have multifactorial PH due to combination of group 1 PAH, group 2 secondary to left heart disease, and group 3 secondary to ILD. Given distinct therapeutic implications, the dominant cause of PH should be concluded in these patients with multifactorial PH.

Another diagnostic challenge is pulmonary veno-occlusive disease (PVOD). PVOD has a similar, but often more acute clinical presentation combined with the hemodynamic characteristics to SSc-PAH. PVOD has a poor prognosis and worsens despite PH-specific treatment.²⁴ Interestingly, histological review of transplanted lung biopsies of 18 SSc-PH patients due to ILD revealed that 15 patients had concomitant PVOD pathology.²⁵ A

separate pathologic study reported four out of eight patients with SSc-PAH had PVOD.²⁶ These results suggest a high incidence of PVOD in patients PH due to ILD and potential contribution to prognosis in this population. Therefore, consideration of PVOD is helpful for accurate prognostication and to prompt early referral of these patients for lung transplantation evaluation.

Objective Testing

As mentioned earlier, the current gold standard technique for diagnosis of PH is RHC. However, RHC is an invasive test with associated complication risks and high costs, making it an inappropriate screening tool for PH. Additionally, it may not be available at every hospital due to lack of equipment or trained personnel. On the contrary, ECHO is a noninvasive, widely available, relatively low-cost tool that can be used for PH screening. However, it is not a definitive diagnostic test. This is in part due to its operator-dependent nature and indirect estimation of pulmonary arterial pressures (PAP) from right ventricular pressure (RVP) and tricuspid regurgitation velocity (TRV). TRV is a view-dependent measurement, and technically adequate signal may not be obtained due to body habitus and in cases of absent or severe TR.²⁷ In one study, ECHO estimation of PAP was possible in only 44% of patients with advanced lung disease.²⁸ Studies also show a wide range of variability in correlations between invasive and ECHO measurements of PH, especially in the presence of ILD.²⁸ These results highlight that ECHO only provides a probability of PH; therefore, results should be interpreted in the context of individual patients, and patients with high suspicion should be referred for RHC for definitive diagnosis.

Exercise ECHO

Studies suggest that abnormal increase in PA pressures with exercise in patients with SSc can be an early clue to PAH due to subclinical RV dysfunction in these cases, and exercise ECHO can be a helpful tool to detect these changes that are yet to develop at rest.²⁹ However, data regarding use of exercise ECHO is currently limited and more studies need to be performed to evaluate the usefulness of this noninvasive tool.

Screening of Pulmonary Hypertension in SSc: Challenges and Potential Solutions

Despite reported survival benefit of using a screening program in SSc patients, one of the challenges for PH

screening is physician nonadherence.⁷ A study done in the UK showed that only 34.7% of SSc patients received an ECHO and 53.1% had pulmonary function test (PFT) done in one year.³⁰ Potential reasons for the physician nonadherence was queried in a survey study performed in Australia and revealed cost of screening and concern for inability to interpret the results as contributory reasons.⁸ Around 40% of participants had reported requiring better guidelines, reminder system, and guideline simplification to screen more effectively.⁸ As the studies suggest, lack of consensus on which screening algorithm to use constitutes an important barrier for screening.

Consensus Recommendations

Four screening algorithms have been published recently and will be discussed below, highlighting the key differences (Figure 1). These include the consensus recommendations from European Society of Cardiology/European Respiratory Society (ESC/ERS), Australian Scleroderma Interest Group (ASIG), and American College of Chest Physicians/American Heart Association (ACCP/AHA), and the DETECT algorithm.

Both the ESC/ERS and ACCP/AHA guidelines recommend initial screening upon SSc diagnosis by ECHO with subsequent RHC if positive screen on ECHO.^{31,32} These guidelines are cognizant of the limitations of using ECHO as discussed above.

Comparatively, the ASIG algorithm incorporates NT-proBNP and PFT for initial screening with subsequent ECHO if initial screening is positive.³³ Positive findings to prompt ECHO referral on PFTs include if the DLCO <70% predicted and FVC/DLCO ≥ 1.8 , and/or NT-proBNP >210 pg/mL at initial screening. If ECHO returns high risk, then the patient is referred for RHC. If all testing is negative at baseline, then repeat NT-proBNP and PFT in one year and annually.³³

The DETECT Algorithm

The DETECT study targeted a high risk for PAH population, and enrolled 644 patients with DLCO predicted <60% from multiple countries in North America, Europe and Asia.³⁴ The subsequent DETECT algorithm identified a combination of clinical, laboratory, electrocardiographic parameters and PFT for initial screening with subsequent ECHO if high risk, and RHC if ECHO results are also high risk.³⁴ This set of variables are telangiectasia, NT-proBNP, serum urate, anti-centromere antibody, FVC/DLCO ratio, and right axis deviation on electrocardiogram. Based on

these variables, risk is calculated via web-based calculator and considered “high” if >300 (<http://detect-pah.com>). High risk patients are referred to ECHO and variables are incorporated into web calculator again, which gives risk points. If risk point is >35, then patient is referred to RHC.

The following limitations to use of DETECT algorithm should be noted: (1) online DETECT algorithm calculator is currently not accessible to US residents, (2) it has not been validated for use in SSc patients with DLCO $\geq 60\%$ predicted, and (3) it does not provide further recommendations if the initial screening or ECHO results are low risk.

In studies evaluating performance of these algorithms, sensitivity of the DETECT algorithm has shown to be 96–100%, but specificity was only 35.3–48%.^{34–36} Positive predictive value (PPV) of the DETECT algorithm was 35–68.6%, and negative predictive value (NPV) was 98–100%.^{34,35} Sensitivity of ASIG algorithm was similar to the DETECT algorithm in two different studies at 94.1–100%.^{35,37} However, ASIG algorithm had higher specificity at 54.5%, better PPV at 60–61.5% and similar NPV at 92.3–100%.³⁷ In these studies, ESC/ERS had the lowest sensitivity at 91.4–96.3%, specificity at 31.8–32.3%, PPV at 51.6–55.3% and NPV at 87.5–90.9%.^{35–37} Overall, the DETECT and ASIG algorithms performed better than ESC/ERS guideline (Table 3).

In addition to clinical performances, cost-effectiveness of these screening algorithms is an important area for further study. For instance, using ECHO in every asymptomatic patient at the first initial screening step in ESC/ERS algorithm may not be cost-effective. On the other hand, the DETECT algorithm uses non-ECHO variables, but includes PFT and laboratory tests which can be costly.

PAH Specific Management: Challenges and Potential Solutions

Medications currently used in SSc-PAH are mainly extrapolated from IPAH studies. Unlike IPAH, calcium channel blockers are not used for PAH specifically given the rarity of vasoreactivity in SSc-PAH (1%) and low probability to observe a sustained response.³⁸ However, this does not preclude the use of these medications for the management of Raynaud's phenomenon.

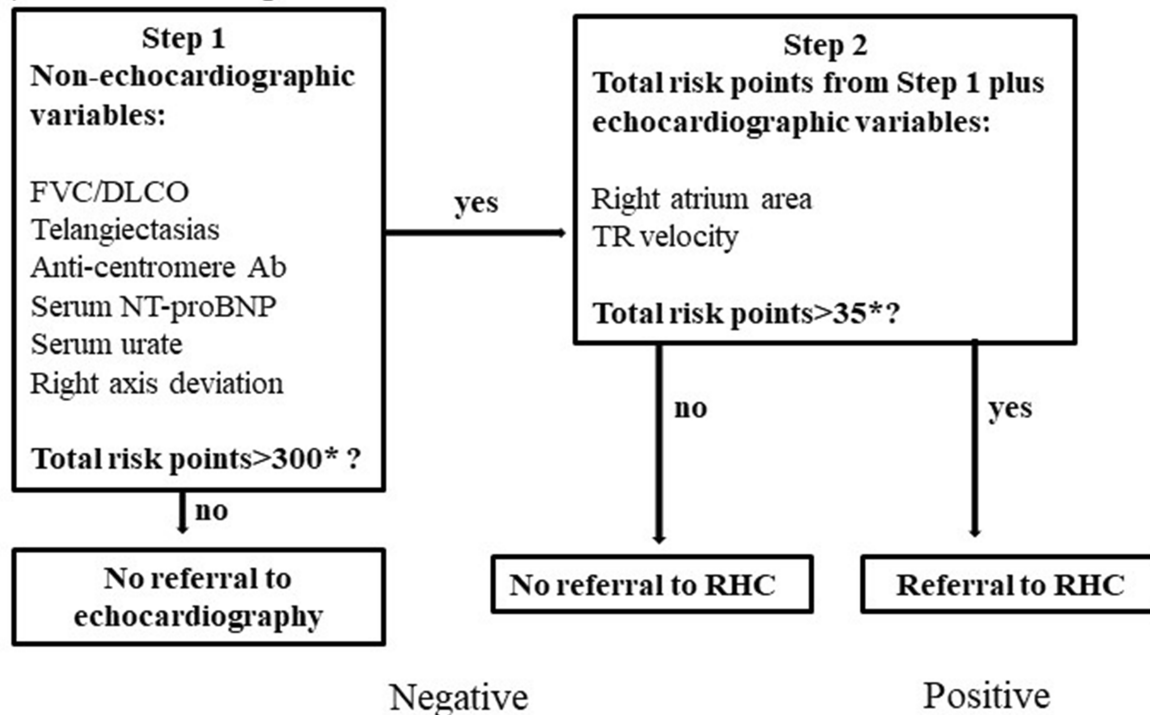
Anticoagulation use has long been discussed as an adjunct to SSc-PAH treatment given observations of in situ microvascular thrombosis in lung histology of these patients. An observational study done with SSc-PAH patients showed no

a) ESC/ESR guidelines

Positive screen on echocardiography (referral to RHC recommended)

- TRV > 3.4 m/s
- or TRV > 2.8 ≤ 3.4 m/s and symptoms (current dyspnea, current syncope/near syncope, presence of peripheral edema)
- or TRV ≤ 2.8 m/s and symptoms and additional suggestive echo variable (e.g. RA area > 18 cm²)

b) The DETECT algorithm



c) The ASIG algorithm

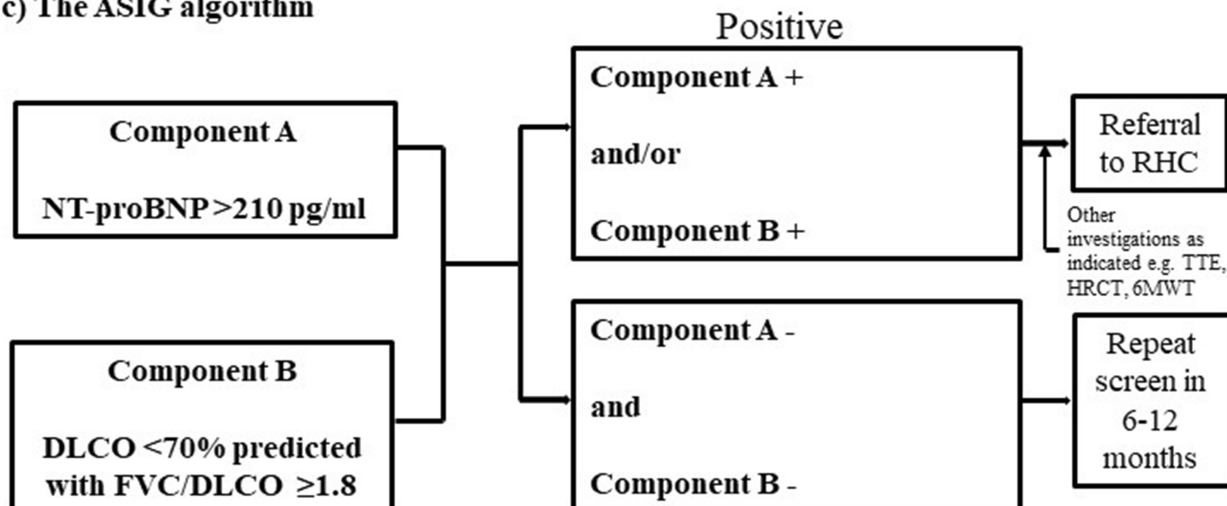


Figure 1 Comparison of SSc-PH screening algorithms.

Notes: These are consensus recommendations from European Society of Cardiology/European Respiratory Society (ESC/ERS; a), the DETECT algorithm (b), and Australian Scleroderma Interest Group (ASIG; c). Copyright © 2015. Springer Nature. Reproduced from Hao Y, Thakkar V, Stevens W, et al. A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis. *Arthritis Res Ther.* 2015;17:7.³⁵ Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.

Table 3 Comparison of Reported Performance Characteristics of most commonly used Consensus Recommendations for Screening of Pulmonary Hypertension in Patients with Systemic Sclerosis

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
ESC/ERS guidelines	71.0% ³⁴ 91.4% ³⁶ 94.1% ³⁷ 96.3% ³⁵	31.8% ³⁷ 32.3% ³⁵ 69.0% ³⁴ 85.7% ³⁶	40.0% ³⁴ 51.6% ³⁷ 55.3% ³⁵ 88.9% ³⁶	87.5% ³⁷ 89.0% ³⁴ 89.3% ³⁶ 90.9% ³⁵
The ASIG algorithm	94.1% ³⁷ 100% ³⁵	54.5% ^{35,37}	60.0% ³⁵ 61.5% ³⁷	92.3% ³⁷ 100% ³⁵
The DETECT algorithm	96.0% ³⁴ 100% ^{35,36}	35.3% ³⁵ 42.9% ³⁶ 48.0% ³⁴	35.0% ³⁴ 55.1% ³⁵ 68.6% ³⁶	98.0% ³⁴ 100% ^{35,36}

Abbreviations: ESC, European Society of Cardiology; ERS, European Respiratory Society; ASIG, Australian Scleroderma Interest Group.

associated survival benefit of warfarin exposure in these patients.³⁹ Therefore, given lack of reported survival benefit and high risk of gastrointestinal bleeding in SSc patients due to gastric antral vascular ectasia, telangiectasias or erosive esophagitis, anticoagulation is currently not recommended in these patients. However, evidence behind this recommendation is weak, and further studies need to be performed. Currently, an Australian multicenter, double-blind, placebo-controlled trial investigating apixaban use in SSc-PAH is ongoing which may shed light on anticoagulation use in these patients (ACTRN12614000418673).⁴⁰

Treatment regimens include four classes of medications which are endothelin-receptor antagonists (ERA), prostacyclin analogs (PA), phosphodiesterase-5 (PDE-5) inhibitors and guanylate cyclase stimulators (GCS). We will discuss evidence behind the use of each class here. All the currently registered ongoing trials in SSc-PAH and PH trials with planned CTD-PAH enrollment are summarized in Table 2.

Endothelin Receptor Antagonists

ERAs include nonselective endothelin-A and B receptor antagonists (bosentan and macitentan) and the endothelin-A specific receptor antagonist, ambrisentan. ERAs can be used alone or in combination with WHO class II and III patients, and in combination with parenteral therapy in WHO class IV patients. Evidence behind use of ERA alone is limited. A randomized clinical trial done in PH included a small group of SSc-PAH patients (N=44) and subgroup analysis showed stabilization of six minute walk distance (6MWD) in these patients treated with initial bosentan therapy compared to placebo.^{41–44} Following this result, nonselective cohort studies looking at bosentan monotherapy in SSc-PAH patients showed

improvement of functional class, 6MWD and hemodynamics after an average of 3–6 months of use and then stabilization of these measures after nine months to one year, which was likely due to the progressive nature of disease.^{44–46}

Data on ambrisentan or macitentan use as monotherapy specifically in SSc-PAH is restricted to two primary studies. First, a single-center 24-week open-label study of ambrisentan in patients with exercise-induced SSc-PAH showed significant improvement in hemodynamics and 6MWD.⁴⁷ The randomized, double-blind, placebo-controlled trial of macitentan (SERAPHIN) showed reduction in mortality and morbidity with macitentan use in patients with PAH.⁴⁸ The trial included 70 and 82 CTD-PAH patients in drug and placebo arms, respectively; however, no subgroup analysis was done to report outcomes in these patients.

Phosphodiesterase-5 Inhibitors

PDE5 inhibitors include oral sildenafil, tadalafil and vardenafil. To our knowledge, no studies have been done on the use of tadalafil and vardenafil as monotherapy in SSc-PAH. Data on sildenafil use specific to SSc-PAH is minimal. An open label, uncontrolled study of sildenafil from India showed improvement in hemodynamic measurements and 6MWD in three months in 17 patients with SSc-PAH.⁴⁹ Post hoc, subgroup analysis of double-blind, placebo-controlled SUPER-1 trial showed improvement in exercise capacity, hemodynamics and functional class with 12 weeks of sildenafil use in patients with CTD-PAH (38 patients with SSc-PAH).⁵⁰

Combination Therapy of ERA and PDE5 Inhibitors

Given loss of clinical improvement after a variable period of time on bosentan monotherapy, one option is adding another

agent to bosentan. In a retrospective study including patients with SSc-PAH and IPAH, addition of sildenafil to bosentan monotherapy in patients with clinical deterioration was associated with improvement in functional class and 6MWD in IPAH, but not in SSc-PAH patients. There were higher rates of liver toxicity and mortality in the SSc-PAH group.⁵¹ It should be noted that sildenafil and bosentan interact, leading to increased bosentan levels and reduction in sildenafil levels.

Studies also investigated outcomes with combination of ERA and PDE5 inhibitors started at different time points of the disease course. An open-label clinical trial of ambrisentan and tadalafil upfront combination therapy showed significant improvement in hemodynamics (reduction in PVR by 55% and RV mass by 14%), functional class, Borg dyspnea score and quality of life of patients with SSc-PAH.⁵² Similarly, subgroup analysis of the AMBITION trial examined the effect of upfront combination ambrisentan-tadalafil treatment versus monotherapy of either agent on risk of clinical failure, and change in NT-proBNP and 6MWD in SSc-PAH patients.⁵³ It showed lower clinical risk (21% vs 40%) as well as greater improvement in NT-proBNP and 6MWD in combination group compared to pooled monotherapy. A retrospective analysis of SSc-PAH patients from the PHAROS registry also showed that patients with initial treatment of ERA alone had increased risk of clinical worsening than patients on combination PDE5 inhibitor and ERA or ERA alone.⁵⁴ Apart from improvements in functional and quality of life measures with combination therapy, recently published retrospective study of Spanish nationwide SSc-PAH cohort examined survival rates in patients treated with monotherapy (ERA or PDE5 alone), and upfront (initiation of drugs within <12 weeks of each other) and sequential (initiation of drugs \geq 12 weeks apart from each other) combination therapy. The study showed higher survival rates in patients treated with upfront and sequential combination therapy than monotherapy; however, sequential combination therapy had higher survival benefit in one- (95.8% vs 94.1% vs 78%), three- (80.5% vs 51.8% vs 40.7%) and five-years (56.5% vs 34.5% vs 31.6%) than upfront combination therapy.⁵⁵ All in all, based on the accumulating evidence over the last six years, initial oral combination treatment is recommended in SSc-PAH patients with WHO class II disease.

Prostacyclin Agonists

The prostacyclin agonists include parenteral epoprostenol, parenteral and inhaled treprostinil and iloprost, and oral selexipag. Except oral selexipag (which can be used in

class II), all the parenteral and inhaled agents are often reserved for patients with WHO class III and IV patients in clinical practice.

Efficacy of parenteral epoprostenol was studied in a 12-week, open-label study which showed improvement in exercise capacity and hemodynamics compared to conventional therapy in 111 patients with SSc-PAH.⁵⁶ Open-label extension of the same study could not provide long term outcomes of these patients treated with epoprostenol due to technical limitations, but reported 3-year survival rate of 52%, which was higher than historical cohorts.⁵⁷ Similarly, subcutaneous treprostinil use showed significant improvement in hemodynamics and nonsignificant trend in quality of life and 6MWD in a subgroup analysis of double-blind, placebo controlled, 12 week trial.⁵⁸ Inhaled iloprost has been reported to improve hemodynamics, functional class and quality of life after mean follow-up of 13.2 months of five patients with CREST syndrome related pulmonary hypertension.⁵⁹ A 24 week open-label study was performed with patients with PAH including 13 patients with CTD-PAH; however, subgroup analysis was not done to specifically report efficacy in this group.⁶⁰ Lastly, selexipag, only oral medication of prostacyclin analogs, has shown to improve morbidity/mortality composite score, and hospitalization rate compared to placebo in subgroup analysis of double-blind, placebo-controlled GRIPHON trial.⁶¹

Guanylate Cyclase Stimulators

Riociguat is an oral guanylate cyclase stimulator. Data is limited to subgroup analysis of PATENT-1 and PATENT-2 trials which showed slight improvement in 6MWD, functional class and hemodynamic parameters compared to placebo with 12 weeks of riociguat use in patients with CTD-PAH (with 40 SSc-PAH patients).⁶²

Outcomes

Three-year survival in SSc-PAH ranges from 61.4–75% depending on availability of treatments at the time of diagnosis and distribution of prognostic indicators in different cohorts; and was around 50–56% in newly diagnosed patients.^{5,9,63} Predictors of mortality in patients with SSc-PAH have been investigated in multiple studies including large PHAROS and REVEAL registries and included age >60, male sex, systolic blood pressure \leq 110 mmHg, pericardial effusion, PVR >32 Woods, DLCO >39% predicted, poor functional status, 6MWD <165 m and BNP >180.^{5,13,63,64} Causes of death were SSc-related within four years of SSc diagnosis, while SSc-related and unrelated causes were equally distributed \geq 4 years after SSc diagnosis.⁶⁴ SSc-related causes of death were

PAH-related in the majority of the patients, followed by infection, renal crisis, and cancer as SSc-unrelated causes of death.^{5,64}

Conclusion

SSc-PAH is a serious complication and the leading cause of death in patients with SSc. Diagnosis of SSc-PAH can be challenging due to nonspecific clinical presentation which can lead to delayed diagnosis. Early recognition and treatment of SSc-PAH is known to improve survival in these patients. Therefore, many screening algorithms have been developed to detect SSc-PAH in early stages. Currently used PAH-specific medications are largely extrapolated from IPAH studies due to smaller number of patients with SSc-PAH. There is great interest in current and future drug trials dedicated to the SSc-PAH population given the overall worse survival and less response to treatment.

Disclosure

Robyn T Domsic is a consultant for Eicos Sciences. The authors report no other conflicts of interest in this work.

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