

# Management of Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis

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Saja Almaaitah<sup>1</sup>  
Kristin B Highland<sup>2</sup>  
Adriano R Tonelli<sup>2</sup>

<sup>1</sup>Medicine Institute, Cleveland Clinic, Cleveland, OH, USA; <sup>2</sup>Department of Pulmonary and Critical Care Medicine, Cleveland Clinic, Cleveland, OH, USA

**Abstract:** Systemic sclerosis (SSc) is a rare and complex immune-mediated connective tissue disease characterized by multi-organ fibrosis and dysfunction. Systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) is a leading cause of death in this population. Pulmonary arterial hypertension (PAH) can coexist with other forms of pulmonary hypertension in SSc, including pulmonary hypertension related to left heart disease, interstitial lung disease, chronic thromboembolism and pulmonary venous occlusive disease, which further complicates diagnosis and management. Available pulmonary arterial hypertension therapies target the nitric oxide, endothelin and prostacyclin pathways. These therapies have been studied in SSc-PAH in addition to idiopathic PAH, often with different treatment responses. In this article, we discuss the management as well as the treatment options for patients with SSc-PAH.

**Keywords:** systemic sclerosis, scleroderma, pulmonary arterial hypertension, pulmonary hypertension

## Introduction

Systemic sclerosis (SSc), also called scleroderma, is a complex immune-mediated connective tissue disease characterized by fibrosis and thickening of the skin and internal organs as well as vascular abnormalities that ultimately leads to multi-organ dysfunction.<sup>1</sup> These immune, fibrotic and vascular abnormalities, including pulmonary arterial hypertension, are highlighted in the revision of the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria for SSc diagnosis.<sup>2</sup> SSc is classified into diffuse and limited cutaneous forms based on the extent of skin involvement. Limited cutaneous systemic sclerosis (lcSSc) has skin involvement distal to the elbows and knees, whereas the skin is involved proximal to the knees and elbows, including the trunk in diffuse cutaneous systemic sclerosis (dcSSc). The term systemic sclerosis sine scleroderma is used when there is no skin involvement, but the patient meets the other criteria for SSc.<sup>3</sup>

The definition of pulmonary arterial hypertension (PAH) was recently modified by the sixth World Symposium on Pulmonary Hypertension (WSPH) proceedings to include an elevation in the mean pulmonary arterial pressure (mPAP) >20 mmHg, a pulmonary vascular resistance (PVR) ≥3Wood units (WU) and a pulmonary artery wedge pressure (PAWP) ≤15 mmHg.<sup>4</sup> This change was based on data obtained from healthy individuals, showing that a normal mPAP at rest is 14 ± 3.3 mmHg.<sup>5</sup> Two standard deviations from this mean give the current mPAP cut-off for upper limit of normal. Evidence from large databases indicate that patients with a mPAP between

Correspondence: Adriano R Tonelli  
Email tonella@ccf.org

20 and 25 mmHg have worse outcomes than those with a mPAP  $\leq$ 20 mmHg, further supporting the modification by the 6<sup>th</sup> WSPH.<sup>4</sup> Two studies in patients with systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH), with mPAP between 21 and 24 mmHg, demonstrated a decrease in functional capacity as shown by an abnormal six-minute walk test (6MWT), even when considering a PVR of  $\geq$  2 (instead of  $\geq$ 3) Wood units.<sup>6,7</sup>

There are five groups of pulmonary hypertension (PH) that are based on the mechanisms of disease, clinical presentation, hemodynamic characteristics, and therapeutic response.<sup>8</sup> Groups 1 to 5 include patients with 1) PAH, 2) PH due to left heart disease, 3) PH due to lung disease and/or hypoxia, 4) PH due to pulmonary artery obstruction and 5) PH due to unclear or multifactorial mechanism, respectively. The prevalence of pulmonary arterial hypertension (PAH) in SSc is estimated to be around 6–12%, a percentage that may increase when using the modified definition for PAH.<sup>9,10</sup> It is the second most frequent cause of PAH in both US and European registries following idiopathic pulmonary arterial hypertension (IPAH).<sup>11</sup> PAH is more common in lcSSc but can be seen in the other variants. Furthermore, PAH can coexist with other forms of PH in SSc, including PH related to left heart disease, interstitial lung disease/hypoxemia, chronic thromboembolism and pulmonary venous occlusive disease (currently included in group 1PH),<sup>8</sup> which further complicates diagnosis and management.

PAH results from an imbalance between vasoconstrictors and proliferative mediators (such as endothelin-1) and vasodilators (such as nitric oxide and prostacyclin). Endothelial injury and intraluminal micro-thrombosis lead to progressive pulmonary arterial remodeling and increase in PVR. The progressive increase in PVR affects the right ventricular function, leading to right ventricular failure and death.<sup>9,12</sup> SSc-PAH is a leading cause of mortality, with a mortality rate of 50% within the first 3 years;<sup>9,13</sup> which is worse than the one observed in patients with IPAH.<sup>14</sup>

## Types of Pulmonary Hypertension in Systemic Sclerosis

Due to the systemic nature of SSc, an overlap between more than one type of PH is common (Table 1 and Figure 1), making the identification of the predominant type of PH not always straightforward,<sup>15</sup> and complicating the management of these patients.

Systemic sclerosis associated with left heart disease (SSc-LHD, group 2 PH) is defined by an elevated mPAP with left heart disease (characterized by PCWP >15 mmHg). Cardiac dysfunction may be seen in >40% of patients with SSc and includes primary myocardial fibrosis, fibrosis of the conduction system leading to arrhythmias, microvascular and atherosclerotic coronary vessel disease and hypertensive crisis.<sup>16–18</sup> Fibrosis of the myocardium may result in either diastolic (heart failure with preserved ejection fraction which is reported in around 18% of SSc patients) or less commonly systolic heart failure (heart failure with reduced ejection fraction which is described in around 2% patients).<sup>16</sup> Studies comparing echocardiography findings in patients with SSc-PAH and IPAH with similar hemodynamics showed that patients with SSc-PAH are more likely to have left atrial enlargement and other indications of left ventricular diastolic impairment. Exercise and/or fluid challenge during RHC may be useful in differentiating group 1 and group 2 PH. In the case of elevated PCWP, a markedly elevated transpulmonary (mPAP – PCWP) or diastolic pulmonary gradient (pulmonary artery diastolic pressure – PCWP) suggests the possibility of combined group 1 and group 2 PH.<sup>19</sup> The treatment consists of volume status optimization, rate control and heart failure medications.<sup>20</sup> Treatment with PAH-specific therapy in group 2 PH or combined group 1 and group 2 is not recommended, as it may result in fluid retention and pulmonary edema (such as the use of macitentan in combined pre and post-capillary pulmonary hypertension, CpcPH).<sup>21</sup>

Interstitial lung disease (ILD) is common in SSc, with evidence of interstitial changes on imaging in up to 90% and chronic respiratory failure in approximately 10% of patients. PH is seen in up to 31% of patients with clinically significant SSc-ILD and results in higher mortality than in SSc-ILD patients without PH.<sup>22</sup> SSc-ILD is more common in the dcSSc type, especially in patients who have positive Scl-70 (anti-topoisomerase)<sup>23</sup> but also may occur in all variants. The presence of a positive Scl-70 antibody is somewhat protective against PAH, but these patients may still develop group 3 PH. ILD may be classified as “limited” or “extensive” based on high resolution computed tomography (HRCT) and pulmonary function testing (PFT). It is suggested that PH associated with the extensive form of SSc-ILD (>20% fibrosis on HRCT or forced vital capacity (FVC) <70% in indeterminate HRCT) could be classified as group 3.<sup>15</sup> Although the etiology of PH is associated with extent of lung disease, the mPAP does not

**Table 1** Summary of Different Phenotypes of Pulmonary Hypertension in SSc

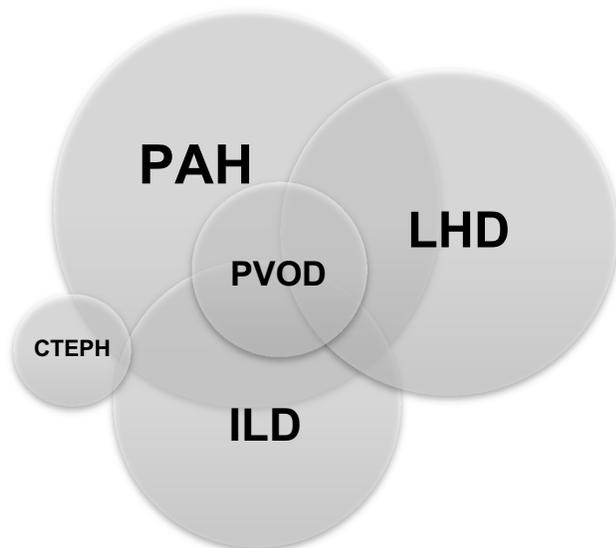
Types of PH in SSc	Prevalence in SSc	Hallmark Clinical Characteristics	RHC Findings	Treatment
PAH (Type 1)	60% of SSc-PH More common in limited cutaneous subtype	mPAP >35 mmHg HRCT: No extensive parenchymal changes Echocardiogram: No/minimal signs of left heart disease	Pre-capillary: mPAP>20 mmHg PCWP≤15 mmHg PVR≥ 3 WU	PAH-targeted therapy Lung transplant
PVOD (Type 1)	Rare, but likely underdiagnosed	PFT: DLCO<50% HRCT: Septal lines, centrilobular ground-glass opacities and lymph node enlargement	Same as PAH	Diuretics Judicious use of PAH-targeted therapy Lung transplant
PH Due to Left Heart Disease (Type 2)	21% of SSc-PH	History/physical: Older age, obesity, hypertension, diabetes, history of atrial fibrillation Electrocardiogram: Left bundle branch block or left ventricular hypertrophy Echocardiogram: Left atrial dilation or left heart valvular insufficiency/stenosis	Post-capillary: mPAP>20 mmHg PCWP>15 mmHg PVR <3 WU (isolated), or ≥3 WU (combined)	Diuretics Treatment of left heart disease
PH Due to ILD (Type 3)	19% of SSc-PH More common in the diffuse cutaneous subtype	PFT: FVC<70% predicted HRCT: Parenchymal changes	Same as PAH, but usually mPAP <35 mmHg	Immunosuppressive therapy Nintedanib Lung transplant
CTEPH (Type 4)	Unknown	Previous history of VTE V/Q scan: screening modality. Mismatch perfusion defect in one or more big segments Pulmonary angiogram: necessary to confirm the diagnosis. Findings include intraluminal webs/bands, abrupt vessel narrowing, and complete and partial vascular obstruction by organized lining thrombi that mimic thickening of the vascular wall	Same as PAH	Anticoagulation Thromboendarterectomy Riociguat Balloon angioplasty

**Abbreviations:** CTEPH, chronic thromboembolic pulmonary hypertension. DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HRCT, high resolution computed tomography; ILD, interstitial lung disease; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PFT, pulmonary function test; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SSc, systemic sclerosis; V/Q, ventilation/perfusion; VTE, venous thromboembolism; WU, Wood units.

seem to correlate with extent of fibrosis on imaging or the forced vital capacity.<sup>22,24</sup> In patients with SSc-ILD, a diffusion capacity (DLCO) <40% of predicted or a reduction in DLCO out of proportion to FVC (FVC/DLCO ratio >1.6) also suggests the presence of pulmonary vascular disease.<sup>11</sup> The PH in group 3 is typically modest with a mPAP <35 mmHg. Likewise, the presence of a mPAP “out of proportion” or >35 mmHg suggests the possibility of concomitant PAH. Treatment of SSc-ILD mainly consists of immune-suppressive therapy, most commonly cyclophosphamide and mycophenolate.<sup>25</sup> Most recently, the antifibrotic nintedanib, a tyrosine kinase inhibitor, was shown to decrease progression of SSc-ILD

in the SENSICIS trial,<sup>26</sup> and murine models have suggested a possible additional benefit of nintedanib on the pulmonary vasculature.<sup>27</sup> Treatment of PH due to ILD with PAH-specific therapies may result in worsening oxygenation due to deterioration of the ventilation-perfusion mismatch and is not recommended outside of clinical trials (Figure 2). However, a more recent study demonstrated that the coexistence of type I and type III is common in patients with SSc, and such patients tolerated concomitant targeted therapy and immunosuppressive therapy.<sup>28</sup>

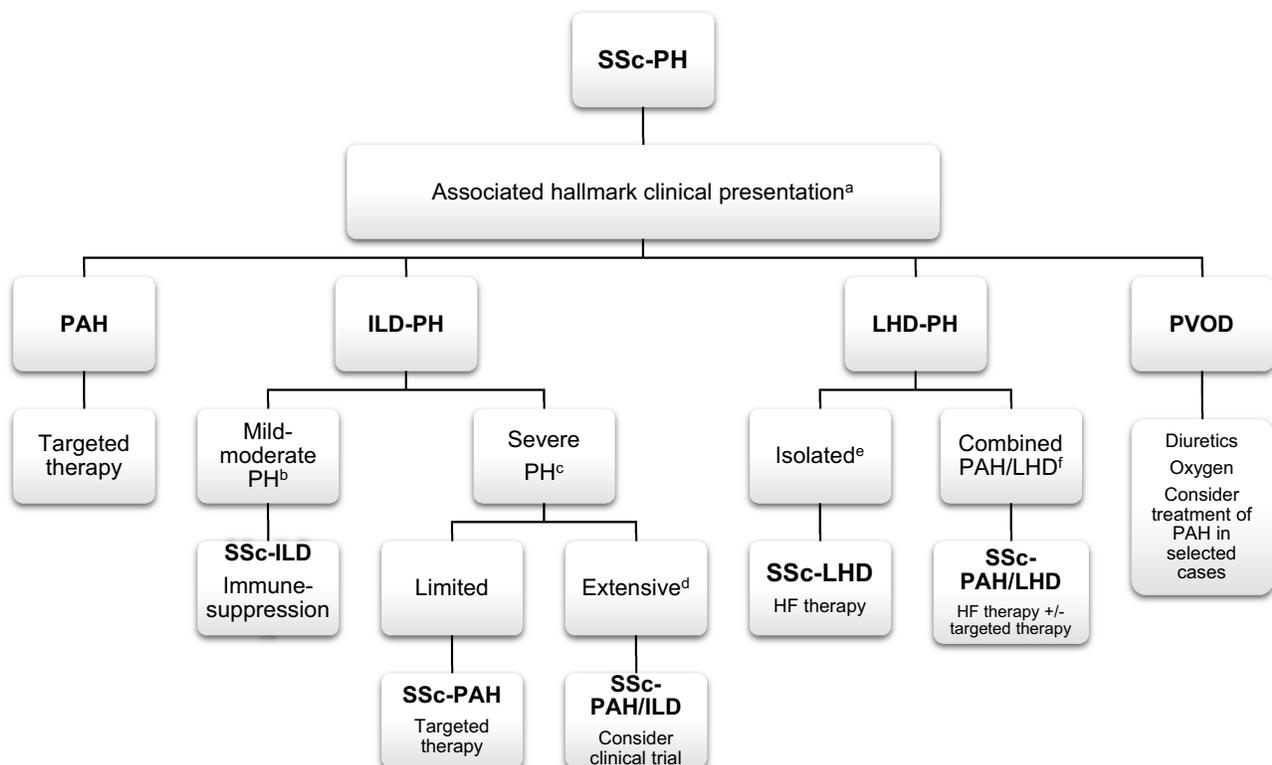
Pulmonary veno-occlusive disease (PVOD) is under-recognized in SSc and its presence carries a very poor prognosis.<sup>29</sup> Although difficult to distinguish from PAH,



**Figure 1** Overlap between different phenotypes of pulmonary hypertension in SSc. **Abbreviations:** CTEPH, chronic thromboembolic pulmonary hypertension; ILD, interstitial lung disease; LHD, left heart disease; PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; SSc, systemic sclerosis.

it should be suspected in patients who develop pulmonary edema after the initiation of PAH-specific therapies. Other indications are a DLCO <50% on PFTs, severe hypoxemia, and the presence of septal lines, centrilobular ground-glass opacities and lymph node enlargement on HRCT.<sup>4</sup> Pathologic findings include intimal fibrosis and obstruction of small pulmonary veins and venules in addition to the arteriopathy seen in PAH.<sup>30</sup> Treatment mainly consists of diuretics to optimize fluid status, very careful use of PAH-specific therapies and ultimately lung or heart-lung transplantation.

Patients with SSc have a 3-fold increased risk of pulmonary thromboembolic disease, especially if anti-phospholipid antibodies are present.<sup>31</sup> Furthermore, SSc is a potential risk factor for developing chronic thromboembolic pulmonary hypertension (CTEPH, group 4 PH),<sup>32</sup> that could be related, at least in part, to higher levels of vWF in patients with SSc.<sup>33,34</sup> As such, patients with SSc-PH should be screened for CTEPH



**Figure 2** Management of different phenotypes of pulmonary hypertension in SSc. <sup>a</sup>As suggested by imaging (HRCT, Echocardiogram), PFT and RHC, see Table 1. <sup>b</sup>Mild-moderate PH includes mPAP < 35 mmHg and normal or mildly dysfunctional RV. <sup>c</sup>Severe PH includes mPAP ≥35 mmHg and/or RV dysfunction more than mild. <sup>d</sup>Extensive ILD refers to >20% fibrosis on HRCT, or FVC<70% in indeterminate HRCT. <sup>e</sup>Isolated LHD refers to DPG<7mmHg and/or PVR≤3WU. <sup>f</sup>Combined PAH/LHD (pre and post capillary PH) refers to DPG≥7 and/or PVR>3 WU.

**Abbreviations:** DPG, diastolic pulmonary gradient; FVC, forced vital capacity; HF, heart failure; HRCT, high resolution computed tomography; ILD, interstitial lung disease; LHD, left heart disease; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricle; SSc, systemic sclerosis; WU, wood units.

as a potential etiology of PH. Screening involves obtaining a ventilation/perfusion (V/Q) scan in all patients newly diagnosed with SSc-PH, even in patients without prior history of pulmonary embolism, as approximately 25% of patients diagnosed with CTEPH have no known history of pulmonary embolism.<sup>35</sup> In the case of abnormal V/Q scan, a pulmonary angiogram should follow to confirm the diagnosis.<sup>36</sup>

## Screening for Pulmonary Hypertension in Systemic Sclerosis

All SSc patients should have pulmonary function testing (PFT), consisting of spirometry, lung volumes and DLCO, to screen for both ILD and PH. A decrease in DLCO <60% or >20% in one year in the absence of significant lung volume abnormalities, or a FVC/DLCO percent >1.6 suggests PH.<sup>11</sup> An elevated NT-proBNP showed a sensitivity and specificity of 90% for the presence of SSc-PAH in one study, and may suggest PAH if elevated > two-fold the upper limit of normal.<sup>37</sup> However, the role of pro-BNP in screening for SSc-PAH is yet to be determined. Transthoracic echocardiography is the best screening tool for PH. It assesses right- and left-sided morphology and function, detects valvular abnormalities and is useful for the estimation of right ventricular pressures.<sup>11,38</sup> When PH is suggested by echocardiography (RVSP > 40 mmHg and/or any degree of RV dysfunction) a RHC is warranted.<sup>39</sup>

HRCT is performed mainly to screen for interstitial lung disease and/or PVOD. However, a HRCT might show an enlarged pulmonary artery and right ventricle in advanced PAH.<sup>38,40</sup> A cardiopulmonary exercise test (CPET) can suggest pulmonary vascular disease in cases of low end-tidal partial pressure of carbon dioxide (EtPCO<sub>2</sub>), high ventilator equivalents for carbon dioxide (VE/VCO<sub>2</sub>), low oxygen pulse (VO<sub>2</sub>/HR) and low peak oxygen uptake (VO<sub>2</sub>).<sup>20,41</sup> The six-minute walk test (6MWT) is a non-invasive submaximal functional test that correlates with maximum exercise capacity as measured by CPET.<sup>42</sup> In addition, heart rate recovery (HRR, as measured by the difference of heart rate at the end of 6MWT and after 1 min of resting) may predict clinical worsening in patients with connective tissue disease associated PAH (CTD-PAH), including SSc.<sup>43</sup> However, the performance characteristics of the 6MWT in SSc are less robust than in IPAH secondary to non-cardiopulmonary limitations of exercise, such as joint pain, skin contractures and muscle weakness. Recently, a combination of features obtained during the 6MWT, ie, distance walked, degree of oxygenation and Borg dyspnea index was found useful in

identifying patients who need further cardiopulmonary evaluation.<sup>44</sup>

Compared with echocardiography, cardiac MRI (CMR) may provide information on the underpinnings of cardiac involvement in patients with SSc, including inflammatory, microvascular and fibrotic mechanisms.<sup>45</sup> Furthermore, CMR provides a more comprehensive assessment of the right ventricular function.<sup>46</sup>

Due to the high morbidity and mortality of PAH, patients newly diagnosed with SSc should be screened for PAH at presentation and annually thereafter for life.<sup>41</sup> Data suggest that SSc-PAH patients who are diagnosed and treated early as a result of screening have improved mortality as compared to patients diagnosed as a result of clinical suspicion.<sup>47–49</sup> The European Society of Cardiology/European Respiratory Society recommends annual echocardiography.<sup>20</sup> If features suggestive of PH are noted, ie, elevated tricuspid regurgitant jet velocity or abnormal right ventricular morphology and function, a right heart catheterization is recommended. The Australian Scleroderma Interest Group (ASIG) recommends screening with NT-proBNP and PFT. An elevated NT-proBNP and/or an elevated FVC/DLCO ratio is an indication to consider RHC.<sup>50</sup> The 2-step DETECT algorithm combines clinical, physiologic and laboratory data to decide who should get an echocardiogram and based on its result who should undergo a RHC to confirm the presence of PH.<sup>13</sup> All three screening strategies<sup>13,20,50</sup> have similar sensitivity, specificity, positive and negative predictive values (Table 2).

## Treatment

As SSc is yet to be a treatable disease, the treatment of SSc-PAH is directed at controlling the progression of PAH.<sup>51</sup> General measures and supportive therapy should be offered to all patients. PAH-specific treatment is generally offered for patients with WHO functional class (WHO FC) II, III or IV.<sup>9</sup> Currently available treatments target the nitric oxide, endothelin or prostanoid pathways (Table 3). The 6th World Symposium Proceedings in PH recommend a treatment strategy based on a multi-parametric risk stratification approach,<sup>52</sup> with the main objective of achieving a low-risk status that is associated with a reduced mortality (annual mortality of <5%).<sup>20</sup> Several risk stratification strategies have been used, including the REVEAL 2.0,<sup>53</sup> French Pulmonary Hypertension Network (FPHN),<sup>54</sup> COMPERA<sup>55</sup> and the Swedish Pulmonary Arterial Hypertension Registrar

**Table 2** Summary of Screening Models

Screening Model	ESC/ERS <sup>20</sup>	DETECT <sup>13</sup>	ASIG <sup>50</sup>
Screening Criteria	<p>High risk:</p> <ul style="list-style-type: none"> <li>• TRV &gt; 3.4 m/s</li> <li>• TRV between 2.9 and ≤3.4 m/s and other echo findings suggestive of PH<sup>a</sup></li> </ul> <p>Intermediate risk:</p> <ul style="list-style-type: none"> <li>• TRV between 2.9 and ≤3.4 m/s and no other echo findings</li> <li>• TRV ≤ 2.8 m/s and other echo findings suggestive of PH<sup>a</sup></li> </ul>	<p>Step 1 (non-echo):</p> <ul style="list-style-type: none"> <li>• FVC/DLCO (0–5)</li> <li>• Telangiectasias (0–1)</li> <li>• Anti-centromere Ab (0–1)</li> <li>• NT pro-BNP (0–10,000)</li> <li>• Serum urate (2–10)</li> <li>• Right axis deviation (0–1)</li> </ul> <p>If &gt;300 points, move to step 2</p> <p>Step 2 (echo):</p> <ul style="list-style-type: none"> <li>• Right atrium area (0–40)</li> <li>• TRV (0–5)</li> </ul>	<p>1. NT pro-BNP ≥ 210 pg/mL</p> <p>2. DLCO &lt; 70% predicted and FVC/DLCO ≥ 1.8</p>
Referral for RHC	<p>1. High risk</p> <p>2. Intermediate risk with symptoms<sup>b</sup></p>	Score >35 points on step 2	Positive 1 and 2

**Notes:** <sup>a</sup>Findings include RV enlargement, flattening of the interventricular septum, RV outflow doppler acceleration <105 ms, early diastolic pulmonary regurgitation velocity >2.2 m/s, pulmonary artery diameter >2.5 cm, inferior vena cava enlargement, right atrial area in end-systole >18 cm<sup>2</sup>. <sup>b</sup>Symptoms include ongoing dyspnea, syncope or near syncope, or presence of peripheral edema.

**Abbreviations:** Ab, antibody; ASIG, Australian Scleroderma Interest Group; DLCO, diffusing capacity for carbon monoxide; ESC/ERS, European Society of Cardiology/European Respiratory Society; FVC, forced vital capacity; echo, echocardiogram; PH, pulmonary hypertension, NT-proBNP, N-terminal-pro-brain natriuretic peptide; RHC, right heart catheterization; RV, right ventricle; TRV, tricuspid regurgitant velocity.

(SPAHR),<sup>56</sup> (Table 4). The two methodologies most commonly used to assess risk are the FPHN and REVEAL 2.0. The FPHN risk assessment totals the number of low-risk criteria (WHO functional class I or II, 6MW distance >440 m, RA pressure <8 mmHg, and cardiac index ≥2.5 L/min/m<sup>2</sup>).<sup>57</sup> The REVEAL 2.0 risk score includes a larger number of variables but provides a greater risk discrimination than the FPHN.<sup>53</sup>

## Vasoreactivity Testing

Vasoreactivity testing is recommended predominantly for patients with idiopathic PAH to identify individuals that can benefit from calcium channel blockers. However, vasoreactivity testing in SSc-PAH is not mandated in recent guidelines as most patients are non-reactive.<sup>58</sup> Therefore, calcium channel blockers are not recommended as they may worsen right heart failure; nevertheless, and under careful vigilance, some SSc individuals receive this medication for their Raynaud phenomenon.<sup>59</sup>

## Treatment Approach

After confirmation of the diagnosis of SSc-PAH, the 6th World Symposium proceedings recommend initiating PAH targeted therapy based on risk stratification (Figure 3).<sup>60</sup> Patients with low-intermediate risk are started generally on combination therapy,<sup>52</sup> with a few exceptions in which monotherapy is an adequate alternative. Choice of medication is usually based on

a number of factors, including comorbidities, side effects, route of administration and patient preference.<sup>52</sup> High-risk patients should be treated with combination therapy that includes a parenteral prostacyclin analogue.<sup>52</sup>

Patients are usually followed up within 1–3 months after initiating therapy to evaluate treatment response, and thereafter, every 3–6 months depending on the patient.<sup>9</sup> Tests suggested during follow up include clinical assessment (WHO FC), 6MWT, NT-proBNP and echocardiogram. A RHC should be considered 3–6 months after initiation or change in therapy, and yearly thereafter.<sup>20</sup> Treatment should be escalated in patients who fail to achieve a low-risk status within 3–6 months. Those failing triple therapy should be considered for lung transplantation.<sup>52</sup>

## Targeted Therapy

### Nitric Oxide Pathway

In healthy individuals, endothelium-derived nitric oxide activates soluble guanylate cyclase (sGC), which increases the production of cyclic guanosine monophosphate (cGMP) that mediates smooth muscle relaxation. cGMP is degraded by phosphodiesterase type 5 (PDE-5). PDE-5 inhibitors (sildenafil and tadalafil) act as selective and potent inhibitors of this enzyme, increasing the levels of cGMP. In contrast, riociguat acts upstream, stimulating sGC.<sup>61,62</sup> The concomitant administration of PDE-5 inhibitors and riociguat is contraindicated due to the increase in adverse

**Table 3** Pivotal Trials for the Medications Used in SSc-PAH with Comparison of the Treatment Response Between SSc-PAH and IPAH

Trial Name/ Author	Medication	Analysis Group	Primary Endpoint	Secondary Endpoint	PAH-CTD vs IPAH Response
SUPER-1 <sup>64,65</sup>	Sildenafil	PAH including CTD	6MWT	WHO FC Hemodynamics	Similar results
PHIRST-1 <sup>66,67</sup>	Tadalafil	PAH including CTD	6MWT	WHO FC Clinical worsening Quality of life	PAH-CTD patients had reduced improvement in regard to all end points
PATENT-1 <sup>68,69</sup>	Riociguat	PAH including CTD	6MWT	WHO FC NT-proBNP Hemodynamics Time to clinical worsening Borg dyspnea scale Quality of life	Improvements were less pronounced in PAH-CTD patients. However, 2-year survival rates were similar
BREATHE-1 <sup>74</sup>	Bosentan	PAH including CTD	6MWT	WHO FC Borg dyspnea index Time to clinical worsening	Improvements were less pronounced in SSc-PAH than in IPAH (46m vs 3m regarding 6MWD)
ARIES-1 <sup>75,76</sup>	Ambrisentan	PAH including CTD	6MWT	WHO FC Borg dyspnea score NT-proBNP Clinical worsening	Time to clinical worsening was similar. Improved survival in both groups though more pronounced in IPAH
SERAPHIN <sup>77</sup>	Macitentan	PAH including CTD	Worsening of PAH or death	6MWD WHO FC Death due to PAH Hospitalization due to PAH Death from any cause	Reduced morbidity without difference between CTD-PAH and IPAH according to a meta-analysis <sup>78</sup>
Badesch DB et al <sup>82</sup>	Epoprostenol	SSc-PAH	6MWT	Hemodynamics Survival	Not applicable
Simonneau G. et al <sup>87,88</sup>	Treprostinil	PAH including CTD-PAH	6MWT	Borg Dyspneal Scale Hemodynamics Quality of life	Improvements were achieved in both groups though less pronounced in CTD-PAH
Caravita S et al <sup>89</sup>	Iloprost	CTD-PAH	6MWT	Hemodynamics NT-proBNP	Not applicable
GRIPHON <sup>90,91</sup>	Selexipag	PAH including CTD-PAH	Composite death from any cause and any complication from PAH	6MWD All-cause mortality	Primary endpoint was consistent to IPAH 6MWD improved in IPAH while it minimally progressed in CTD

**Abbreviations:** 6MWD, six-minute walk distance; distance; 6MWT, six-minute walk test; CTD, connective tissue disease; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; WHO FC, world health organization functional class; NT-proBNP, N-terminal-pro brain natriuretic peptide.

effects such as headache, hypotension, dizziness, vomiting and even death, as was shown in the PATENT Plus trial.<sup>63</sup>

### Phosphodiesterase-5 Inhibitors

Both sildenafil and tadalafil are approved for the treatment of SSc-PAH.<sup>51</sup> SUPER-1/SUPER-2 trials demonstrated the

efficacy of sildenafil therapy in improving the 6MW distance, cardiac hemodynamics and WHO FC in patients with PAH, including those with CTD-PAH (45% of whom had SSc). Improvements in the distance walked during the 6MWT were similar for patients with CTD-PAH or IPAH.<sup>64,65</sup> Tadalafil was studied in the PHIRST-

**Table 4** Summary of PAH Risk Scoring System

Registry	REVEAL 2.0 <sup>53</sup>	FPHN <sup>54</sup>	COMPERA <sup>55</sup>	SPAHR <sup>56</sup>
Variables Included	<ul style="list-style-type: none"> <li>• PAH etiology</li> <li>• Demographics</li> <li>• Comorbidities</li> <li>• NYHA/WHO FC</li> <li>• Vital signs</li> <li>• All-cause hospitalizations ≤6 months</li> <li>• 6MWT</li> <li>• BNP</li> <li>• Echocardiogram</li> <li>• PFT</li> <li>• RHC</li> </ul>	<ul style="list-style-type: none"> <li>• WHO FC I/II</li> <li>• 6MWT &gt;440 m</li> <li>• RAP &lt;8 mmHg</li> <li>• CI ≥2.5 L/min/m<sup>2</sup></li> </ul>	<ul style="list-style-type: none"> <li>• WHO FC</li> <li>• 6MWT</li> <li>• BNP</li> <li>• NT-proBNP</li> <li>• RAP</li> <li>• CI</li> <li>• SvO<sub>2</sub>%</li> </ul>	<ul style="list-style-type: none"> <li>• WHO FC</li> <li>• 6MWT</li> <li>• NT-proBNP</li> <li>• Echocardiogram               <ul style="list-style-type: none"> <li>○ RA area</li> <li>○ Pericardial effusion</li> </ul> </li> <li>• Hemodynamics               <ul style="list-style-type: none"> <li>○ RAP</li> <li>○ CI</li> <li>○ SVO<sub>2</sub>%</li> </ul> </li> </ul>
Risk Scores	Low ≤ 6 Intermediate 7–8 High ≥ 9	Low 3–4 Intermediate 2 High 0–1	Low <1.5 Intermediate 1.5–2.5 High ≥2.5	Low 1 Intermediate 2 High ≥3

**Abbreviations:** 6MWT, six-minute walk test; BNP, brain natriuretic peptide; CI, cardiac index; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FPHN, French pulmonary hypertension network; NT-proBNP, N-terminal-pro brain natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PFT, pulmonary function test; RA, right atrium; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; RHC, right heart catheterization; SPAHR, Swedish Pulmonary Arterial Hypertension Registry; SvO<sub>2</sub>%, mixed venous oxygen saturation; WHO FC, World Health Organization functional class.

1/PHIRST-2 trials, which demonstrated its ability to improve 6MW distance, quality of life and reduce clinical worsening, in a PAH population that included CTD-PAH patients. However, treatment with tadalafil in patients with CTD-PAH was less efficacious than in patients with IPAH.<sup>66,67</sup> Interestingly, PDE-5 inhibitors were shown to improve healing and prevent the development of digital ulcers in patients with SSc.<sup>51</sup>

### Guanylate Cyclase Stimulator

Riociguat was evaluated in the PATENT-1/PATENT-2 trials and demonstrated considerable efficacy in CTD-PAH including SSc-PAH, improving the 6MW distance, pulmonary hemodynamics (such as PVR and the cardiac index) and WHO FC. These improvements were less pronounced in patients with CTD-PAH than IPAH; however, 2-year survival rates were similar in both PAH types.<sup>68,69</sup> In addition, a case series demonstrated that in patients with SSc-PAH with unsatisfactory response to PDE-5 inhibitors, switching to riociguat was associated with improved respiratory and cardiac hemodynamics.<sup>70</sup> Long-term treatment with riociguat has been associated with a reduction in right heart size and an improvement in right ventricular function in patients with PAH (14% of patients with CTD-PAH) and CTEPH.<sup>71,72</sup>

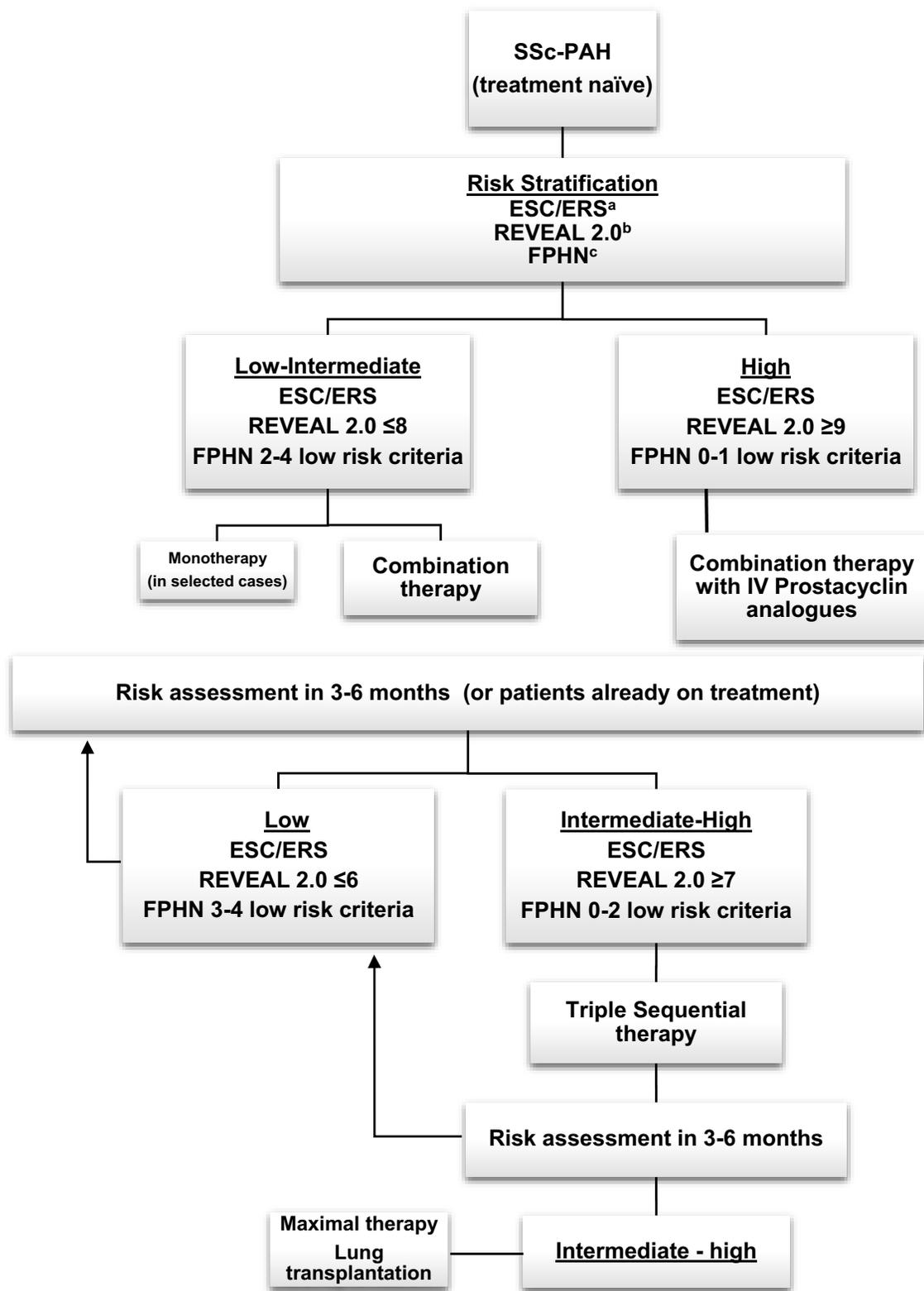
### Endothelin Receptor Antagonists

Endothelin-1 binds to endothelin receptors on the pulmonary vasculature and results in vasoconstriction.<sup>73</sup>

Bosentan, ambrisentan and macitentan are endothelin receptor antagonists (ERA) approved for the treatment of SSc-PAH. In the BREATHE-1 trial, bosentan prevented the deterioration of walking distance in 6MWT, predominantly in patients with IPAH (3-m improvement in SSc-PAH vs 46 m in IPAH).<sup>74</sup> In the ARIES-1/ARIES-2 trials, ambrisentan improved the 6MW distance and slowed clinical worsening in CTD-PAH, though survival was better in the IPAH population.<sup>75,76</sup> The SERAPHIN trial showed that macitentan reduced morbidity and mortality in PAH patients, after-which a meta-analysis showed similar outcomes between IPAH and CTD-PAH.<sup>77,78</sup> ERA side effects include elevated liver function tests (bosentan), peripheral edema and anemia (all).<sup>20</sup> In the RAPIDS-2 study,<sup>79</sup> bosentan prevented the formation of new digital ulcers but did not improve the rate of ulcer healing.

### Prostacyclin Pathway Agonists

Prostacyclin is produced by endothelial cells and causes potent pulmonary artery vasodilation. Dysregulation of the prostacyclin pathway has been shown in patients with PAH.<sup>80</sup> Epoprostenol, treprostinil and iloprost are approved for the treatment of SSc-PAH.<sup>51</sup> Epoprostenol is given intravenously due to its short half-life. Treprostinil may be administered intravenously, subcutaneously, orally or by inhalation.<sup>81</sup> Iloprost is only administered by inhalation in the US, although an intravenous formulation is



**Figure 3** Treatment approach to pulmonary arterial hypertension in Systemic Sclerosis. <sup>a</sup>ESC/ERS risk assessment is based on clinical signs of right heart failure, syncope, WHO functional class, 6MWT, CPET, NT-proBNP, Imaging (echocardiography, MRI) and cardiac hemodynamics. <sup>b</sup>REVEAL criteria: see table 4. <sup>c</sup>FPHN low risk criteria: WHO class I/II, 6MWT >440m, RAP <8, CI ≥2.5.

**Abbreviations:** 6MWT, six-minute walk test; CPET, cardiopulmonary exercise testing; CI, cardiac index; ESC/ERS, European Society of Cardiology/European Respiratory Society; FPHN, French pulmonary hypertension Network; IV, intravenous; MRI, magnetic resonance imaging; NT-proBNP, N-terminal- pro brain natriuretic peptide; RAP, right atrial pressure; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; SSc-PAH, systemic sclerosis associated pulmonary arterial hypertension; WHO, world health organization. Data from these studies.<sup>14,44,45</sup>

available in Europe. Intravenous epoprostenol improved exercise capacity and cardiopulmonary hemodynamics (decrease in mPAP and PVR and improvement in WHO FC) in patients with SSc-PAH.<sup>82,83</sup> Similar results were demonstrated with intravenous and subcutaneous treprostinil as well as inhaled iloprost.<sup>84–88</sup> Intermittent intravenous iloprost infusion (composed of iloprost infusion for 6 hrs per day for 5 days every 6 weeks) decreased the systolic PAP, improved the distance walked during the 6MWT and protected against PAH progression in patients with SSc.<sup>89</sup> Prostaglandins are also commonly used to treat ischemic digital ulcers in patients with SSc.<sup>51</sup> Selexipag, an oral selective IP-receptor agonist, was evaluated in the GRIPHON trial, where it decreased the risk of death or complications related to PAH patients including SSc, findings that were consistent with those seen in patients with IPAH.<sup>90,91</sup>

### Combination Therapy versus Initial Monotherapy

Combination therapy is the approach of choice for drug naïve SSc-PAH patients. The ATPAHSS-O and the AMBITION trials showed that upfront combination therapy with ambrisentan and tadalafil in SSc-PAH improved cardiac hemodynamics (PVR and stroke volume, NT-proBNP) and 6MW distance, and lowered the risk of clinical worsening, when compared to monotherapy with either drug alone.<sup>92,93</sup> More recently, the SERAPHIN and the long-term GRIPHON trials demonstrated lower morbidity and mortality rates with the addition of macitentan and selexipag on a background therapy, respectively.<sup>94,95</sup>

## General Measures

### Oral Anticoagulation

Data on the use of oral anticoagulation remain conflicting for patients with IPAH;<sup>96</sup> recent data have discouraged the use of anticoagulation for patients with SSc-PAH, since these patients are at increased risk of bleeding secondary to gastric antral vascular ectasia and arterial vascular malformations in the intestines. In the COMPERA trial, oral anticoagulation was associated with a survival benefit in IPAH, but not in other forms of PAH, such as SSc-PAH.<sup>97</sup> In fact, long-term use of warfarin was associated with worse prognosis in patients with SSc-PAH in the REVEAL Registry.<sup>98</sup> Furthermore, anticoagulation with warfarin was not associated with an effect on survival in PAH (12% had SSc-PAH) or idiopathic PAH patients treated with SQ treprostinil.<sup>99</sup> A prospective cohort study showed that anticoagulation with warfarin was associated with improved

survival; however, 46% of SSc-PAH received treatment for indications other than PAH.<sup>48</sup> There is an ongoing trial (SPHInX) that aims to evaluate the efficacy and safety of apixaban, a direct oral anticoagulant, in SSc-PAH.<sup>100</sup>

### Immunosuppressive Therapy

While immunosuppressive therapy has been associated with improved clinical outcome and survival in PAH associated with some forms of CTD (such as glucocorticoids and cyclophosphamide in systemic lupus erythematosus and mixed connective tissue disease),<sup>101</sup> SSc-PAH is refractory to corticosteroids or immunosuppressive therapy.<sup>102</sup>

### Supportive Therapy

Despite the lack of specific data, experts recommend the use of diuretics to manage volume overload and digoxin for atrial arrhythmias and right heart failure. Long-term oxygen therapy is recommended to maintain arterial blood oxygen pressure above 60 mm Hg or oxygen saturation above 90%.<sup>103,104</sup> In terms of non-medical management, exercise training was found to improve work capacity, quality of life and possibly survival in patients with CTD-PAH including SSc.<sup>105</sup> Pregnancy is contraindicated in SSc-PAH given substantial mortality rate, estimated to be up to 50%,<sup>106</sup> and teratogenic effect of some PAH-specific medications such as riociguat and ERAs. If a patient becomes pregnant, a discussion about pregnancy termination should ensue. Patients who decide to continue with pregnancy are optimized on PAH therapies, followed-up closely in an expert center with experience in managing this high-risk pregnancy.<sup>20</sup> Other general measures also include immunization against influenza and pneumococcal infections.<sup>20</sup>

### Refractory Disease

Despite the continuous advances in the management of PAH, a significant proportion of patients with SSc-PAH experience disease progression.<sup>107</sup> Atrial septostomy has been investigated as a palliative measure for patients with SSc-PAH who continue to deteriorate despite maximal medical treatment, and was found to improve exercise capacity and possibly survival in selective cases.<sup>108</sup> In patients with SSc-PAH refractory or poorly responsive to PAH therapy, lung transplantation is currently the only option. At least one study showed that patients with SSc-PAH experience similar 2-year survival rates after lung transplant when compared to IPAH or idiopathic pulmonary fibrosis.<sup>109,110</sup> Unfortunately, patients with SSc are commonly deemed inappropriate candidates to lung transplantation due to risk of post-transplant aspiration in the

setting of esophageal dysmotility, severe renal impairment, severe Raynaud phenomenon, non-healing digital ulcerations that pose a risk of infection, and very rarely, severe chest wall skin thickening leading to restriction.<sup>111</sup> Available data have mainly focused on lung transplantation for patients with SSc interstitial lung disease with or without PH rather than isolated SSc-PAH.<sup>112,113</sup>

### Prognosis

Despite important advances in the treatment of PAH in the recent years, SSc-PAH still carries a poor prognosis, with survival rates of 81%, 64% and 52% over the first, second and third years, respectively.<sup>114</sup> Moreover, the mortality rate of SSc-PAH is worse than that of IPAH and non SSc CTD-PAH, probably due to the multi-organ involvement of SSc (when compared to IPAH) and the poorer response to treatment (when compared to IPAH and CTD-PAH).<sup>14,115</sup> Predictors of worse outcome include age >60 years old, male sex, WHO FC IV, higher mPAP, low systolic blood pressure <110 mmHg, 6MW distance <165 m, DLCO <39% predicted, presence of pericardial effusion and anti-U1 ribonucleoprotein (RNP) negative status.<sup>114,116,117</sup>

### Future Studies and Medications

Several medications are currently being studied for the treatment of SSc-PAH. One of the medications is ifetroban, a thromboxane A<sub>2</sub>/prostaglandin H<sub>2</sub> receptor antagonist. Ifetroban works by alleviating blood vessel contraction, increasing vasodilation and thereby decreasing PAH.<sup>118</sup> Another potential treatment is rituximab, a monoclonal antibody against a protein called CD20, which is found on the surface of B-cells. It is thought that rituximab may slow the progression of fibrosis in the lungs by lowering antibodies against the platelet-derived growth factor. Rituximab is currently being tested for this indication in a Phase 2 clinical trial in patients with SSc-PAH, though preliminary data did not show statistical significance in improvement of the 6MW distance.<sup>119,120</sup> Bardoxolone methyl is currently being studied in patients with PAH including CTD-PAH. Bardoxolone methyl works by inducing nuclear factor erythroid 2-related factor 2 (Nrf2) and suppressing nuclear factor-κB (NF-κB). Bardoxolone methyl is thought to target several cells involved in SSc-PAH, such as smooth muscle cells, endothelial cells and macrophages.<sup>121</sup>

## Conclusion

Systemic sclerosis-associated pulmonary arterial hypertension is a devastating complication carrying a poor prognosis. Current therapies targeting SSc-PAH have resulted in improved quality of life, cardiac hemodynamics and survival. Most recent guidelines focus on routine screening for PAH in patients with SSc, and when PAH-SSc is diagnosed, initial aggressive combination treatment is important to reach a low-risk status. Several promising medications are still being studied in this patient population.

## Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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