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Controversies and advances in connective tissue disease related pulmonary arterial hypertension

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Pulmonary hypertension in connective tissue diseases

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Authors' contributions

KM: editorial design, preparation of manuscript.

MN: editorial design, preparation of manuscript.

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Main Text

Pulmonary arterial hypertension (PAH), a subcategory of pulmonary hypertension (PH), is a chronic and progressive disorder characterized by abnormal vascular proliferation and remodeling, vasoconstriction and thrombosis of the pulmonary vasculature, leading

to elevated pulmonary vascular resistance (PVR), ultimately resulting in right heart failure and death [1]. Of all the connective tissue diseases (CTD), pulmonary arterial hypertension (PAH) occurs most commonly in systemic sclerosis (SSc) accounting for approximately 74% of all CTD-PAH cases, followed by systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD), both of which account for 8% of CTD-PAH [2]. The remaining cases of CTD-PAH are typically associated with primary Sjögren's syndrome (pSS), idiopathic inflammatory myopathies (IIM) and rheumatoid arthritis (RA) [2, 3]. In contrast to above prevalence reports which largely consist of Caucasian populations, a large Chinese study identified SLE as the predominant cause of CTD-PAH accounting for 58.4% whilst SSc accounted for only 26.3% of cases [4].

In SSc, PAH occurs with a prevalence of 8-12% and is the leading cause of mortality accounting for 25-40% of SSc related deaths [2, 5]. In SLE, the prevalence of PAH ranges from 1-5% [6] depending on the ethnicity of the population studied with a recent Chinese study reporting a prevalence of SLE-PAH as high as 12.8% [6] Similar to SSc, the presence of PAH in SLE is an independent predictor of mortality [7]. The prevalence of PAH and its consequences in terms of morbidity and mortality is less well described in other CTDs such as MCTD, pSS, IIM and RA but is reported to range from 0.4-4% without as substantial an impact on survival as seen in SSc and SLE [2, 8-10]. Thus, most of the current knowledge regarding screening for CTD-PAH is based on SSc-PAH.

Screening for PAH in CTDs

Timely recognition of PAH is difficult as early disease is clinically silent and the non-heterogeneous nature of the symptoms, such as fatigue and dyspnea, makes diagnosis challenging particularly in those with an underlying CTD. Once symptoms occur PAH is at an advanced stage and associated with a high one-year mortality rate, evidenced in SSc-PAH where the one-year mortality is as high as 30% [11, 12]. Therefore, systematic screening of asymptomatic at-risk populations is recommended to detect PAH at an earlier stage to allow prompt introduction of specific PAH vasodilator therapies when PAH may be more amendable to treatment.

Of all the CTDs, SSc and SSc spectrum disorders, are the only conditions in which annual screening for PAH is recommended [13, 14]. This is based on the high prevalence of PAH in SSc, its significant morbidity and mortality in addition to the availability of, and survival benefit associated with early introduction of PAH specific vasodilator therapies [15]. Annual PAH screening compared with diagnosis through routine clinical care in SSc is associated with improved survival even after adjustment for lead-time bias [11, 12, 16, 17].

Current PAH screening tools available for SSc patients include the 2009 ESC/ERS guidelines, the detection of PAH in SSc (DETECT) algorithm and the Australian Scleroderma Interest Group (ASIG) algorithm which incorporate the use of annual transthoracic echocardiography (TTE) and other modalities, such as pulmonary function tests (PFTs), and /or N-terminal pro-brain natriuretic peptide (NT-ProBNP), a marker of myocardial stress [18-20]. These tools identify high-risk asymptomatic patients who should be referred for right heart catheristation (RHC) to confirm the presence or absence of pulmonary hypertension (PH). These alternative PAH screening algorithms have been developed to shift the predominant screening focus from TTE due to their operator dependence, need for specialized cardiac centers, cost and inability to measure a systolic pulmonary arterial pressure (sPAP) in 20-30% of patients [21, 22].

The DETECT algorithm, as outlined in Figure 1, is a two-step decision tree. The first step evaluates the results of six non-echocardiographic variables and creates a total score that determines the need for referral for TTE and progression to Step 2. Step 2 determines the need for RHC by evaluating TTE features (right atrium (RA) area and tricuspid regurgitate (TR) velocity) and again creates a total score to determine the need for referral for RHC [23]. Creation of this total score to allow progression through the steps requires the use of a nomogram, which is complex and cumbersome to use. The DETECT algorithm was initially derived in a SSc cohort with disease duration > 3 years and DLCO predicted of ≤ 60%, but has been externally validated in cohorts not meeting these criteria and demonstrated to have comparable performance to the 2009 ESC/ERS guidelines [24-29].

The ASIG algorithm, outlined in Figure 2, has shifted focus from TTE in entirety and instead recommends PFTs to evaluate the forced vital capacity (FVC)/diffusing capacity of the lungs for carbon monoxide (DLCO) ratio and serum NT-proBNP annually. A RHC referral is advised if either (i) the ratio of FVC % predicted to DLCO % predicted is ≥1.8 with DLCO predicted <70% suggesting discrepant reduction in diffusing capacity or (ii) serum NT-proBNP ≥210 ng/L (or pg/mL) [28]. The ASIG algorithm has been compared to the DETECT algorithm and the 2009 ESC/ERS guidelines in an Australian SSc cohort referred for RHC. The ASIG and DETECT algorithms were both superior to the 2009 ESC/ERS guidelines. Moreover, the ASIG algorithm was as sensitive as the DETECT algorithm but more specific (54.5% and 35.3% respectively) [28]. Furthermore, the ASIG algorithm was associated with a substantial cost savings compared with TTE based algorithms [30, 31]. Current research is under way to prospectively validate the ASIG algorithm in addition to evaluating its performance and feasibility as the predominant PAH screening method in Australia.

Despite recent evidence that PAH may occur in SLE with a similar prevalence to that seen in SSc and that earlier detection is associated with milder PAH and reduced mortality, no such PAH screening recommendations exist for SLE [6]. There is, however, a multi-center trial currently underway in China to investigate the role of PAH screening in SLE using TTE and a biomarker-based PH screening procedure as used in the DETECT study described above [32].

The low prevalence of PAH occurring in the other CTDs, including pSS, IIM and RA, does not justify the extensive screening of asymptomatic patients with these conditions and thus there are currently no PAH screening recommendations in place for these CTDs.

Diagnosis of CTD-PAH

Screening algorithms detect patients suspected of having PH who should be referred for a diagnostic RHC. Prior to 2018, PH was defined at the 1st World Symposium on Pulmonary Hypertension (WSPH) in 1973 as present in a subject if the mean pulmonary

arterial pressure (mPAP) at rest was ≥ 25mHg whilst lying in a supine position [33]. It was recognised at the time that this upper limit of normal mPAP of 25 mmHg was somewhat empirical and arbitrarily defined [33]. These haemodynamic parameters were re-addressed at the 6th WSPH in 2018 and re-defined based on a scientific approach, with PH defined as mPAP >20 mmHg present in a subject supine [33]. This mPAP of 20mmHg was derived as it is two standard deviations above the upper limit of normal mPAP at rest independent of gender or ethnicity (14.0±3.3 mmHg)[34].

PH is classified into five major groups; Group 1 - Pulmonary arterial hypertension (PAH); Group 2 - PH secondary to left heart disease; Group 3 - PH due to chronic lung disease and/or hypoxemia; Group 4 - PH secondary to chronic thromboembolic pulmonary hypertension; and Group 5 - PH due to an unclear and multifactorial etiology [35]. As all of these PH groups can occur in SSc; the clinical picture together with the RHC hemodynamic parameters, particularly the mPAP, pulmonary arterial wedge pressure (PAWP) and the peripheral vascular resistance (PVR), and results of other imaging modalities including high resolution CT (HRCT) scan lung, PFTs, TTE and ventilation perfusion (V/Q) scans can help to differentiate between them.

Pre-capillary PH, defined haemodynamically on RHC as concurrent mPAP >20mmHg, PAWP ≥15mmHg and a PVR ≥3Woods units (WU) [33], occurs in Group 1 PAH (CTD-PAH), Group 3 and Group 4 PH. In order to distinguish between these PH groups in SSc, the presence of severe interstitial lung disease (ILD) on HRCT lung and restrictive pattern on PFT may direct one towards Group 3 PH whilst the presence of chronic thromboembolic disease on V/Q scanning may direct one's attention to Group 4 PH.

Group 1 PAH (CTD-PAH) is the most common form of PH in SSc. It is particularly important to distinguish PAH from other causes of PH in SSc as specific PAH vasodilator therapy is available and its prompt initiation is associated with a survival advantage [15]

In an attempt to detect PH at an earlier stage, measuring exercise haemodynamic parameters by increasing cardiac output has been trialled [36]. This is based on data

suggesting that mPAP will not rise until there has been ≥50% of the pulmonary microcirculation lost [36]. The concept of exercise PH is a contentious entity and will remain so until further information is known regarding how haemodynamic parameters change with age and how exercise-related changes in PAWP in Group 2 PH can be distinguished from pre-capillary PH.

State-of-the-art pharmacotherapy in CTD-PAH

Despite the availability of multiple pulmonary vasodilator therapies that interfere with the endothelin (ambrisentan, macitentan and bosentan), nitric oxide (sildenafil, tadalafil and riociguat) and prostacyclin (epoprostenol and iloprost) pathways, PAH remains a life-threatening clinical condition (Figure 3) [37]. The recent improvement in SSc-PAH symptoms, function and survival seen in the last decade [15, 38], is largely due the concept of combination pulmonary vasodilator therapy and escalation of treatments based on systematic assessment of clinical response rather than the discovery of new vasodilator therapeutic pathways [37].

The use of dual upfront combination vasodilator therapy from PAH diagnosis, specifically targeting the endothelin and the nitric oxide pathways, rather than monotherapy or sequential therapy (the addition of another vasodilator agent to monotherapy rather than upfront dual combination therapy), is associated with a significant reduction in the rate of clinical failure (50%), defined as hospitalizations for PAH progression, and improved exercise capacity [15, 38].

Until the recent approval of selexipag, an oral prostacyclin agonist, the only available agents targeting the prostacyclin pathway were parenteral epoprostenol, treprostinil or iloprost. Parenteral administration of medication is particularly restricting in SSc patients given the high prevalence of hand disability, joint contractures, sclerodactyly, skin thickening and difficulty gaining venous access. Therefore, the approval of selexipag has increased the treatment armamentarium for SSc-PAH particularly for CTD-PAH. Furthermore, selexipag can be administered earlier in the SSc-PAH disease course in those with World Health Organisation (WHO) functional class II and III, whereas the

parenteral agents (epoprostenol, treprostinil, iloprost) are reserved for patients with WHO functional class IV or those who need a bridge to lung transplantation. The studies of prostacyclin agonists in SSc-PAH have shown improvements in pulmonary hemodynamic parameters, functional class, exercise capacity, and survival [39-41]

Anticoagulation in the treatment of PAH is a contentious issue, with some studies showing a survival benefit in patients with idiopathic PAH (IPAH) and CTD-PAH [42, 43] and others not showing a survival benefit [44] (Figure 4). Furthermore anticoagulation in SSc is not without risk given the potential for gastrointestinal haemorrhage in those with gastric antral vascular ectasia. Therefore the decision about anticoagulation in the treatment of SSc-PAH has to be made on a case-by-case basis after an individual risk–benefit analysis.

In contrast to SSc-PAH where there is no therapeutic role for immunosuppressive therapy, there may be a concomitant role for the combination of PAH specific vasodilator therapy and immunosuppressive therapy with cyclophosphamide, mycophenolate mofetil, cyclosporine A, tacrolimus and /or prednisolone in those with active inflammatory SLE and concomitant PH and interstitial lung disease (ILD) or pulmonary vasculitis. In these patients, treatment strategies employing both immune-modulators and pulmonary vasodilators to target multiple convergent pathophysiologic pathways are likely more beneficial as evidenced by a significant improvements in hemodynamic parameters of mPAP, cardiac index (CI), and PVR, compared to a single therapeutic modality [45-47]

Risk stratification to guide treatment in CTD-PAH

Unlike IPAH where the current treatment strategies are based on PAH severity at diagnosis as assessed by a multi-parametric risk stratification approach [37], no such tools have been validated for use in the treatment of CTD-PAH specifically SSc-PAH. Currently a number of risk stratification algorithms exist including the French Pulmonary Hypertension Network (FPHN) registry risk equation, the PH connection equation, the Scottish composite score, the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk equation and risk score, and the 2015 ESC/ERS PH

guidelines risk table [37]. These algorithms provide treatment recommendations based on the PAH severity at diagnosis (classified into low-, intermediate- and high-risk) and on follow up defined by various clinical and haemodynamic measurements that predict 12-month mortality. For example, the 2015 ESC/ERS PH guidelines define PAH severity using modifiable clinical (right heart failure, progression of symptoms, syncope), functional (WHO functional class), exercise (6MWD), biochemical (NT-porBNP), echocardiographic (RA area, pericardial effusion) and haemodynamic variables (RAP, CI and mixed venous oxygen saturation) with known prognostic significance at 12-months [35] whereas the FPHN use the presence of four low risk criteria including WHO FC I or II, 6MWD >440m, RAP<8mmHg and CI ≥ 2.5L/min/m^2 [48].

These risk stratification algorithms recommend the most appropriate initial therapeutic strategy, including commencement of monotherapy, combination or sequential triple therapy depending on risk status (low-, intermediate- or high-risk). Treatment escalation occurs if low-risk status is not achieved in planned follow-up assessment based on the risk stratification tool used. The therapeutic strategy for high-risk status further recommends the initiation of parenteral prostacyclin and consideration of lung transplantation in the appropriate patient. As SSc-PAH is not a contra-indication for transplant and given the prognosis for SSc-PAH is worse than IPAH with a 3-year survival of 50-60%, SSc-PAH patients with the following characteristics should be also be referred early to a transplant centre: (i) WHO III/IV and/or clinical evidence of right ventricular failure and/or rapid symptom progression despite optimal therapy; (ii) CI <2L/min/m^2 or RAP >15mmHg despite optimal therapy; and (iii) suspected pulmonary veno-occlusive disease [49].

Physical exercise and rehabilitation in CTD-PAH

Once patients are clinically stable on their specific PAH therapy, consideration to the implementation of a supervised rehabilitation programme in centres experienced in both PAH patient care and rehabilitation of compromised patients should be given. Based on the 2015 ESC/ERS PH guidelines [35] extrapolating data from studies largely performed in patients with IPAH, PAH patients should be advised to be active within their symptom

limits, but to avoid excessive physical exertion if it causes distressing symptoms. Recent studies confirm the positive effect of training in PAH patients in particular an improvement in exercise and functional capacity (6MWD and cardiorespiratory function) and improved quality of life [50-52].

Lung transplantation in SSc-PAH

Bilateral lung transplantation is the method of choice in appropriate PAH patients on maximal triple combination therapy, with priority for those in intermediate- and high-risk groups as defined by the above risk stratification tools [53]. These groups have been chosen as they are expected to have a survival benefit with lung transplantation despite its 10% 12-month mortality rate [53]. Despite SSc-PAH being a multisystem condition, the outcome of lung transplantation in SSc-PAH is similar for IPAH [54, 55].

Conclusion

Despite the increased awareness of PAH as an entity in CTD, there is little literature available to guide expert recommendations regarding the need for PAH screening, risk stratification tools and treatment, except for SSc. There is a need, however, for a greater understanding across the varied medical specialties that encounter these conditions including rheumatology, respiratory medicine and cardiology, with an emphasis on the importance and effectiveness of early PAH detection in SSc through screening, early diagnosis, risk stratification and treatment implementation in high-risk individuals.

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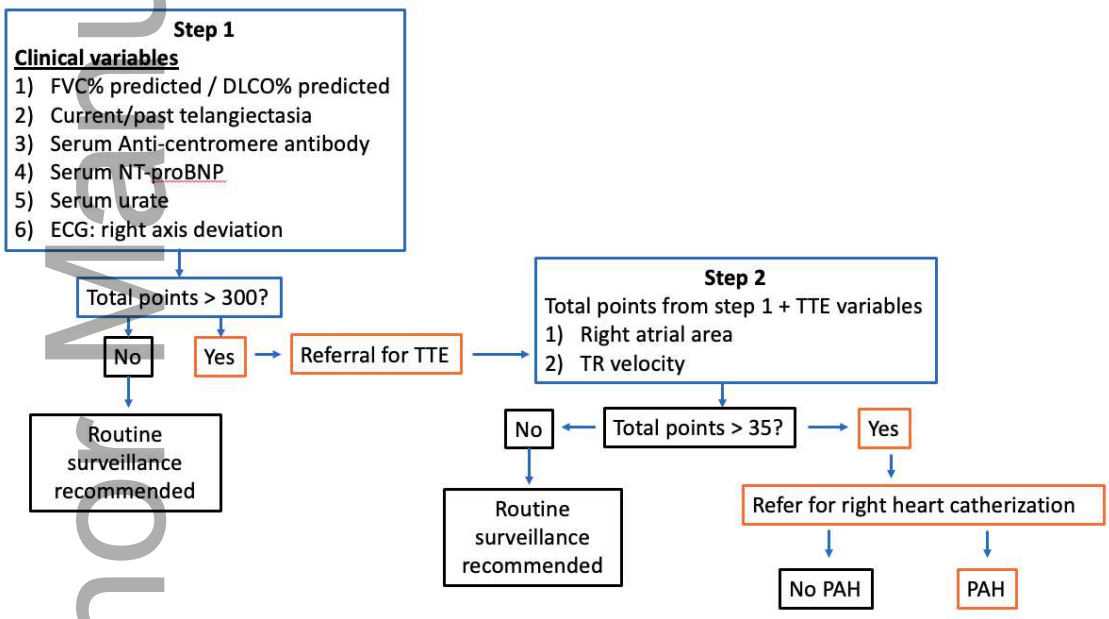
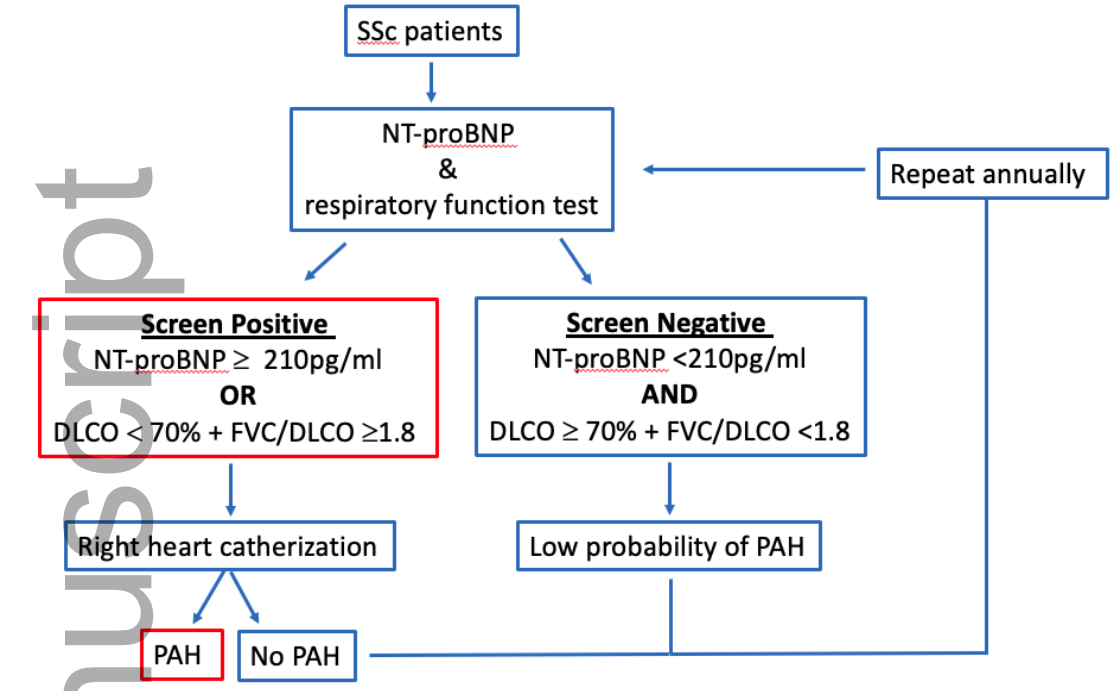
Figure 1 DETECT Algorithm



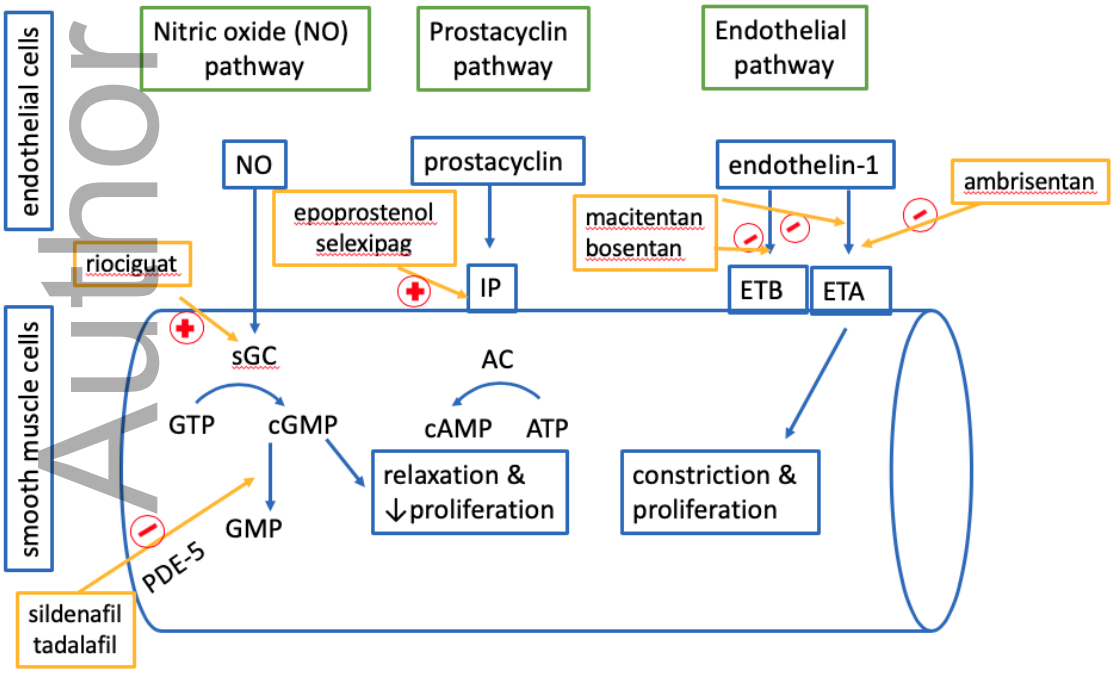
Abbreviations: forced vital capacity (FVC)/diffusing capacity of the lungs for carbon monoxide (DLCO) ratio, N-terminal pro-brain natriuretic peptide (NT-ProBNP), electrocardiogram (ECG), tricuspid regurgitation (TR), pulmonary arterial hypertension (PAH), transthoracic echocardiogram (TTE)

Figure 2 ASIG Screening Algorithm



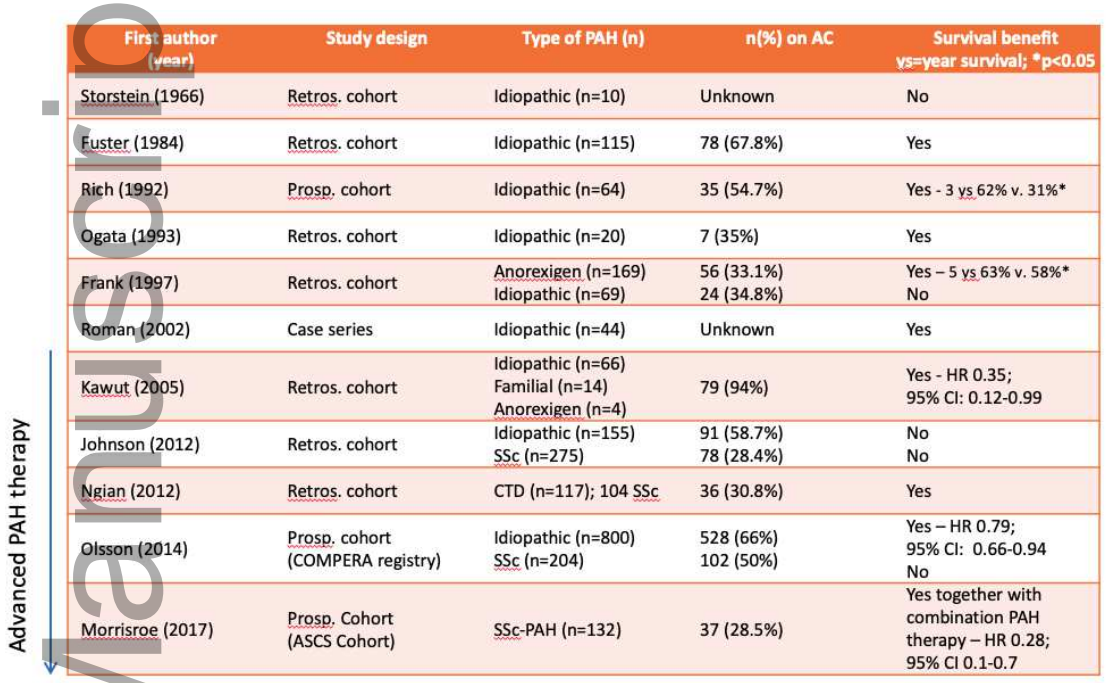
Abbreviations: pulmonary arterial hypertension (PAH), systemic sclerosis (SSc), forced vital capacity (FVC)/diffusing capacity of the lungs for carbon monoxide (DLCO) ratio, N-terminal pro-brain natriuretic peptide (NT-ProBNP)

Figure 3 Pulmonary vasodilator therapies



Abbreviations: adenylate cyclase (AC), adenosine triphosphage (ATP), cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), guanosine triphosphate (GTP), IP receptor, soluble guanylate cyclase (sGC), endothelin (ET)

Figure 4 Observational Studies of anticoagulation in SSc-PAH



First author (year)	Study design	Type of PAH (n)	n(%) on AC	Survival benefit vs=year survival; *p<0.05
Storstein (1966)	Retros. cohort	Idiopathic (n=10)	Unknown	No
Fuster (1984)	Retros. cohort	Idiopathic (n=115)	78 (67.8%)	Yes
Rich (1992)	Prosp. cohort	Idiopathic (n=64)	35 (54.7%)	Yes - 3 vs 62% v. 31%*
Ogata (1993)	Retros. cohort	Idiopathic (n=20)	7 (35%)	Yes
Frank (1997)	Retros. cohort	Anorexigen (n=169) Idiopathic (n=69)	56 (33.1%) 24 (34.8%)	Yes – 5 vs 63% v. 58%* No
Roman (2002)	Case series	Idiopathic (n=44)	Unknown	Yes
Kawut (2005)	Retros. cohort	Idiopathic (n=66) Familial (n=14) Anorexigen (n=4)	79 (94%)	Yes - HR 0.35; 95% CI: 0.12-0.99
Johnson (2012)	Retros. cohort	Idiopathic (n=155) SSc (n=275)	91 (58.7%) 78 (28.4%)	No No
Ngian (2012)	Retros. cohort	CTD (n=117); 104 SSc	36 (30.8%)	Yes
Olsson (2014)	Prosp. cohort (COMPERA registry)	Idiopathic (n=800) SSc (n=204)	528 (66%) 102 (50%)	Yes – HR 0.79; 95% CI: 0.66-0.94 No
Morrisroe (2017)	Prosp. Cohort (ASCS Cohort)	SSc-PAH (n=132)	37 (28.5%)	Yes together with combination PAH therapy – HR 0.28; 95% CI 0.1-0.7

Abbreviations: retrospective (retros), prospective (prosp.), anticoagulation (AC), hazard ratio (HR), confidence interval (CI), Australian Scleroderma Cohort Study (ASCS)