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# Recent developments in connective tissue disease associated pulmonary arterial hypertension

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ABSTRACT

Connective tissue disease associated pulmonary arterial hypertension (CTD-PAH) has benefited from the major treatment advances that have occurred within pulmonary hypertension over the past three decades. Inclusion of CTD-PAH cases in pivotal clinical trials led to regulatory approval and drug availability. This has improved outcomes but there are additional challenges for management. First, the multifaceted co-morbidity related to the associated CTD needs treatment alongside PAH and may impact on diagnosis and evaluation of treatment response. Secondary, cardiac involvement, interstitial lung disease and predisposition to thromboembolism in CTD may lead to compound phenotypes where PH has multiple mechanisms as well as precapillary pulmonary vasculopathy of PAH. In general, especially for systemic sclerosis, CTD-PAH has worse long-term survival than idiopathic or familial PAH. However, CTD also present an opportunity for screening and early detection and treatment for associated PAH, and this may in the future be a major advantage over idiopathic disease where presentation inevitable only occurs at symptomatic stages and diagnosis may be delayed. This article reviews and summarises some of the recent developments in investigation and management of CTD-PAH.

## 1. Introduction

Connective tissue diseases (CTDs) are a group of systemic rheumatic disorders that variably feature autoimmunity, endothelial dysfunction, fibrosis and hypercoagulability. Their clinical spectrum is extremely wide, spanning from mild phenotypes to life-threatening systemic and organ-specific inflammation and/or fibrosis. Cardiopulmonary involvement is not infrequent in CTDs and bears a high impact on morbidity and mortality. A significant complication in this context is pulmonary hypertension (PH), a severe clinical condition characterised by increased blood pressure in the pulmonary circulation. Pulmonary arterial hypertension (PAH) defines a subcategory of PH characterized by structural changes in the pulmonary vasculature, which cause an increase in pulmonary pressure and pulmonary vascular resistances in the pulmonary circulation, leading to progressive right-sided heart failure [1]. PAH represents a relatively frequent complication of CTDs, bearing a high clinical, social and psychological burden. It also represents a challenge for clinicians due to its difficult early diagnosis, progressive nature, and sub-optimal response to treatment. This review presents the most recent advances in definition, screening and therapeutic management of CTD-PAH.

## 2. Classification

PH is classified clinically in 5 groups, as presented in Table 1, according to similar pathophysiological, hemodynamic, clinical, and therapeutic characteristics [2]. The most common type of PH encountered in CTDs is group 1 PH, also known as PAH, and CTDs themselves are amongst the most common causes of PAH in the general population, second only to idiopathic PAH (IPAH) [2]. PAH is histologically characterized by vascular remodelling of pulmonary arterioles or capillaries. Of note, part of the PAH group is the rare pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis (PVOD/PCH), in which preferential remodelling of pulmonary venules and veins represents the culprit pathological process [3].

Importantly, despite PAH being the most common represented type, CTDs may feature in other PH categories as well. Patients may develop overt or subclinical myocardial involvement, which can cause group 2

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**Table 1**
2022 clinical classification of PH by European Society of Cardiology (ESC) and European Respiratory Society (ERS).

| | | |
|---|---|---|
| **Group 1: Pulmonary arterial hypertension** | Idiopathic | Non-responders at vasoreactivity testing<br>Acute responders at vasoreactivity testing |
| | Heritable | |
| | Associated with drugs and toxins | |
| | Associated with | Connective tissue diseases<br>HIV<br>Portal hypertension<br>Congenital Heart Disease<br>Schistosomiasis |
| | Pulmonary arterial hypertension with features of venous/capillary involvement | |
| | Persistent PH of the newborn | |
| **Group 2: PH associated with left heart disease** | Heart failure | With preserved ejection fraction<br>With reduced or mildly reduced ejection fraction |
| | Valvular heart disease | |
| | Congenital/acquired cardiovascular conditions leading to post-capillary PH | |
| **Group 3: Associated with lung disease and/or hypoxia** | Obstructive lung disease or emphysema | |
| | Restrictive lung disease | |
| | Lung disease with mixed obstructive | |
| | Hypoventilation syndrome | |
| | Hypoxia without lung disease | |
| | Developmental lung disorders | |
| **Group 4: PH associated with pulmonary artery obstruction** | Chronic thrombo-embolic PH | |
| | Other pulmonary artery obstructions | |
| **Group 5: PH with unclear and/or multifactorial mechanisms** | Haematological disorders | |
| | Systemic disorders | |
| | Metabolic disorders | |
| | Chronic renal failure | |
| | Pulmonary tumour thrombotic microangiopathy | |
| | Fibrosing mediastinitis | |

PH [4]. Similarly, interstitial lung disease (ILD) is frequently associated with CTDs and can be the underlying cause of group 3 PH [5]. Chronic thrombo-embolic PH (group 4) may occur as well, especially in the context of antiphospholipid syndrome [6]. Coexistence of different phenotypes is not uncommon in CTD-PH and poses additional clinical challenges in diagnosis and management.

## 3. Epidemiology

PAH may arise in the context of several CTDs, such as systemic sclerosis (SSc), systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), primary Sjogren syndrome (pSS), inflammatory myopathies and rheumatoid arthritis (RA) [7]. SSc is the most common disease associated with PAH, and 8–13 % of patients are expected to develop PAH during the disease course [8,9]. The UK PH registry documented a 74 % prevalence of SSc-PAH amongst CTD-PAH, followed by MCTD and SLE, both accounting for 8 % [10]. Moreover, SSc-PAH had the highest mortality rate, with 3-year survival of 47 %, compared with 74 % for SLE and 67 % for MCTD (although the difference with the latter was not statistically significant) [10]. Pulmonary hypertension secondary to lung disease in SSc had the poorest prognosis, with a 3-year survival of 28 % [10]. In the US REVEAL registry CTD-PAH accounted for 29 % of cases of PAH, second only to IPAH, and SSc was the aetiology of 62 % of cases of CTD-PAH. Five-year survival was significantly different between SSc-PAH and non SSc CTD-PAH, with values of 39.6 % and 63.3 % respectively [11]. The risk of SSc-PAH increases over time, with cumulative incidence of 2 %, 9 % and 15 % at 5, 10 and 15 years, respectively [12].

SLE is the second most common cause of CTD-PAH in North America and Europe: prevalence of SLE as a cause of CTD-PAH has been documented to be 13.5 % in REVEAL registry [11], 8 % in the UK PH registry [10], and between 0.5 % and 17 % in French cohorts [13,14]. In contrast, data coming from East Asian cohorts indicate SLE as the first cause of CTD-PAH. Indeed, in a recent population-based study in Taiwan the leading cause of CTD-PAH was SLE (57 %), followed by SSc (30 %) and pSS (9 %) [15]. Accordingly, SLE has been reported as the cause of CTD-PAH in 49–70 % of patients in China, with SSc being the aetiology of just 6 % of cases, and pSS and MCTD representing 9 and 12 % of cases, respectively [16,17]. In a Japanese cohort instead, MCTD has been identified as the leading cause of CTD-PAH, accounting for 43 % of cases, with SLE and SSc following, with prevalenceso] of 29 and 19 %, respectively [18].

These data come from cohorts enrolled in the last 30 years and based on PAH diagnosis confirmed by right heart catheterization (RHC). It is important to highlight that in view of the recent revisions of the haemodynamic parameters for PAH diagnosis [1], these epidemiological data would need to be adjusted.

## 4. Diagnosis

Diagnosis of PH needs to be supported by haemodynamic assessment of pulmonary circulation by RHC. Since 1973, PH has been defined by the presence of a mean pulmonary arterial pressure (mPAP) ≥25 mmHg measured by RHC at rest. As mPAP at rest in the general population was documented to be around 14 mmHg [19,20], the threshold for PH diagnosis was lowered to 20 mmHg in 2019 [21]. PAH is a pre-capillary vascular pathology, characterized by vascular remodelling of the pulmonary arterioles, and therefore by increased values of pulmonary vascular resistance (PVR). Based on recent observations [22,23], the upper limit of normality and lowest prognostically relevant threshold for PVR has been lowered from 3 to 2 Woods units (WU) [1]. Values of pulmonary wedge pressure (PWP) in PAH need to be ≤ 15 mmHg, to discriminate it from post-capillary PH. In special cases, repeated measures of PWP after fluid challenge allow to unmask left ventricular diastolic dysfunction and type 2 PH [1]. Diagnosis of PAH demonstration of pre-capillary PH and exclusion of other causes of pre-capillary PH, such as respiratory associated PH or PH related to chronic thromboembolism.

Of note PVOD/PCH presents the same haemodynamic parameters of PAH but is associated with poorer prognosis, limited response to PAH therapy and risk of pulmonary oedema with these treatments [24], thereby differential diagnosis between these two conditions is essential. Patients with PVOD/PCH usually present with lower DLCO levels and with peculiar radiological features at chest CT, such as thickened interlobular septal walls, centrilobular ground-glass changes and mediastinal lymphadenopathy [24]. Presence of more than one of these radiological signs is not infrequent in SSc-PAH and has been found to directly correlate with higher mPAP and higher risk of pulmonary oedema with conventional PAH therapies [25,26]. This suggests a significant involvement of the venous component in the pathogenesis of SSc-PAH [27], a finding corroborated by the higher frequency of obstructive vascular lesions in pulmonary venules in histological samples of CTD-PAH with respect to IPAH [28].

## 5. Screening

PAH is a severe CTD complication and has a significant impact on quality of life, morbidity and mortality. A high level of suspicion for PAH should be maintained in CTD patients, and timely investigations should be made in presence of suggestive symptoms. Nevertheless, symptoms of PAH are insidious, can be attributed to other causes in the context of CTD (e.g. ILD, heart involvement, musculoskeletal disease, anaemia) and appear late in the disease course. Diagnosis is thereby frequently delayed, with a significant impact on prognosis [29–31]. Effective screening strategies are of utmost importance to provide early diagnosis, prompt treatment and better prognosis. A validated annual screening strategy is recommended only for SSc, justified by the high incidence of SSc-PAH [12,32]. Several screening algorithms have been proposed, based on a combination of clinical evaluation, blood biomarkers, lung function tests and transthoracic echocardiography, and annual evaluation of these parameters is thus recommended [1,33]. Lung function tests are particularly useful as early markers of PAH development, as serial decline in carbon monoxide transfer coefficient (KCO) is associated with pulmonary vasculopathy [34]. A recent landmark analysis showed that SSc patients display a progressive decline in diffusion lung capacity for carbon monoxide (DLCO) and KCO from 5 to 7 years before PAH diagnosis [35], probably reflecting the early stages of pulmonary dysfunction preceding the onset of proper PAH. Thereby it is important not only to consider the annual changes in lung function parameters but also their trajectory over time.

The most employed screening algorithms are the DETECT, the Australian Scleroderma Interest Group (ASIG) and the 2015 ERS/ESC algorithm [33].

DETECT algorithm is to be applied to non-early SSc (>3 years since first non-Raynaud's phenomenon) with a forced vital capacity ≥40 % and DLCO <60 mL/min/mmHg. It is based on 2 steps: step 1 gives a composite score based on current or past presence of telangiectasias, presence of serum anticentromere antibodies (ACA), NT-proBNP and urate serum levels, right axis deviation on ECG, and FVC % predicted/DLCO % predicted; patients exceeding a score of 300 are referred to step 2, which evaluates right atrium area and tricuspid regurgitation velocity. A composite score including step 1 and step 2 risk points is then made, providing indication for RHC referral. When first described, DETECT algorithm provided a sensitivity of 95.8 % and a specificity of 47.8 % [36]. After the recent changes in the haemodynamic definition of PAH [1], its performance has been re-tested, showing a reduction of sensitivity to 88.2 % and a slight increase in specificity to 50.8 % [37]. BEYOND-DETECT, a follow-on study from the DETECT study, is presently ongoing (IRAS ID 206414). ASIG algorithm comprises 2 steps. At first, NT-proBNP levels and lung function tests are evaluated: if DLCO <70 % with an FVC/DLCO ≥1.8, and/or NT-proBNP ≥210 pg/mL the patient is referred for echocardiography. Referral to RHC is then made on the basis of echocardiographic findings, on a case-by-case basis [38]. When evaluated, ASIG algorithm provided a sensitivity of 94.1 % and a specificity of 54.5 % [39]. The 2022 ESC/ERS guidelines deploy an algorithm based on echocardiograph variables (tricuspid regurgitation velocity and presence of other echocardiographic signs of PH) to stratify the probability of PH to low, intermediate, and high categories. Patients with intermediate and high probability of PH should be referred to a specialized centre and be considered for RHC [1].

RHC to exclude PH is recommended in SSc patients with unexplained breathlessness irrespective of screening algorithms [1].

Current guidelines recommend adopting similar screening strategies also to CTDs that have features of SSc spectrum, such as MCTD, or in presence of high-risk phenotypes [1,33]. No validated screening strategies exist for SLE-PAH, but some associated risk factors have been described, suggesting close monitoring and early referral for echocardiography and RHC in these patients. Identified risk factors include longer disease duration, presence of serositis, arthritis, ILD, acute or subacute cutaneous lupus, DLCO<70 %, scleroderma pattern at nailfold capillaroscopy, positive anti-RNP, anti-SSA or anti-SSB antibodies, low disease activity [40]. Furthermore, presence of malar rash and positive anti-dsDNA or antiphospholipid antibodies have been associated to a lower risk of SLE-PAH [40].

Fig. 1 provides a schematic overview of evaluation and referral pathways for CTD patients that are suspected of having PH. This should always involve a specialist PH Centre for cases requiring specialized diagnostic tests and PAH specific therapy.

## 6. Biomarkers

PAH subtends a complex pathophysiological process, orchestrated by the combined action of vasoactive and pro-angiogenic factors, inflammatory cytokines, products of autoimmunity, platelet activation and endothelial to mesenchymal transition. This results in vascular remodelling and progressive loss of function. Due to the high reserve of the pulmonary vasculature, pulmonary vascular dysfunction greatly precedes the actual rise in pulmonary arterial resistance and pressure, which when roughly 50–70 % of the pulmonary vascular bed is lost [41]. Chronic rise in mean pulmonary artery pressure results then in tissue hypoxia and right ventricular failure, which represents the late stage of PAH.

Within the spectrum of CTDs, different pathological processes can variably participate in PAH pathogenesis. Indeed, while SSc-PAH is characterized by prominent vascular remodelling, immune complexes-mediated pulmonary vasculitis is the predominant histopathological finding in SLE-PAH [42].

Several biomarkers have been identified, each related to one of the mechanisms contributing to the early and late stages of PAH development. Some of these are already employed for early diagnosis, prognostic evaluation, or to monitor response to treatment, while others are promising candidates to enter clinical practice. A brief overview of the most significant biomarkers is presented in Table 2 [43].

It is important to highlight the role of autoantibodies in predicting risk and prognosis of CTD-PAH. Among SSc-specific autoantibodies, ACA have the strongest association with PAH: they are detected in 45 % of patients with SSc-PAH [44], and PAH represents the leading cause of mortality in this subset of patients [45]; moreover, ACA positivity has been included in the DETECT algorithm [36]. The subset of anti-p4.2 ACA were recently found associated with DLCO values < 70 % even in absence of pulmonary fibrosis and of a formal diagnosis of PAH, thus suggesting a possible role in predicting pulmonary vascular disease [46]. PAH has been diagnosed in 25–33 % of patients with anti-U3RNP (anti-fibrillarin) antibodies and represents the main cause of death in this subset of patients [44,47]. Rarer autoantibodies such as anti-Th/To antibodies were reported to be significantly associated with PAH, with a prevalence of 25 % in SSc-PAH patients and a 33 % prevalence of PAH amongst anti-Th/To positive patients [44]. Among more common SSc-antibodies, anti-RNA polymerase III (ARA) have been associated with an increased risk of PH, while anti-topoisomerase I (ATA) reduced the hazard [12].

In SLE, anti-U1RNP have been associated both to PAH diagnosis and severity [48,49], and a higher prevalence of anti-phospholipid antibodies was detected in SLE-PAH [50].

## 7. Evidence-based treatment

General measures which should be sought in every patient with CTD-PAH include as supervised exercise training, immunization against SARS-CoV2, influenza and Streptococcus pneumoniae, correction of iron deficiency and oxygen administration when required [1]. Every patient with CTD-PAH should be managed with PAH-specific therapy and treated to target based on their risk class [1]. Most importantly, every patient with CTD-PAH should be managed and followed up at a specialized centre [1]. Immunosuppressive treatment with a combination of cyclophosphamide and glucocorticoids might be beneficial in patients with PAH associated to SLE, MCTD or pSS [51,52], while it is not recommended in SSc [1]. Furthermore, a trend towards better survival has been shown in SLE-PAH patients under treatment with hydroxychloroquine [53]. Currently approved therapies are the same of

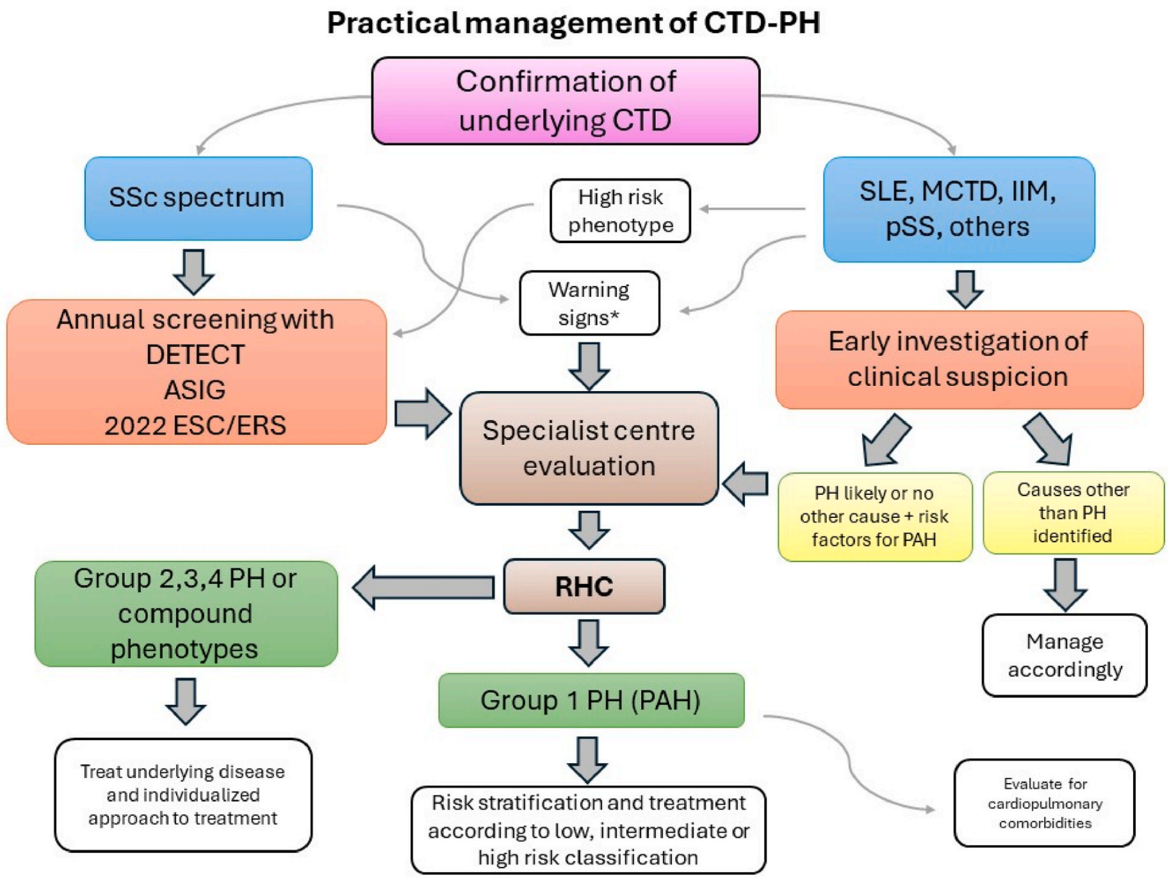


**Fig. 1. Practical management of CTD-PAH.** CTD: Connective tissue disease; SSc: systemic sclerosis; SLE: systemic lupus erythematosus; MCTD: mixed connective tissue disease; IIM: idiopathic inflammatory myopathies; pSS: primary Sjögren syndrome. *Warning signs include rapid progression of symptoms, severely reduced exercise capacity, syncope on mild exertion or pre-syncope, signs of right heart failure. Pulmonary hypertension in CTD needs to be considered in all relevant patients. SSc spectrum CTD require regular screening in line with current recommendations. The DETECT score, ASIG algorithm, or ESC/ERS algorithm can be applied to cases to stratify risk and determine need for RHC referral. Other CTD should be assessed according to clinical suspicion or screened similarly to SSc in case of high-risk phenotypes. All cases with suspected PH should be referred for assessment and management by a specialist PH centre and presence of warning signs should prompt early referral. Further evaluation after RHC will determine the predominant mechanism for PH and facilitate appropriate management according to latest ESC/ERC guidelines [1]. In PAH, treatment should be guided by risk stratification before and after therapy, using both clinical, biochemical, imaging and haemodynamic parameters [1].

IPAH and target 3 main pathways: endothelin pathway, the prostacyclin pathway, and the nitric oxide (NO) pathway. Remarkably, while the definition of PAH has been recently revised, indication for therapy remains based on the previous definition (i.e. mPAP $\geq$25 mmHg, PAWP $\leq$15, PVR $>$3) as all the available evidence applies to these patients. The benefits of standard of care PAH therapy in patients with mild PAH (mPAP between 21 and 24 mmHg, PVR between 2 and 3 WU) are yet to be evaluated.

### *7.1. Endothelin pathway*

Endothelin-1 (ET-1) mediates vasoconstriction and proliferation of pulmonary smooth muscle cells by binding to ET type A and B receptor (ETRA and ETRB). Three licensed endothelin-receptor antagonists (ERA) are available: bosentan, ambrisentan and macitentan. Bosentan, a dual ETR inhibitor, has been associated to significant improvements in 6-min walking distance (6MWD) and a trend towards improvement of pulmonary haemodynamics [54–56]. Ambrisentan is an ETRA inhibitor and has been associated to an increase in 6MWD in about 60 % of CTD-PAH patients [57]. Macicentan is a dual ETR inhibitor, associated with a significant reduction in morbidity mortality with respect to placebo, with the effect maintained in case of combination with another PAH-specific treatment [58].

### *7.2. Nitric oxide pathway*

PAH is characterized by reduced concentrations of nitric oxide (NO). NO binds to soluble guanylate cyclase (sGC), stimulating the production of cyclic guanosine monophosphate (cGMP), which mediates vasodilation and inhibits vascular proliferation [59]. This mechanism is negatively regulated by phosphodiesterases, which proteolytically inactivate cGMP. Phosphodiesterase 5 is highly expressed in the pulmonary vasculature [60], therefore PDE-5 inhibitors increase the availability of cGMP and are widely used in the treatment of IPAH and CTD-PAH. The three available PDE5 inhibitors are sildenafil, tadalafil and vardenafil (although the letter never tested in CTD-PAH). Sildenafil has been associated with increased 6MWD and improved mPAP and PVR when compared to placebo in CTD-PAH [61]. Riociguat is a sGC stimulator, which increases cGMP production irrespective of NO concentrations. It has the theoretical advantage of being less depenent on endothelial production of NO, and demonstrated a positive effect in PAH-CTD when compared to placebo, by increasing 6MWD and improving pulmonary haemodynamic [62].

### *7.3. Prostacyclin pathway*

Prostacyclin binds to its receptor on platelets and endothelial cells, causing increase in intracellular cyclic adenosine monophosphate

**Table 2**
Biomarkers associated with CTD-PAH.

| Mechanism | Sub-mechanism | Agent | Significance |
|---|---|---|---|
| Endothelial dysfunction | *Imbalance between vasoactive mediators* | Endothelin 1 (ET-1) | Increased levels in SSc-PAH [89], decreasing with treatment with anti-ET-1 agents [90] and correlated with RV dysfunction on echocardiography [91]. Increased levels in SLE [92] and possible correlation with PAH development [93] |
| | | Nitric Oxide (NO) | Possible marker of treatment response in SSc PAH [90] |
| | | Asymmetric dimethylarginine (ADMA) | Association with SSc-PAH, especially when combined to NT-proBNP levels [94] |
| | *Vascular remodelling* | Serum receptor for advanced glycation end products (sRAGE) | Higher levels in SSc-PAH, correlated with PAH-related mortality. |
| | | Growth Differentiation Factor 15 (GDF-15) | Increased levels in SSc patients with PAH compared to SSc patients without PAH [95,96] |
| | | Follistatin-3 (FLS-3) and midkine (MDK) | Increased concentrations in SSc PAH vs SSc [97] |
| | | Chemerin | Increased levels in SSc-PAH vs SSc, with positive correlation with PVR [98] |
| | | Matrix metalloproteinase 10 | Pro-MMP10 was increased in SSc-PAH vs SSc and healthy controls [99] |
| | | Tissue inhibitor of metalloproteinases 4 (TIMP-4) | Serum levels correlated with sPAP in SSc-PAH patients [100] |
| | | Uric acid | Increased levels in SSc PAH [101], with positive response to vasodilator therapy [102]. Included in DETECT score [36] |
| | | Serum placental growth factors (sPlGF) | Higher levels in SSc-PAH vs IPAH and healthy controls, correlated to functional class and BNP levels [103] |
| | | Endostatin | Increased levels in SSc-PAH, associated to mortality, functional class, BNP and pulmonary haemodynamics [103–105] |
| | *Platelet activation* | Thrombomodulin | Increased levels in SSc-PAH and MCTD-PAH compared to non-PAH counterparts [106,107] |
| Autoimmunity | *Functional antibodies* | Anti-Endothelial Cells Antibodies (AECA) | Association with vasculopathic manifestations of SSc [108,109] |
| | | Anti-endothelin-1 receptor A (ETAR) and anti-angiotensin receptor type 1 (AT1R) antibodies | Higher titres of both antibodies in patients with SSc vasculopathic manifestations [110,111]. Higher titres of anti-ETAR in SLE-PAH with correlation with mPAP [112]. |
| | | Anti-bone morphogenic protein receptor (BMPR) antibodies | Anti-BMPR1A increased in patients with SLE-PAH vs SLE and healthy controls [113]. |
| Inflammation | *Proinflammatory cytokines* | TNFα, IL-1β, IL-6, IL-8, IL-13 | Increased serum levels in SSc-PAH [114]. IL-6 increased in MCTD-PAH [115]. |
| | | IL-18 binding protein isoform a | Increased serum levels in SSc patients, correlated to sPAP [116] |
| | | Pentraxin 3 | Elevated levels in CTD-PAH compared to healthy controls [117] |
| Cardiac dysfunction | | BNP and NT-proBNP | Increased levels in SSc-PAH, predictive of diagnosis and mortality [118]. NT-proBNP part of DETECT algorithm [36] |
| | | High-sensitive troponin T and I (Hs-TnT and Hs-TnI) | Elevated Hs-TnT levels strongly associated with PAH, especially when combined to NT-proBNP [119]. Hs-TnI correlated with sPAP in SSc-PAH [120] |

(cAMP) concentrations and causing vasodilation, anti-proliferative, cytoprotective and anti-thrombotic effects. Five licenced agents act on the prostacyclin pathway: iloprost, epoprostenol, treprostinil, beraprost and selexipag. Epoprostenol is a prostacyclin analogue administered intravenously. In a RCT on SSc-PAH, when added on top of PAH conventional therapy, it improved 6MWD and functional symptoms, as well as reducing both mPAP and PVR [63]. Due to its short half-life, it needs to be administered by a continuous infusion pump, exposing the patient to the risks associated with continuous iv therapy. Iloprost is a prostacyclin analogue, and the inhaled formulation has been tested in a randomized controlled trial (RCT) including CTD-PAH. Inhaled iloprost improved symptoms, 6MWD and pulmonary haemodynamic with respect to placebo [64]. Limited data are available for intravenous iloprost, extensively used in the treatment of SSc peripheral vasculopathy [65]; in a retrospective multicentre analysis iv iloprost given after the inhaled formulation documented an initial haemodynamic and clinical improvement, however with a poor long-term survival [66]. Treprostinil is a prostacyclin analogue available in oral, inhaled, subcutaneous and iv formulations. Subcutaneous treprostinil has been associated with improvement in 6MWD, functional symptoms and pulmonary haemodynamic when compared to placebo in various forms of PAH, including CTD-PAH [67]. Chronic subcutaneous therapy has been associated with frequent injection-site reaction, thus intravenous therapy via implantable pump can be selected as an alternative option [68]. Inhaled treprostinil added on top of either sildenafil or bosentan improved the 6MWD, NT-proBNP and quality of life measures in patients with PAH [69]. Moreover, inhaled treprostinil was recently evaluated in a RCT for PH secondary to ILD and was associated with improvement 6MWD and reduced hazard for clinical worsening [70]. As ILD is not infrequent in CTD and may contribute to PH development, treprostinil may represent an amenable option in compound phenotypes. Inhaled Treprostinil is presently not available in Europe. Beraprost is an orally administered prostacyclin analogue; two RCTs have documented a short-term improvement in exercise capacity, however not associated to benefits in long-term outcomes or pulmonary haemodynamic [71]. Selexipag is a selective prostacyclin receptor antagonist, orally administered. The GRIPHON trial showed that selexipag alone or added on PAH-specific therapy (ERA and/or PDE5i) was associated with a 40 % reduction in risk of composite morbidity/mortality when compared with placebo, with a preserved efficacy in the CTD-PAH subgroup [72]. Interestingly, risk reduction was greater in SSc-PAH than in SLE-PAH (44 % vs 34 %) [72].

## 8. Risk stratification and treatment to target

The available studies on PAH support a risk-based, goal-orientated treatment approach, where the aim is to obtain and or maintain a low-risk status. This applies to the subgroup of CTD-PAH as well. Initially formulated in 2015, and later update in the revised version of 2022, the ERS/ESC algorithm for risk stratification comprehends presence of clinical signs of right heart failure, functional assessment (progression of symptoms, WHO functional class, 6MWD), parameters of cardiopulmonary exercise testing, cardiac biomarkers (BNP or NT-proBNP), imaging measures (from echocardiography or cardiac magnetic resonance) and haemodynamic data from RHC [1,73]. This allows to stratify the patients in three categories: low, intermediate, and high risk. Patients at low or intermediate risk should receive initial combination therapy with PDE5i and ERA [1]. Association of tadalafil to macitentan or ambrisentan should be the first choice, even though any combination of drugs can be sought [1]. In case of intolerance or contraindication to one medication, an agent of the same class can be selected [65]. Of note, bosentan has been reported to decrease plasma concentrations of sildenafil when co-prescribed for PAH, therefore it would be better to avoid this combination [74]. High risk patients should receive upfront combination of ERA, PDE5i and intravenous or subcutaneous prostacyclin analogue [1]. At follow up (every 3–6 months or in case of clinical worsening), a four-strata model is recommended, based on a combination of WHO functional class, 6MWD and BNP or NT-proBNP. This model subdivides patient's risk in low, intermediate-low, intermediate-high, and high. Low-risk patients should maintain current treatment, intermediate-low patients should add a prostacyclin receptor agonist (i.e. selexipag) or switch PDE5i to sGC stimulator (i.e. riociguat), while intermediate-high or high-risk patients should add intravenous or subcutaneous prostacyclin analogue if not already on it and/or be considered for lung transplantation [1]. It is important to consider that a significant percentage of CTD patients, especially patients with SSc, receive therapy with PDE5i, ERA or both for the treatment of peripheral vasculopathy manifestations related to the disease, such as severe Raynaud's phenomenon or digital ulcers [65]. In such patients, ongoing treatment may delay the formal diagnosis of PAH, and they are intuitively expected to meet the indication for triple PAH-specific therapy closer to diagnosis as the rest of patients. The impact of this delayed diagnosis on overall prognosis is yet to be determined but not expected to be significant.

As mentioned, a significant percentage of patients with CTD-PAH (as IPAH) have cardio-pulmonary comorbidities, either related to their primary disease or to age and general population's risk factors. Patients with cardio-pulmonary comorbidities were either under-represented or excluded from clinical trials, therefore no evidence-based recommendation can be made for this category. Risk stratification is accordingly of limited usefulness in guiding therapeutic decision-making. Current guidelines recommend initial monotherapy, with PDE5i being the most widely used agent in registry data [75]. Further management should be tailored on an individual basis as most patients do not respond or have worsening symptoms with combination therapy [1]. A recent sub-analysis of the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) documented that most CTD-PAH patients received initial monotherapy while 10–27 % of patients were managed with an initial combination therapy, with significantly better survival [76].

## 9. Novel emerging therapies

No substantial improvement in PAH survival has been obtained in the past 10 years. The continued high morbidity and mortality evidence the urge for additional treatment options that target new pathways involved in pulmonary vascular remodelling.

Sotatercept is a fusion protein composed of human IgG Fc domain linked to the extracellular domain of human activin receptor type IIa. It acts as a ligand trap for selected TGF-β superfamily members (namely activin A, activin B, growth differentiation factor 8 and 11), inhibiting their function and restoring the pulmonary vascular homeostasis by increasing growth-inhibiting and proapoptotic signalling [77,78]. In the STELLAR study, a phase III multicentre randomized double-blind trial, subcutaneous sotatercept on top of double or triple PAH-specific therapy significantly increased 6MWD and a significantly reduced risk of composite clinical worsening and death (hazard ratio 0.16) compared to placebo, along with significant improvement in several functional and biochemical secondary endpoints [79]. SOTERIA trial (NCT04796337), a long-term follow-up study of sotatercept for PAH Treatment is presently ongoing.

As addressed in previous sections, patients with PVOD/PCH have usually a poor response and high risk of pulmonary oedema related to conventional PAH therapies. Imatinib, a multitarget tyrosine kinase inhibitor, represents a possible therapeutic option. Among its actions, imatinib's inhibitory effect on platelet derived growth factor (PDGF) and stem cell factor receptor (c-Kit) is supposed to counteract smooth muscle cell hyperplasia and proliferation and being effective PAH [80,81]. In a small observational study treatment with oral imatinib improved 6MWD, functional class and short-term survival in PVOD/PCH patients, qualifying as a possible option as a bridge to lung transplantation. Oral imatinib has been explored in the treatment of PAH but the improvement in hemodynamic and 6MWD was outweighed by the high frequency of severe adverse events (mostly serious bleeding events) and discontinuation rate [82]. Inhaled imatinib is supposed to have a limited systemic exposure and a better safety profile and its efficacy is currently being tested on top of at least dual PAH therapy in a phase IIb/IIIa clinical trial (IMPAHCT trial - NCT05036135). Seralutinib is another potent tyrosine kinase inhibitor, specifically targeting PDGF receptors, C-Kit, and increasing bone morphogenic protein receptor type 2 signalling. Inhaled seralutinib has a 10-fold greater potency for PDGFα/β inhibition and its safety and efficacy in PAH are currently being tested in a phase 2 randomized, double-blind, placebo-controlled trial (NCT04456998) [83].

Several drugs targeting other pathways are currently being tested in clinical trials [84]. Ifetroban, a selective thromboxane receptor antagonist, has been shown to partially reverse platelet activation and deposition induced by hypoxia. Oral ifetroban is currently being tested in a phase II multicentre, randomized, placebo-controlled trial on diffuse cutaneous SSc or SSc-PAH (NCT02682511). Rodatristal ethyl is an antagonist of tryptophan hydroxylase, the enzyme deputed to the synthesis of serotonin. Increased levels of serotonin induce excessive growth and contraction of pulmonary artery smooth muscle cells, and tryptophan hydroxylase 1 is found elevated in pulmonary endothelial cells of PAH [85]. ELEVATE-2 trial (NCT04712669) is a phase 2b, double-blind, multicentre trial evaluating safety and efficacy of rodatristal ethyl versus placebo in patients with PAH [86].

Oestrogen modulators are being investigated in treatment of PAH as well, owing the putative role of oestrogens in mediating proliferation of pulmonary smooth muscle cells [87]. Anastrozole, an aromatase inhibitor reducing conversion of testosterone into oestradiol, is under investigation in a multicentre double-blind, placebo-controlled phase 2 randomized clinical trial on PAH patients receiving background therapy (PHANTOM trial - NCT03229499). Similarly, the oestrogen receptor inhibitor tamoxifen is being tested in a single-center, double-blind randomized placebo-controlled phase 2 trial (T2PAH - NCT03528902).

Bardoxolone methyl is an oral activator of nuclear factor erythroid 2-related factor 2 (Nrf2), which reduces oxidative stress and nuclear factor kappa light chain enhancer of activated B cells (NF-kB) activation. An interim report of the LARIAT phase 2 clinical trial demonstrated a significant functional improvement in the subset of CTD-PAH patients [88]. Unfortunately, the two follow-up phase 3 trials have been terminated due to difficulties related to COVID-19 pandemic, but further studies exploring the therapeutic role of bardoxolone in CTD-PAH are warranted.

## 10. Concluding remarks

Pulmonary arterial hypertension is a severe complication of connective tissue diseases, especially of systemic sclerosis. Several advances have been made in the past two decades in diagnosis, risk stratification and therapeutical management, resulting in a significant improvement in survival and quality of life. Nevertheless, PAH remains a chronic progressive disease with poor long-term survival and lung transplantation, when feasible, represents the only option for treatment-refractory patients. The recent approval of new pharmacological therapies and the platform of drugs currently under evaluation in clinical trials may represent a brighter future for PAH management, however further evidence is warranted.

## CRediT authorship contribution statement

**Stefano Rodolfi:** Resources, Writing – original draft, Writing – review & editing. **Voon H. Ong:** Validation, Visualization, Writing – review & editing. **Christopher P. Denton:** Conceptualization, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Christopher P Denton reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with GlaxoSmithKline Inc that includes: consulting or advisory, funding grants, and speaking and lecture fees. Christopher P Denton reports a relationship with Boehringer Ingelheim Pharmaceuticals Inc that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with Bayer HealthCare Pharmaceuticals Inc that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with Sanofi Aventis Inc that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with Roche that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with CSL Behring Spa that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with Corbus Pharmaceuticals Holdings Inc that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with Acceleron Pharma that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with Horizon Pharmaceuticals Inc that includes: consulting or advisory, funding grants, and speaking and lecture fees. Christopher P Denton reports a relationship with Lilly Pharma Holding GmbH that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with Arxx that includes: consulting or advisory, funding grants, and speaking and lecture fees. Christopher P Denton reports a relationship with Novartis Pharmaceuticals Corporation that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with certa therapeutics that includes: consulting or advisory and speaking and lecture fees. Christopher P Denton reports a relationship with AbbVie Inc that includes: funding grants. Christopher P Denton reports a relationship with Servier Pharma Srl that includes: funding grants. Voon H Ong reports a relationship with Boehringer Ingelheim GmbH that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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