Prediction of new onset of resting pulmonary arterial hypertension in systemic sclerosis

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PULMONARY ARTERIAL HYPERTENSION IN SYSTEMIC SCLEROSIS

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1. SUMMARY

Pulmonary arterial hypertension (PAH) is a frequent and severe complication of systemic sclerosis (SSc) due to combined vasculopathy and fibrogenesis. Early diagnosis and treatment are highly challenging in SSc-PAH and require referral to a n expert PAH centre. Diagnostic algorithms evolved in the last decade. Novel therapeutic options notably targeting pulmonary vascular remodeling are needed.

2. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a frequent and severe complication of systemic sclerosis (SSc), occurring in 8 to 12 % of cases[1–4]. Pulmonary hypertension (PH) and interstitial lung disease (ILD) are the two most important complications that affect the lungs in SSc, respectively related to vasculopathy and interstitial fibrosis. Both phenomena are key pathophysiologic manifestations of SSc that share overlapping characteristics. Indeed, several mechanisms of PH may occur and coexist in scleroderma, including PAH associated with connective tissue disease (CTD), corresponding to group 1.4.1 of the updated PH clinical classification (Box I), due to vasculopathy of the small pulmonary arteries, and PH due to chronic respiratory disease in the context of severe ILD (PH group 3). During the course of SSc, PH group 2 (due to heart disease) tends to occur more frequently, mainly through the development of myocardial fibrosis leading to systolic or diastolic left heart dysfunction. Pulmonary veno-occlusive disease (PVOD) can also occur in SSc (PH group 1.6) [5].

Box 1. Updated clinical classification of pulmonary hypertension (PH), adapted from [5]
PAH: pulmonary arterial hypertension; SSc: systemic sclerosis; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction.

1 PAH
- 1.1 Idiopathic PAH
- 1.2 Heritable PAH
- 1.3 Drug- and toxin-induced PAH
- 1.4 PAH associated with:
  - 1.4.1 Connective tissue disease, such as SSc
  - 1.4.2 HIV infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease
  - 1.4.5 Schistosomiasis
- 1.5 PAH long-term responders to calcium channel blockers
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

2 PH due to left heart disease
- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular heart disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3 PH due to lung diseases and/or hypoxia
- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive/obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

4 PH due to pulmonary artery obstructions
- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions

5 PH with unclear and/or multifactorial mechanisms
- 5.1 Hematological disorders
- 5.2 Systemic and metabolic disorders
- 5.3 Others
- 5.4 Complex congenital heart disease

3. CLINICAL FEATURES

SSc-PAH patients tend to be asymptomatic in the early course of the disease or only present symptoms related to other organ involvement. PAH symptoms are unspecific, such as dyspnea on exertion and fatigue, which are often attributed to SSc global functional impairment.

PAH can complicate the course of both limited and diffuse SSc. According to the PHARAOS registry, comprising 22 US scleroderma expert centers, the characteristics of patients who developed PAH included age > 60 years old, female gender (84 %), limited cutaneous SSc (90 %) and a diffusion capacity (DL_{CO}) < 50 % predicted [6]. The common association of ILD, PVOD or left heart diastolic dysfunction makes SSc-PAH more complex than other forms of PAH, such as idiopathic or heritable cases. In that setting, clinical response to PAH drugs can be less convincing, at least in a subset of SSc-PAH patients.

3.1. Updated hemodynamic definition of pulmonary hypertension

The diagnosis of PAH must be confirmed by right heart catheterisation (RHC), which allows the measurement of mean pulmonary arterial pressure (mPAP) together with pulmonary arterial wedge pressure (PAWP), pulmonary vascular resistance (PVR) and cardiac output. Precapillary PH is hemodynamically defined according to the 6th World Symposium on PH by a mPAP > 20 mmHg with pulmonary vascular resistance (RVP) ≥ 3 Wood unit, in the presence of a pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg [5]. The diagnosis of PAH is made when the previous hemodynamic criteria are met and once other causes of pre-capillary PH, such as chronic thromboembolic PH (group 4) and PH due to chronic lung disease (group 3), are ruled out, which can be challenging in SSc.

3.2. Incidence and prognosis

PAH occurs in up to 12 % of scleroderma patients [3] and represents a leading cause of morbidity and mortality in SSc, exceeding ILD in some registries [7]. In a selected cohort of SSc patients with a DL_{CO} < 60 % predicted, mPAP appeared to rise progressively during a 3-year follow-up. It was possible to identify a mPAP > 25 mmHg in almost one fourth of patients using prospective RHC during follow-up [8]. In the French PAH registry, CTD (mainly represented by SSc) accounted for 15.3 % of all PAH cases [2].

In high risk SSc patients, such as patients with a DL_{CO} < 60 %, as in the DETECT study [9], PAH prevalence reaches 19 %. Prevalence of group 2 and group 3 PH in this study was 6 %.

Despite advances and progresses in PAH therapy, prognosis of SSc-PAH is worse than other forms of the disease with a 1-year mortality reaching up to 30 % [6]. In a recent French report, over the period 2006-2017, survival improved over time in patients aged ≤ 70 years but not in older SSc-PAH patients [10]. In a meta-analysis of nine studies comprising 2,700 SSc patients, 55 % died of SSc-related causes [11]. Among these, 35 % were related to lung fibrosis, 26 % to PAH, 26 % to heart failure and arrhythmias, and 4 % to renal crisis.

3.3. Early detection of pulmonary hypertension in scleroderma

There is growing evidence that in SSc-PAH, as in other CTD-PAH, patients with a mild elevation in mPAP (21-24 mmHg) demonstrate symptoms, particularly at exercise, and may have a poorer outcome compared to controls with mPAP ≤ 20 mmHg. The updated hemodynamic definition of PH does not necessarily imply to treat all these patients, however SSc patients with mildly elevated mPAP should be closely monitored [5].

In a recent prospective study in Heidelberg and Zurich [12], among 284 SSc patients, 146 (49.2%) had mPAP ≤ 20 mmHg, 19.3 % had mPAP 21-24 and 29.4 % had mPAP ≥ 25 mmHg. In the 21-24 group, only 4 patients (1.4%) had PVR values ≥ 3 WU and could be

classified as SSc-PAH according to the recently proposed definition. Interestingly, 9.8% of cases presenting with mPAP 21-24 and PVR ≥ 2WU already presented signs of disease with decreased 6-minute walking distance (6MWD), tricuspid annular plane systolic excursion (TAPSE) and pulmonary arterial compliance, and most importantly reduced long-term survival. Thus, a PVR threshold of 2 WU was already associated with significant pulmonary vascular disease in SSc and might be a better cut-off for earlier detection of PAH [12].

4. PATHOPHYSIOLOGY

PAH is a manifestation of vascular injury and endothelial cell dysfunction [13]. Vascular changes are early expressions of SSc and comprise apoptosis, endothelial cell activation, inflammatory cell recruitment, intimal proliferation and adventitial fibrosis. These mechanisms lead to vessel obliteration, together with a procoagulant state which may eventually increase mPAP [14,15]. PAH is associated with the formation of neo-intimal vascular lesions within the arteries, as a result of an augmented proliferation of endothelial cells (ECs) and smooth muscle cells (SMCs) [16]. It was long assumed that resident α – smooth muscle actin-positive cells were issued from SMCs, however experimental evidence demonstrated that in SSc-PAH the formation of this neo-intima is caused by endothelial-to-mesenchymal transition (EndoMT) [17],[18]. EndoMT is a biological process in which ECs progressively evolve and transform their endothelial phenotype into a mesenchymal or myofibroblastic phenotype, a key process in angiogenesis and tissue regeneration [19]. Doing so, ECs are able to dissociate from the endothelial monolayer surface of the vessel and migrate toward the inner tissue. Chronic activation of EndoMT pathways causes the loss of endothelium integrity and invasion of the sub-endothelial area by proliferative mesenchymal cells [20]. SSc-PAH pathophysiology is far from being entirely revealed, however several recent studies gave new insights into key mechanisms.

The blockade of interleukin-1 (IL-1) signalling in an animal model of SSc-PAH worsened pulmonary fibrosis, enhanced T helper type 2 inflammation and increased the activation of pro-fibrogenic macrophages, whereas IL-1 stimulation *in vitro* reduced collagen expression in pulmonary arterial SMCs and parenchymal fibroblasts [21].

Microarray experiments revealed that the matrix metalloproteinase 10 (MMP-10) gene was the top upregulated gene in SSc-associated PH endothelial progenitor-derived endothelial cells [22]. MMP-10 is overexpressed in the serum and pulmonary arteries of patients with SSc-PAH and its blockade reduces PH in a murine model, representing a putative treatment target [22].

Lysyl oxidase (LOX) is an extracellular enzyme that cross-links collagen fibrils and is located in the proliferating endothelium in lung arterioles [23]. LOX was found to be increased in serum of SSc patients [24]. A recent multicentre study demonstrated that serum LOX levels are increased in established SSc and inversely correlated with the DL_{CO}, thus suggesting a pathophysiological role for LOX in SSc-PAH [23].

5. SCREENING AND EARLY DIAGNOSIS STRATEGIES

Reducing the time to diagnosis is crucial in all forms of PAH, including SSc-PAH, to initiate early management and improve clinical outcome [25].

5.1. Doppler echocardiography

Once SSc diagnosis is established, regular assessment of cardiovascular involvement is mandatory. Echocardiography allows the evaluation of the systolic and diastolic left ventricular function, measurement of left and right heart chambers, assessment of valves and pericardium, and estimation of systolic pulmonary artery pressure (sPAP). Doppler

transthoracic echocardiography (TTE) is recommended whenever PAH is suspected and has the highest level of evidence of current tests used to screen for PAH (Table I) [26]. Considering the high prevalence of PAH in SSc, annual screening is widely recommended, followed by RHC if an elevated tricuspid regurgitant jet velocity, with or without other echocardiographic signs of PH [26].

The peak tricuspid regurgitation velocity (TRV) is an important parameter to estimate sPAP. Although higher TRV values (> 2.8 m/s) are associated with an increased probability of PH, there can be individual discrepancies between estimated sPAP and RHC measures [27]. Other echocardiographic PH signs comprise notably the flattening of the interventricular septum, an elevated early diastolic pulmonary regurgitation velocity (> 2.2 m/sec) and a right atrial area > 18 cm^2 [26].

Table I. Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension of any cause, from *[26]*.

TTE: Transthoracic echocardiography; PH: pulmonary hypertension.

Peak tricuspid regurgitation velocity (m/s)	Presence of other TTE 'PH signs'	Echocardiographic probability of PH
< 2.8 or not measurable	No	Low
< 2.8 or not measurable	Yes	Intermediate
2.9-3.4	No	
2.9-3.4	Yes	High
> 3.4	Not required	

The DETECT study algorithm (Figure 1.A.) has provided an evidence-based multimodal approach to early detection of PAH in a cohort of scleroderma patients at increased risk of PAH (SSc for more than 3 years and predicted pulmonary diffusing capacity for carbon monoxide (DL_{CO}) <60%) [9]. Six simple assessments occur in Step 1 of the algorithm determined referral to Doppler echocardiography. In Step 2, the Step 1 prediction score together with two echocardiographic variables determined referral to RHC. DETECT showed that this two-step algorithm including electrocardiographic, echocardiographic and laboratory biomarkers selecting patients to undergo RHC had greater sensitivity than Doppler echocardiography on its own in detecting SSc-PAH. In that study, using only Doppler echocardiography at rest missed about 50 % of PH diagnosis. Results from this study suggest that TRV and right atrial area are the two key TTE parameters to select patients for RHC referral [9].

5.2. Diffusion capacity for carbon monoxide

Diffusion capacity for carbon monoxide (DL_{CO}) measures gas exchange through the alveolar membrane, which is dependent on the thickness of the alveolar membrane and abundance of the lung capillary bed. The vast majority of SSc-PAH patients have decreased DL_{CO} values whereas a reduced DL_{CO} with preserved pulmonary volume on spirometry (forced vital capacity: FVC) has been proposed as a marker of pulmonary vasculopathy [26]. A FVC/DL_{CO} ratio (both expressed as percentage of predicted values) $\geq$ 1.8 suggests a more pronounced reduction of gas transfer when compared to lung volume, thus increasing the likelihood of pulmonary vascular disease. This parameter features in the Australian Scleroderma Interest Group (ASIG) algorithm (Figure 1.B.) [28].

5.3. Cardiopulmonary exercise testing

Dumistrescu et al. investigated the utility of cardiopulmonary exercise testing (CPET) for early detection of PAH in 173 SSc patients who also underwent RHC [29]. A peak oxygen consumption (VO_2) above 18.7 ml/kg/min was found to be the most accurate parameter for excluding SSc-PAH in 100% of patients [29]. Moreover, a nadir ventilator efficiency (ie, minute ventilation relative to carbon dioxide production, VE/VCO_2 ratio) > 45.5 had a positive predictive value of 1.0.

Recently, Santaniello and colleagues reported that selected CPET parameters were predictive for the presence of PAH in SSc patients and could, together with the DETECT algorithm, improve the diagnostic workup of SSc-PAH and reduce the number of referrals for RHC [30].

5.4. Clinical signs and biomarkers

In a French study, no relationship was found between the presence of digital ulcers and SSc-PAH [31]. Epidemiologic studies do not clearly demonstrate a strong link between digital ulcers and other vascular complications. Some autoantibodies are commonly associated with some SSc subgroups: anticentromere antibodies are more commonly found in patients with limited SSc-associatated PAH, anti-Scl70 - anti-topoisomerase antibody-type of anti-nuclear autoantibodies- are characteristic of diffuse SSc with a more important risk of ILD, and anti–RNA polymerase III antibodies are associated to severe disease with major organ and diffuse cutaneous involvement [32].

Blood levels of B-type natriuretic peptide (BNP) and its N-terminal inactive fragment, N-terminal pro-BNP level (NT pro-BNP), are markers of myocardial wall stress and are elevated in PH [33]. In a SSc cohort study, high NT pro-BNP serum levels and low DL_{CO} were independent predictors of the occurrence of PAH [34]. In the same cohort, NT pro-BNP was an independent predictor of 3-year mortality in SSc patients. A NT pro-BNP value of 125 ng/l, suggested for the diagnosis of a reduced left ventricular ejection fraction or PAH, was

confirmed as a reliable threshold to predict mortality and thus should be considered as part of the routine evaluation of SSc patients [34]. Of note, elevated NT pro-BNP levels can also reveal left ventricular dysfunction and can be seen in renal insufficiency without PH correlation. In the DETECT study, elevated serum urate levels were predictive of PAH [9]. Urate is the final product of purine degradation and elevated levels are thought to reflect impaired oxidative metabolism as a consequence of tissue ischaemia in PAH [35].

5.5. Current screening/early diagnosis algorithms

Validated screening strategies for PAH currently only exist for patients with SSc, as compared to other PAH subtypes (Figure 1). The French ItinerAIR Sclérodermie study (Figure 1.C.) had a pioneering role in demonstrating the ability of a screening strategy based on Doppler echocardiography and symptoms to identify SSc patients with milder haemodynamic impairment [4]. As indicated above, the DETECT algorithm is a non-invasive prediction score to screen for SSc-PAH in patients with a disease duration > 3 years and a DL_{CO} < 60 % of predicted [9]. In the first step, six clinical parameters are assessed, including clinical signs and biomarkers, to identify which patients should undergo a TTE (Step 2). High risk patients from Step 2 should then be referred for a RHC. Compared with screenings based on TTE alone, the DETECT algorithm identified PAH-SSc patients with less severe haemodynamic impairment. DETECT was also able to identify patients with mPAP > 20 mmHg, relevant with the recent recommendations of the World Symposium [5]. The ASIG algorithm combines pulmonary function tests and NT pro-BNP serum value, without TTE assessment with a sensitivity and specificity for PAH detection of respectively 94.1 % and 54.5 % [28].

Following the 6th World Symposium on PH, the recommended diagnostic workup for SSc-PAH was updated [36]. For SSc patients with uncorrected $DL_{CO} \geq 80\%$ of predicted, annual screening may be considered with TTE alone. For DLCO values < 80 %, the proposed algorithm is shown in Figure 2.

6. CARDIAC INVOLVEMENT

Myocardium involvement in SSc causes fibrosis and impaired microcirculatory function [37]. Myocardial fibrosis is the pathological hallmark of this complication and has been reported in up to 80 % of necropsy study cases [38]. The worse SSc-PAH morbidity, mortality and decreased response to vasodilator therapy, as compared to other PAH cases, might be related at least in part to the inadequate compensation of the right ventricle to elevated afterload. Failure of the right ventricle to cope with SSc-PAH leads to inadequate coupling between right ventricle contractile function and increased pulmonary afterload due to PAH. Recently, Nagel et al. highlighted the key role of the right ventricle in SSc [39]. They prospectively studied RV and pulmonary vascular hemodynamics at rest and during exercise in SSc patients with mild PAH (21-24 mmHg). This subgroup of patients demonstrated decreased 6MWD and reduced augmentation of the RV output during exercise [39].

7. TREATMENT

SSc-PAH constitutes a clinical challenge to properly diagnose and treat. Medical treatment tends to be more complex than in idiopathic PAH as patients are often less responsive to specific therapy, although they tend to have milder hemodynamic impairment. This is likely related to the heterogeneous extent of vasculopathy and the variety of clinical phenotype of SSc-PAH, with a frequent overlap between two or more mechanisms of PH.

7.1. PAH therapy

Basic therapy includes diuretics in case of right ventricular failure and long-term oxygen therapy in case of hypoxaemia. Long-term favourable response to calcium channel blocker is reported in virtually no SSc-PAH cases and high dose calcium channel blocker therapy is thus not recommended for PAH (while it can be used at low doses for the treatment of Raynaud's phenomenon). The long-term risk benefit ratio of oral anticoagulation is not favourable in SSc-PAH because of an increased risk of bleeding [40]. Corticosteroids and immunosuppressants are neither indicated nor efficacious in SSc-PAH [41].

The three pathways of endothelial cell dysfunction targeted by currently approved PAH medications are the nitric oxide pathway, endothelin pathway and prostacyclin pathway. Treatments comprise endothelial receptor antagonists (ERA), phosphodiesterase type 5 inhibitors (PDE-5i), soluble guanylate cyclase stimulator, prostacyclin analogues and prostacyclin receptor agonist. Synergistic action of drugs acting on each of the three pathways is the cornerstone of the modern strategy to treat PAH with initial or sequential combination therapy [26].

Patients with CTD have been included in most of the major RCTs for regulatory approval of PAH medications. These studies have demonstrated efficacy of PAH drugs in CTD-associated PAH, where the majority cases have SSc. Following the 2015 ESC/ERS PH guidelines [26], treatment of patients with SSc-PAH should follow the same algorithm as in idiopathic PAH as we now have a robust experience with oral and parenteral vasodilators use in SSc-PAH.

Patients presenting with low or intermediate risk (including New York Heart Association (NYHA) functional class II-III) should be started either on initial monotherapy or oral combination [26,42]. In high-risk SSc-PAH patients (NYHA functional class IV), guidelines underscore that initial combination therapy should include a parenteral prostacyclin [26,42]. After treatment initiation, every patient should be regularly reassessed for risk/functional class

to evaluate treatment response and consider reinforcement, when needed. An algorithm for SSc-PAH treatment is displayed in Figure 3. Subgroup analysis of patients with SSc-PAH enrolled in RCTs (with ERA, PDE5i, soluble guanylate cyclase stimulator, prostacyclin analogues and prostacyclin receptor agonist) have shown favourable effects. The choice of therapy in SSc-PAH may also take into account other manifestation of vasculopathy such as digital ulcers.

In the first SSc-PAH dedicated randomized controlled trial, continuous intravenous epoprostenol therapy was shown to improve exercise capacity, symptoms and hemodynamics [43]. Retrospective analysis however shows a better effect of i.v. epoprostenol on survival in idiopathic PAH as compared with SSc-PAH. The GRIPHON study included 170 patients with SSc-PAH and revealed a 41 % risk reduction in the composite morbidity/mortality endpoint in patients treated with selexipag versus placebo [44,45]. SSc-PAH subgroup analysis of the AMBITION trial, testing the efficacy of the combination ambrisentan and tadalafil, showed reduction in clinical failure by 55 % compared to monotherapy with either agent [46].

7.2. Lung transplantation

Despite PAH therapy, a subset of patients progress to end stage disease with severe functional impairment. In case of inadequate clinical response, SSc-PAH patients should be considered for lung transplantation, as SSc is not a contraindication for lung transplantation per se. Recent studies suggest similar post-transplant outcomes in SSc-ILD patients compared to those with other causes of ILD [47,48]. A recent multicentric retrospective analysis demonstrated that female sex and PAH in combination were associated with lower post-transplant survival [48]. A multidisciplinary team should consider SSc specificities during pre-transplantation evaluation, especially gastro-intestinal, cardiac, renal and cutaneous involvements.

7.3. Future treatment directions

Currently available PAH therapies target endothelial dysfunction and improve symptoms and survival. However, no available treatments yet reverse abnormal pulmonary vascular proliferation and remodelling.

The important roles of autoimmunity and inflammation in the pathogenesis of both SSc and PAH suggest that newer biological treatments should potentially target specific inflammatory pathways. Several clinical trials are exploring the impact of various anti-inflammatory agents in PAH. These include notably rituximab, a chimeric anti-human CD20 (ClinicalTrials.gov identifier NCT01086540) in SSc-PAH patients; tocilizumab, a humanised anti-IL-6 receptor antibody in PAH patients (ClinicalTrials.gov identifier NCT02676947); FK506 (tacrolimus), a calcineurin inhibitor that has been shown to upregulate Bone Morphogenetic Protein Receptor type II expression [49]. FK506 was however disappointing in a phase IIa trial in PAH patients, with no statistical improvement of 6MWD or TTE parameters [50].

Nintedanib is a small molecule that inhibits a variety of tyrosine-kinase pathways, including platelet-derived growth factor receptor, fibroblast growth factor receptor and vascular endothelial growth factor receptor tyrosine kinases. It demonstrated a potential to inhibit the proliferation of pulmonary SMCs, thus preventing vascular occlusion while inhibiting the apoptosis of ECs in a murine model of SSc [51]. Nintedanib recently demonstrated a reduced decline in FVC among nintedanib-treated SSc patients, although no clinical benefit was observed for other SSc characteristics including DL_{CO} [52].

The results of the antioxidant bardoxolone methyl in phase II trials of SSc-PAH (ClinicalTrials.gov identifier NCT02657356) points towards a possible role for oxidative stress and chronic inflammation, via mitochondrial dysfunction, in SSc-PAH.

8. CONCLUSIONS

PAH is a severe manifestation of two of the hallmarks of SSc, vasculopathy and fibrogenesis. A major issue in handling PAH-SSc patients is possible overlapping causes of PH such as lung fibrosis and/or diastolic dysfunction. Referral to a specialised centre with multidisciplinary team discussion is recommended for all SSc cases with clinical parameters suggesting PAH. Specific PAH therapy should be introduced according to guidelines, once confounding causes of PH are ruled out. We urgently need innovative therapeutic options for this very severe condition. Some preclinical and clinical studies are currently underway and could pave the way for potent tailored therapies for SSc-PAH patients.

References:

[1] Mukerjee D, George DS, Coleiro B, Knight C, Denton CP, Davar J, et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis 2003;62:1088–93. https://doi.org/10.1136/ard.62.11.1088.

[2] Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 2006;173:1023–30. https://doi.org/10.1164/rccm.200510-1668OC.

[3] Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010;37:2290–8. https://doi.org/10.3899/jrheum.100245.

[4] Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: A French nationwide prospective multicenter study. Arthritis Rheum 2005;52:3792–800. https://doi.org/10.1002/art.21433.

[5] Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53. https://doi.org/10.1183/13993003.01913-2018.

[6] Chung L, Domsic RT, Lingala B, Alkassab F, Bolster M, Csuka ME, et al. Survival and Predictors of Mortality in Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: Outcomes From the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry. Arthritis Care Res 2014;66:489–95. https://doi.org/10.1002/acr.22121.

[7] Simeón-Aznar CP, Fonollosa-Plá V, Tolosa-Vilella C, Espinosa-Garriga G, Campillo-Grau M, Ramos-Casals M, et al. Registry of the Spanish Network for Systemic Sclerosis: Survival, Prognostic Factors, and Causes of Death. Medicine (Baltimore) 2015;94:e1728. https://doi.org/10.1097/MD.0000000000001728.

[8] Coghlan JG, Wolf M, Distler O, Denton CP, Doelberg M, Harutyunova S, et al. Incidence of pulmonary hypertension and determining factors in patients with systemic sclerosis. Eur Respir J 2018;51:1701197. https://doi.org/10.1183/13993003.01197-2017.
[9] Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014;73:1340–9. https://doi.org/10.1136/annrheumdis-2013-203301.
[10] Hachulla E, Launay D, Boucly A, Mouthon L, de Groote P, Cottin V, et al. Survival Improved in Patients Aged ≤ 70 Years With Systemic Sclerosis-Associated Pulmonary Arterial Hypertension During the Period 2006 to 2017 in France. Chest 2020;157:945–54. https://doi.org/10.1016/j.chest.2019.10.045.
[11] Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology 2012;51:1017–26. https://doi.org/10.1093/rheumatology/ker269.
[12] Xanthouli P, Jordan S, Milde N, Marra A, Blank N, Egenlauf B, et al. Haemodynamic phenotypes and survival in patients with systemic sclerosis: the impact of the new definition of pulmonary arterial hypertension. Ann Rheum Dis 2020;79:370–8. https://doi.org/10.1136/annrheumdis-2019-216476.
[13] Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, et al. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. Eur Respir J 2019;53:1801887. https://doi.org/10.1183/13993003.01887-2018.
[14] Sgonc R, Gruschwitz MS, Boeck G, Sepp N, Gruber J, Wick G. Endothelial cell apoptosis in systemic sclerosis is induced by antibody-dependent cell-mediated cytotoxicity via CD95. Arthritis Rheum 2000;43:2550–62. https://doi.org/10.1002/1529-0131(200011)43:11<2550::AID-ANR24>3.0.CO;2-H.
[15] Cerinic MM, Valentini G, Sorano GG, D'Angelo S, Cuomo G, Fenu L, et al. Blood coagulation, fibrinolysis, and markers of endothelial dysfunction in systemic sclerosis. Semin Arthritis Rheum 2003;32:285–95. https://doi.org/10.1053/sarh.2002.50011.
[16] Hemnes AR, Humbert M. Pathobiology of pulmonary arterial hypertension: understanding the roads less travelled. Eur Respir Rev 2017;26:170093. https://doi.org/10.1183/16000617.0093-2017.
[17] Stenmark KR, Frid M, Perros F. Endothelial-to-Mesenchymal Transition: An Evolving Paradigm and a Promising Therapeutic Target in PAH. Circulation 2016;133:1734–7. https://doi.org/10.1161/CIRCULATIONAHA.116.022479.
[18] Hopper RK, Moonen J-RAJ, Diebold I, Cao A, Rhodes CJ, Tojais NF, et al. In Pulmonary Arterial Hypertension, Reduced BMPR2 Promotes Endothelial-to-Mesenchymal Transition via HMGA1 and Its Target Slug. Circulation 2016;133:1783–94. https://doi.org/10.1161/CIRCULATIONAHA.115.020617.
[19] Ranchoux B, Antigny F, Rucker-Martin C, Hautefort A, Péchoux C, Bogaard HJ, et al. Endothelial-to-Mesenchymal Transition in Pulmonary Hypertension. Circulation 2015;131:1006–18. https://doi.org/10.1161/CIRCULATIONAHA.114.008750.
[20] Ranchoux B, Tanguay VF, Perros F. Endothelial-to-Mesenchymal Transition in Pulmonary Hypertension. In: Nakanishi T, Baldwin HS, Fineman JR, Yamagishi H, editors. Mol. Mech. Congenit. Heart Dis. Pulm. Hypertens., Singapore: Springer; 2020, p. 63–70. https://doi.org/10.1007/978-981-15-1185-1_6.

[21] Birnhuber A, Crnkovic S, Biasin V, Marsh LM, Odler B, Sahu-Osen A, et al. IL-1 receptor blockade skews inflammation towards Th2 in a mouse model of systemic sclerosis. Eur Respir J 2019;54:1900154. https://doi.org/10.1183/13993003.00154-2019.
[22] Avouac J, Guignabert C, Hoffmann-Vold AM, Ruiz B, Dorfmuller P, Pezet S, et al. Role of Stromelysin 2 (Matrix Metalloproteinase 10) as a Novel Mediator of Vascular Remodeling Underlying Pulmonary Hypertension Associated With Systemic Sclerosis. Arthritis Rheumatol Hoboken NJ 2017;69:2209–21. https://doi.org/10.1002/art.40229.
[23] Vadasz Z, Balbir Gurman A, Meroni P, Farge D, Levi Y, Ingegnoli F, et al. Lysyl oxidase-a possible role in systemic sclerosis-associated pulmonary hypertension: a multicentre study. Rheumatol Oxf Engl 2019;58:1547–55. https://doi.org/10.1093/rheumatology/kez035.
[24] Rimar D, Rosner I, Nov Y, Slobodin G, Rozenbaum M, Halasz K, et al. Brief Report: Lysyl Oxidase Is a Potential Biomarker of Fibrosis in Systemic Sclerosis. Arthritis Rheumatol 2014;66:726–30. https://doi.org/10.1002/art.38277.
[25] Kiely DG, Lawrie A, Humbert M. Screening strategies for pulmonary arterial hypertension. Eur Heart J Suppl J Eur Soc Cardiol 2019;21:K9–20. https://doi.org/10.1093/eurheartj/suz204.
[26] Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903–75. https://doi.org/10.1183/13993003.01032-2015.
[27] D'Alto M, Romeo E, Argiento P, D'Andrea A, Vanderpool R, Correra A, et al. Accuracy and precision of echocardiography versus right heart catheterization for the assessment of pulmonary hypertension. Int J Cardiol 2013;168:4058–62. https://doi.org/10.1016/j.ijcard.2013.07.005.
[28] Thakkar V, Stevens W, Prior D, Youssef P, Liew D, Gabbay E, et al. The inclusion of N-terminal pro-brain natriuretic peptide in a sensitive screening strategy for systemic sclerosis-related pulmonary arterial hypertension: a cohort study. Arthritis Res Ther 2013;15:R193. https://doi.org/10.1186/ar4383.
[29] Dumitrescu D, Nagel C, Kovacs G, Bollmann T, Halank M, Winkler J, et al. Cardiopulmonary exercise testing for detecting pulmonary arterial hypertension in systemic sclerosis. Heart 2017;103:774–82. https://doi.org/10.1136/heartjnl-2016-309981.
[30] Santaniello A, Casella R, Vicenzi M, Rota I, Montanelli G, De Santis M, et al. Cardiopulmonary exercise testing in a combined screening approach to individuate pulmonary arterial hypertension in systemic sclerosis. Rheumatology 2020;59:1581–6. https://doi.org/10.1093/rheumatology/kez473.
[31] Tiev KP, Diot E, Clerson P, Dupuis-Siméon F, Hachulla E, Hatron P-Y, et al. Clinical features of scleroderma patients with or without prior or current ischemic digital ulcers: post-hoc analysis of a nationwide multicenter cohort (ItinérAIR-Sclérodermie). J Rheumatol 2009;36:1470–6. https://doi.org/10.3899/jrheum.081044.
[32] Allanore Y, Distler O, Matucci-Cerinic M, Denton CP. Review: Defining a Unified Vascular Phenotype in Systemic Sclerosis. Arthritis Rheumatol 2018;70:162–70. https://doi.org/10.1002/art.40377.

[33] Blyth KG, Groenning BA, Mark PB, Martin TN, Foster JE, Steedman T, et al. NT-proBNP can be used to detect right ventricular systolic dysfunction in pulmonary hypertension. Eur Respir J 2007;29:737–44. https://doi.org/10.1183/09031936.00095606.
[34] Allanore Y, Komocsi A, Vettori S, Hachulla E, Hunzelmann N, Distler J, et al. N-terminal pro-brain natriuretic peptide is a strong predictor of mortality in systemic sclerosis. Int J Cardiol 2016;223:385–9. https://doi.org/10.1016/j.ijcard.2016.08.246.
[35] Nagaya N, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Nakanishi N, et al. Serum Uric Acid Levels Correlate with the Severity and the Mortality of Primary Pulmonary Hypertension. Am J Respir Crit Care Med 1999;160:487–92. https://doi.org/10.1164/ajrccm.160.2.9812078.
[36] Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, et al. Diagnosis of pulmonary hypertension. Eur Respir J 2019;53:1801904. https://doi.org/10.1183/13993003.01904-2018.
[37] Rangarajan V, Matiasz R, Freed BH. Cardiac complications of systemic sclerosis and management: recent progress. Curr Opin Rheumatol 2017;29:574–584. https://doi.org/10.1097/BOR.0000000000000439.
[38] Follansbee WP, Miller TR, Curtiss EI, Orie JE, Bernstein RL, Kiernan JM, et al. A controlled clinicopathologic study of myocardial fibrosis in systemic sclerosis (scleroderma). J Rheumatol 1990;17:656–62.
[39] Nagel C, Marra AM, Benjamin N, Blank N, Cittadini A, Coghlan G, et al. Reduced Right Ventricular Output Reserve in Patients With Systemic Sclerosis and Mildly Elevated Pulmonary Artery Pressure. Arthritis Rheumatol 2019;71:805–16. https://doi.org/10.1002/art.40814.
[40] Olsson Karen M., Delcroix Marion, Ghofrani H. Ardeschir, Tiede Henning, Huscher Doerte, Speich Rudolf, et al. Anticoagulation and Survival in Pulmonary Arterial Hypertension. Circulation 2014;129:57–65. https://doi.org/10.1161/CIRCULATIONAHA.113.004526.
[41] Sanchez O, Sitbon O, Jaïs X, Simonneau G, Humbert M. Immunosuppressive Therapy in Connective Tissue Diseases-Associated Pulmonary Arterial Hypertension. Chest 2006;130:182–9. https://doi.org/10.1378/chest.130.1.182.
[42] Galiè N, Channick RN, Frantz RP, Grünig E, Jing ZC, Moiseeva O, et al. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur Respir J 2019;53:1801889. https://doi.org/10.1183/13993003.01889-2018.
[43] Badesch DB, Tapson VF, McGoon MD, Brundage BH, Rubin LJ, Wigley FM, 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. https://doi.org/10.7326/0003-4819-132-6-200003210-00002.
[44] Gaine S, Chin K, Coghlan G, Channick R, Di Scala L, Galiè N, et al. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. Eur Respir J 2017;50:1602493. https://doi.org/10.1183/13993003.02493-2016.
[45] Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med 2015;373:2522–33. https://doi.org/10.1056/NEJMoa1503184.
[46] Coghlan JG, Galiè N, Barberà JA, Frost AE, Ghofrani H-A, Hoeper MM, et al. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the

AMBITION trial. Ann Rheum Dis 2017;76:1219–27. https://doi.org/10.1136/annrheumdis-2016-210236.
[47] Launay D, Savale L, Berezne A, Le Pavec J, Hachulla E, Mouthon L, et al. Lung and heart-lung transplantation for systemic sclerosis patients. A monocentric experience of 13 patients, review of the literature and position paper of a multidisciplinary Working Group. Presse Medicale Paris Fr 1983 2014;43:e345-363. https://doi.org/10.1016/j.lpm.2014.01.020.
[48] Pradère P, Tudorache I, Magnusson J, Savale L, Brugiere O, Douvry B, et al. Lung transplantation for scleroderma lung disease: An international, multicenter, observational cohort study. J Heart Lung Transplant 2018;37:903–11. https://doi.org/10.1016/j.healun.2018.03.003.
[49] Spiekerkoetter E, Tian X, Cai J, Hopper RK, Sudheendra D, Li CG, et al. FK506 activates BMPR2, rescues endothelial dysfunction, and reverses pulmonary hypertension. J Clin Invest 2013;123:3600–13. https://doi.org/10.1172/JCI65592.
[50] Spiekerkoetter E, Sung YK, Sudheendra D, Scott V, Del Rosario P, Bill M, et al. Randomised placebo-controlled safety and tolerability trial of FK506 (tacrolimus) for pulmonary arterial hypertension. Eur Respir J 2017;50:1602449. https://doi.org/10.1183/13993003.02449-2016.
[51] Huang J, Maier C, Zhang Y, Soare A, Dees C, Beyer C, et al. Nintedanib inhibits macrophage activation and ameliorates vascular and fibrotic manifestations in the Fra2 mouse model of systemic sclerosis. Ann Rheum Dis 2017;76:1941–8. https://doi.org/10.1136/annrheumdis-2016-210823.
[52] Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease. N Engl J Med 2019;380:2518–28. https://doi.org/10.1056/NEJMoa1903076.

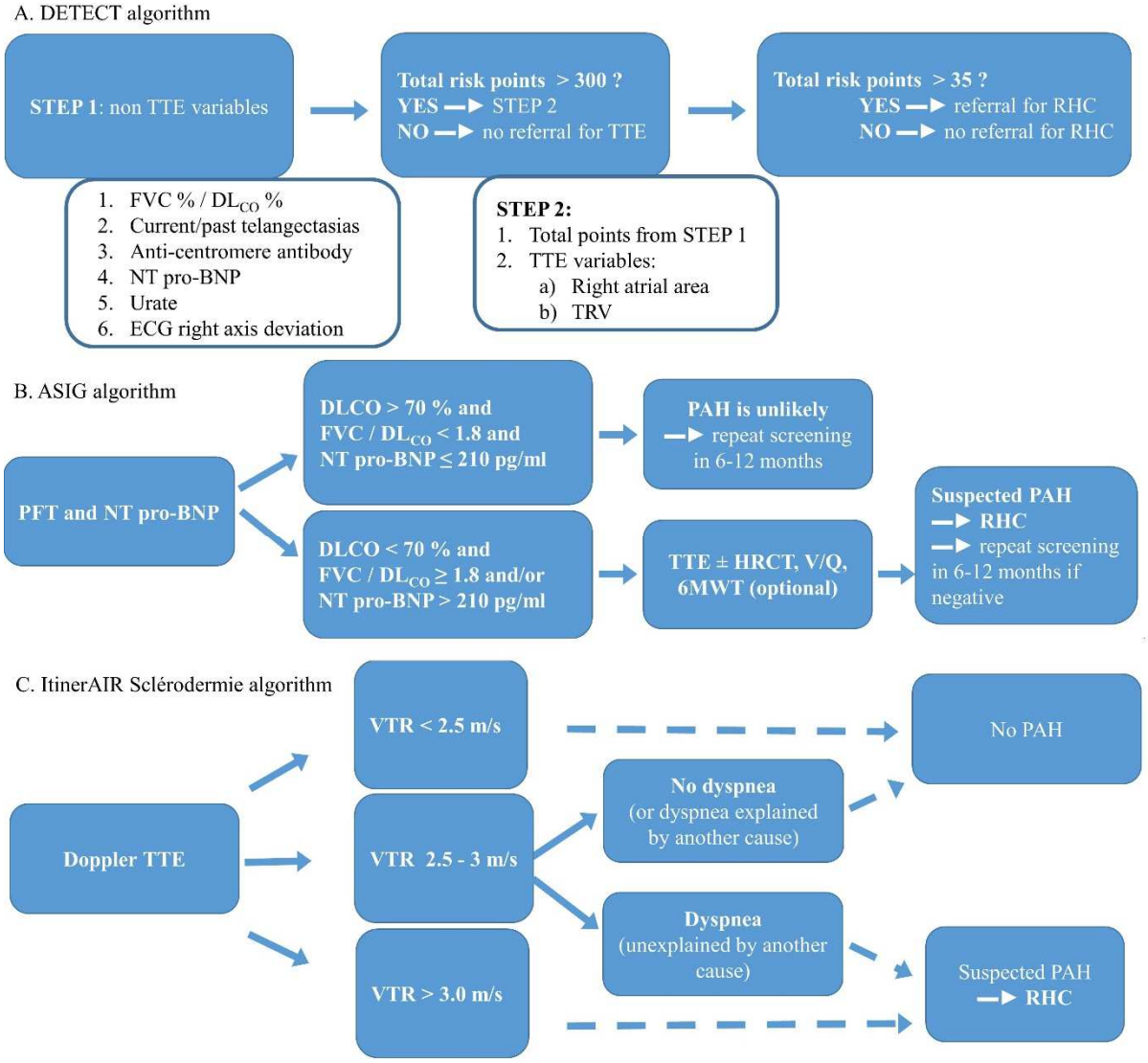

Figure 1. Summary of three approaches to screen for SSC-PAH, adapted from [25]. A. The DETECT study [9]. B. The algorithm of the Australian Scleroderma Interest Group [28]. C. The ItinerAIR Sclérodermie algorithm [4]. TTE: Transthoracic echocardiography; RHC: right heart catheterisation; PFT: pulmonary function tests; DL_{CO}: diffusion capacity for carbon monoxide (in percent predicted); FVC: forced vital capacity (in percent predicted); HRCT: high resolution computed tomography; V/Q: ventilation perfusion scan; NT pro-BNP: N-terminal pro-brain natriuretic peptide; TR: tricuspid regurgitant jet; VTR: peak velocity of tricuspid regurgitation.

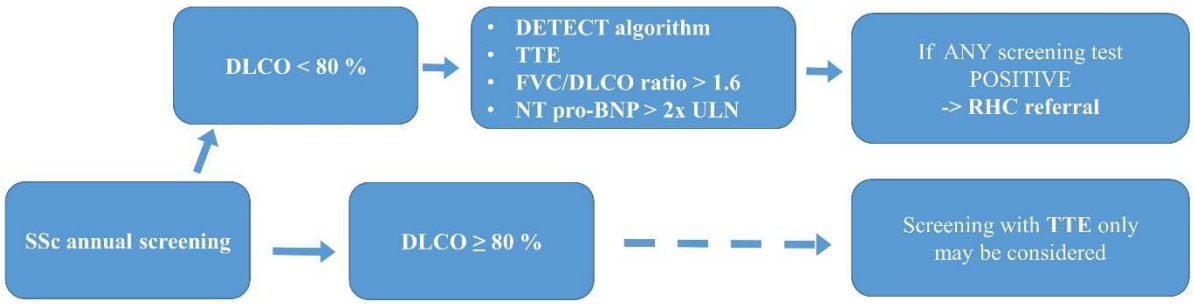

Figure 2. 6th World Symposium on PH proposed diagnostic algorithm for SSc-PAH, adapted from [36]**.** ULN: upper limit of normal; TTE: transthoracic echocardiography; RHC: right heart catheterisation; DL_{CO}: diffusion capacity for carbon monoxide (in percent predicted); FVC: forced vital capacity (in percent predicted); NT pro-BNP: N-terminal pro-brain natriuretic peptide.

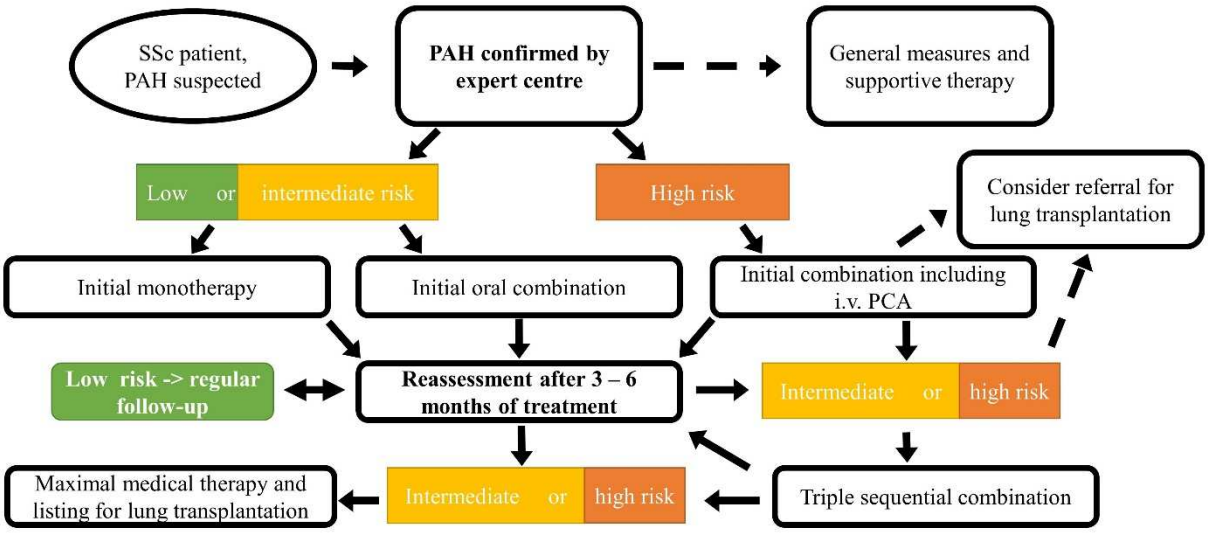

Figure 3. Proposed treatment algorithm for SSc-PAH, adapted from [26,42]**.** SSc: systemic sclerosis; PAH: pulmonary arterial hypertension; PCA: prostacyclin analogue.