Aggressive treatment of SSc-associated PAH by up-front combination therapy

J G Coghlan and C P Denton

Royal Free London NHS Foundation Trust

and UCL Division of Medicine

Abstract

Pulmonary arterial hypertension is an important complication of systemic sclerosis with high mortality but should be regarded as a treatable manifestation of the disease. Management draws on experience from other forms of pulmonary arterial hypertension and benefits from an increasing number of licensed therapies. Outcome is variable but recent clinical trials suggest that combination therapies used early in the disease may be associated with better outcome. This is important because previous clinical trials using short term gain in exercise capacity did not show significant benefit compared to that observed for idiopathic or heritable forms of PAH. Thus, it is important to identify cases as early as possible and to manage cases that are in a high-risk group using early combination therapy. This review summarises the most recent analyses of clinical trial data, with a focus on those patients with SSc associated PAH and provides the evidence base that supports current treatment recommendations for aggressive PAH occurring in systemic sclerosis, including the early use of combination PAH specific drugs in appropriate cases.

Introduction

Long-term event-driven clinical trials for patients with WHO Group I pulmonary hypertension (PAH) have demonstrated benefits of targeted vasodilator therapies, including a substantial proportion of cases in which different PAH specific drugs were used in combination. They have also re-affirmed the treatment effects that occur for key subtypes of PAH, especially that associated with connective tissue disease (PAH-CTD) and systemic sclerosis (PAH-SSc). The recent Ambition trial has demonstrated the efficacy of upfront combination therapy in delaying clinical failure among patients with pulmonary arterial hypertension (PAH)[1]. An identical efficacy to that observed in idiopathic PAH (IPAH) with confidence intervals below unity is evident in the subgroup of patients with systemic sclerosis (SSc)[2]. In isolation, as a post-hoc analysis of a very carefully selected population one might not get too excited about this observation, however similar findings in the GRIPHON trial[3] and the SERAPHIN trial[4] provide grounds for asserting that there is a genuine effect being observed here. Further there is published data demonstrating the mechanism of benefit[5], with a much greater haemodynamic response and improve right ventricular function using upfront combination therapy in the SSc population. The consequence is quite profound, given the misgivings that have been expressed in respect of the value of treating patients with CTD including those with scleroderma[6]. To explore the magnitude of the shift in perspectives required, we shall set out the background reasons for concern in respect of PAH-SSC and explore the 'explanations proposed, dissect the recent 'outcome' trials, and finally consider not just the aggression of therapy in terms of intensity, but also timing.

PAH-SSc 'a challenging subgroup'.

While patients with SSc have a similar histological basis for PAH[7] and the initial open label randomised trial suggested a high level of effort response in a short-term trial[8], subsequent short-term trials were disappointing[9], as the treatment effect in terms of the primary endpoint (6MWD) appeared consistently inferior to that of the IPAH population. The only meta-analysis using individual patient data confirmed attenuated benefit in the PAH-CTD population[6] in terms of the primary endpoint in these trials (6MWD) and time to clinical worsening, while being associated with increased risk of adverse events (but not serious adverse events) in those exposed to active therapy[10]. The authors suggested that exclusion

of the PAH-CTD population might reduce the necessary study size and associated costs. **Figure 1** shows that impact on 6MWD and clinical worsening from this meta-analysis, of note the impact on these endpoint is not significantly different between the IPAH and SSc sub-populations. The efficacy in the SSc population in terms of 6MWD persists after correction for comorbidities and background medications, driven by deterioration in the placebo group. However, the 'apparent' benefit in terms of clinical worsening becomes non-significant unless the SERAPHIN trial is censored at 18 weeks, as shown below the 3mg dosing was ineffective in the CTD population and when all follow up is included this trial provides 72% of effect observed, thus potentially biasing the analysis.

Proposed explanations for the limited improvement on therapy include the older age of SSc[11] PAH patients, the prevalence of left heart[12], lung disease[13] and the higher prevalence of pulmonary veno-occlusive disease (PVOD)[14]. The negative results in older trials was counter-intuitive given the excellent clinical response seen in registries with substantial improvements in survival[15,16]. One very recent publication has suggested no progress in SSc survival in the past decade[17], intriguingly this paper provides further support for the need for aggressive treatment of PAH-SSc patients, as maximal administered therapy (despite a 50% 3-year mortality) was monotherapy in 40%, oral combination therapy in only 37% and prostanoid usage of any type was almost 50% less frequent in the PAH-SSc patients. One thing is clear from the confusing data published on the PAH-SSc population, that a more rigorous approach to diagnosis is essential in this population. To provide a secure diagnosis of "clean" (WHO Group I) PAH-SSc a rigorous assessment to exclude other forms of PH is needed. We propose such an approach in **Figure 2,** recognising that most trials and registries have not mandated such rigour and so outcomes and analyses should take that into account.

It is notable that the increased rate of adverse events in CTD patients in the meta-analysis, this was driven by GI bleeding and infections[10]. The former may reflect the high use of anticoagulants in PAH-CTD patients (SSc being associated with angiodysplasia and gastric antral vascular ectasia) before recent[16] showed that this did not improve outcomes in these patients and may well have been contributed to by drug-drug interactions with warfarin. Increased infection rate may reflect frequent use of corticosteroids and other

immunosuppression in non-SSc CTDs and so may not be as relevant to the PAH-SSc subgroup.

Is co-morbid cardiopulmonary disease the reason for poor outcomes in trials?

Lung fibrosis associated pulmonary hypertension (PH-SSc) has been reported as being associated with a particularly dismal prognosis[18,19]. Most trials do not require HRCT exclusion of lung disease, relying instead on spirometric assessment alone. This allows patients with combined fibrosis and emphysema and a proportion of patients with significant fibrosis to be recruited. Fortunately, most expert centres use accepted criteria or Goh et al (2008) to exclude significant fibrosis when diagnosing SSc PAH, thus identifying significant emphysema and fibrosis before attributing the PH to vasculopathy. However, one must accept that with current inclusion and exclusion criteria, a proportion of patients with significant lung disease could contaminate the results for all populations recruited. From the UK national registry, we see that this could affect around 30% of patients diagnosed as having IPAH[20] – a similar level to the prevalence of lung disease to that seen in SSc. One may conclude that parenchymal lung disease remains a confounder – but not especially so in the SSc subpopulation.

Pulmonary hypertension associated with left heart disease has been reported as having a worse prognosis than PAH-SSc[21] thus, underestimating the prevalence of post-capillary PH in studies could theoretically lead to a much worse outcome in SSc PH subgroups. Fox et al found that 2/3 of patients with PH-SSc had post-capillary PH[12], most being identifiable by the presence of an elevated wedge pressure, but one in three being identified only on assessment of the left ventricular end diastolic pressure (14%) or unmasked on fluid challenge (17%). The reliability of fluid challenge in this setting remains to be established[22], and the issues in respect of the haemodynamic definition of post-capillary PH in SSc are complex[23]. In the AMBITION study, the modification of the recruitment criteria would have excluded most such patients, however recruitment in the GRIPHON & SERAPHIN studies used standard criteria. If this explanation were correct one would expect a different therapeutic response in the studies that failed to rigorously exclude 'occult' left heart disease.

It is worth observing that in the study by Bourji et al[21], the patients with left heart disease had higher mean pulmonary artery pressures than the PAH-SSc patients and despite elevated wedge pressures 75% were treated with advanced therapies, over half with ERAs. Thus, the poorer prognosis in this subgroup may have had many contributors.

Gunther et al[14] found that over 60% of SSc PAH patients had two or more CT features of PVOD and that this was associated with a 50% incidence of pulmonary oedema on therapy and early death. A high prevalence of PVOD as reported by Gunther et al could readily explain a poor response to therapy and higher SAE rate on therapy. However, the population studied was highly selected (failed therapy referred for transplantation), and no other reports of a high prevalence of pulmonary oedema followed. In an analysis of 66 patients referred to our service, we observed only 11% with two or more features of PVOD and only 6% developed pulmonary oedema on therapy[24] – insufficient to explain the apparent poor response to therapy reported.

PAH-CTD in recent outcome trials

The four recent large scale long-term outcome trials[1,3,4,25] have reported almost identical benefit in the IPAH and PAH-CTD subgroups and unlike previous studies have tended to include a sufficiently large CTD population to allow subpopulation analysis. **Table 1** shows the number of patients in IPAH groups, CTD and SSc in each of these trials and the proportion in the active therapy group on combination therapy. **Figure 3** shows a Forest plot based on data abstracted from these studies and demonstrates the remarkable consistency between the IPAH (and various associated conditions according to study groupings) and CTD populations for the primary endpoint in these trials. In the Compass-2 trial bosentan and sildenafil was ineffective in both populations, possibly reflecting the drug- drug interaction between bosentan and sildenafil, though a high drop-out rate and significant proportion with possible left heart disease may also explain the outcome. For SERAPHIN 10mg; AMBITION and GRIPHON almost identical outcomes are evident. In the SERAPHIN study 64% of patients were on combination therapy, in GRIPHON 80%, while in the study treatment arm of the AMBITION trial 100% were on combination therapy. Numerically superior efficacy in the CTD population is associated with the most aggressive of these regimes. In

the 3mg arm of the SERAPHIN study, efficacy is evident in the IPAH arm but not the CTD arm, suggesting that less intense therapy is effective in the IPAH arm but not the CTD arm.

The SSc population in the AMBITION Trial.

The AMBITION trial[1,2] was almost unique in the field of pulmonary hypertension, in that patients were enrolled 'upfront' prior to any therapy and randomised to ambrisentan and tadalafil initial combination therapy (ambrisentan 10 mg plus tadalafil 40 mg) or to ambrisentan 10mg (plus placebo) or tadalafil 40mg (plus placebo) monotherapy.

Patients were aged 18 to 75 years, had baseline WHO functional class II or III symptoms and the average time from diagnosis to enrolment was only 22 days. Initial inclusion criteria required only standard haemodynamic criteria for precapillary PH and a total lung capacity ≥60% of predicted normal, and forced expiratory volume in 1 second ≥55% of predicted normal. After 6 months, a blinded review of the participants' baseline demographic data revealed a high prevalence of risk factors for left ventricular diastolic dysfunction and a high drop-out rate among such patients. Therefore, the eligibility criteria were amended to include more rigorous haemodynamic requirements (PVR $\geq$ 300dynes.seccm-5 if LVEDP or PCW < 12mmHg, PCW $\geq$ 500 if PCW/LVEDP 12 – 15mmHg) and to exclude patients with ≥3 risk factors for left ventricular diastolic dysfunction: body mass index ≥30 kg/m^2, history of essential hypertension, diabetes mellitus, and historical evidence of significant coronary artery disease.

Given these modified criteria, patients of advanced age and those likely to have cardiac co-morbidity are excluded from the main analysis. Potentially this selects for a more favourable treatment cohort, where a more 'vascular' profile is expected. However, when comparing to registry populations as shown in **Table 2**, the resultant study population is quite typical – slightly younger and less symptomatic, but very similar in terms of pulmonary and haemodynamic parameters.

Results of the AMBITION trial

The results of the AMBITION trial are quite striking. They suggest that with an aggressive

upfront approach, equivalent outcomes are achievable in PAH-SSc and IPAH/HPAH as shown in **Table 3**. The primary endpoint was time to clinical failure – a composite endpoint comprising defined as the first occurrence of death, hospitalisation for worsening PAH (any hospitalisation for worsening PAH, lung or heart/lung transplant, atrial septostomy or initiation of parenteral prostanoid therapy), disease progression (decrease of >15% from baseline 6MWD combined with WHO functional class III or IV symptoms at two consecutive visits separated by ≥14 days) or unsatisfactory long-term clinical response (any decrease from baseline 6MWD at two consecutive post-baseline clinic visits separated by ≥14 days and WHO functional class III symptoms assessed at two clinic visits separated by ≥6 months).

The primary endpoint occurred in 32% of IPAH/HPAH patients and 40% of PAH-SSc patients receiving monotherapy. By contrast in the initial combination therapy group the primary endpoint occurred in 19% of the IPAH/HPAH patients (a 49% reduction) and 21% of SScPAH patients (a 56% reduction). Thus, with an upfront aggressive strategy there is much less difference in outcomes between IPAH/HPAH and PAH-SSc than in previous trials.

In those receiving initial combination therapy (**Table 3**), the likelihood of hospitalisation for PAH, improvement in six-minute walking distance and reduction in NTproBNP was very similar to the effect of combination therapy in the IPAH/HPAH groups. The impact in terms of improvement in 6MWD is particularly striking. In this study, it was not deterioration in 6MWD in the placebo group (who received monotherapy) but rather an impressive positive response to combination therapy that delivered the treatment effect. By contrast there was a trend toward fewer achieving a satisfactory clinical outcome. Although discontinuation rates resulting from adverse events was higher in the PAH-SSc population, neither AE related discontinuation rates nor SAE rates were increased by combination therapy when compared to monotherapy (**Table 3**). Comparing the secondary endpoint outcomes in the monotherapy arms between the SSc and IPAH/HPAH populations it is notable that monotherapy appears less effective in the SSc population in terms of 6MWD (+12 v + 26 m), reduction in N-TproBNP (-38% v – 42%) and 15% fall in 6MWD (44% v 32%), however the magnitude of improvement in each of these in the combination group relative to the monotherapy arms is just as great. Thus, there is a synergistic effect of combination therapy in the SSc subgroup. The suggestion therefore from this analysis is that in the PAH-SSc

population a similar medium-term outcome to IPAH/HPAH can be achieved with a sufficiently aggressive therapeutic approach. There is however a residual note of caution that the degree of improvement is more likely to be insufficient to attain a satisfactory clinical outcome in nearly 70% of patients.

Mechanistic basis for efficacy of upfront combination therapy in PAH-SSc

Hassoun et al[5] evaluated 24 patients with PAH-SSc that received upfront ambrisentan and Tadalafil following the AMBITION protocol. The co-primary endpoints were change in PVR and reduction in RV mass at 36 weeks, both were significant. Upfront combination therapy reduced mPAP from 42± 12 to 30± 7 mmHg, increased cardiac index from 2.6±0.7 to 3.3±1.2 l.min/m2 a significantly greater haemodynamic improvement that recorded in previous monotherapy trials in this population.

As observed in the AMBITION trial 6MWD increased significantly from 343±131 to 395± 99m. Further a clear improvement in right ventricular function was observed right ventricular ejection fraction improved from 46±10 to 57± 9%, while right ventricular end systolic volume fell from 82.1 (65.6–97.7) to 55.8 (49.4–79.2) and left ventricular end diastolic volume increased from 114.0 (84.8–130.2) to 135.3 (112.4–160.1). All these changes reach significance and indicate substantial off-loading with upfront combination therapy, with improved RV function and LV filling. This was an open-label trial with per-protocol analysis, that said of the 17 patients excluded before treatment 12 met exclusion criteria, and only one patient was subsequently excluded as they elected to have palliation.

The GRIPHON trial

The GRIPHON[3] is not directly comparable to the AMBITION trial – both in terms of trial construct and the details reported, thus gives different but complimentary information. GRIPHON was a larger trial that included 170 PAH-SSc patients (15% of population)[26], while the AMBITION trial included 118 PAH-SSc patients (24% of population). The mean age of the scleroderma population was marginally older (60 years old), while the overall population was younger in the GRIPHON trial 48yrs v 54.3yrs in the Ambition trial. Time from diagnosis to trial inclusion in the AMBITION trial was short (median <1mo) and equivalent in both the

IPAH/HPAH and SSc-PAH populations, GRIPHON was a prevalent population study. In the GRIPHON trial time from PAH diagnosis to enrolment was 1.6 years in the SSc population[26], but 2.4 years in the overall population[3] (> 60% of the whole population had IPAH/HPAH/drug or toxin associated PAH). Background therapy of PAH-PAH patients in the GRIPHON trial was almost identical to the whole population; 78% SSc v 80% whole population were on background therapy, 36% PAH-SSc patients were on background combination therapy, compared to 33% of the whole population.

When comparing the studies, we are further limited by the lack of individual reporting of the details of the IPAH/HPAH population in the GRIPHON trial and the IPAH/HPAH population may have reached a more stable phase of the disease, given the likely longer time from diagnosis to enrolment. The primary endpoint was different though similar, comprising disease progression or worsening of PAH that resulted in hospitalisation, initiation of parenteral prostanoid therapy or long-term oxygen therapy, need for lung transplantation or balloon atrial septostomy, or death from any cause). Disease progression was defined as a ≥15% decrease in 6-minute walk distance from baseline, confirmed by a second test on a different day, and worsening in WHO functional class (for patients in functional class II/III at baseline) or need for additional PAH therapy (for patients in functional class III/IV at baseline). The most important difference here is the absence of 'unsatisfactory long term clinical outcome' as an endpoint.

Overall, this was a very encouraging study that reached its key clinical trial endpoints. In those randomised to placebo among the IPAH/HPAH/Drug group the primary endpoint occurred in 43%, compared to 49% in the PAH-SSc group[26]. In the active treatment group the primary endpoint occurred in 28% of the IPAH/HPAH/Drug group compared to 32.5% with PAH-SSc. Again, suggesting that with aggressive management including 80% combination and 36% triple therapy PAH-SSc patients benefit at least as much as IPAH/HPAH patients and event rates approach those seen in the IPAH/HPAH group.

In terms of secondary endpoints, we can only compare outcomes among PAH-SSc with the outcome in the whole population. With this limitation, as shown in Table 4 there is remarkable consistency between the effect of selexipag in all patients and those with systemic sclerosis. Death was an uncommon event as a primary endpoint, however numbers of events were not insignificant up to the end of study (i.e. including follow up of those that

had stopped treatment after meeting a primary endpoint). Here a trend is noted – a possible reduction in mortality in the post-selexipag group for the whole population, with no impact on deaths in the SSc cohort. It is however impossible to attribute a causative relationship in this setting, since the management decisions taken after cessation of trial treatment are unknown.

Adverse events were common in the GRIPHON trial with over 95% reporting some adverse events. Serious adverse events were numerically more common in the SSc subpopulation, but the same trend toward reduced events in the active treatment sub group was seen. Discontinuation due to adverse events were also numerically more common in the SSc cohort (7.1% IPAH v 13.2% PAH-SSc among placebo patients and 14.3% IPAH v 19.5% PAH-SSc in the active therapy arm), again with no trend toward a relative excess of SAE due to therapy when compared to the whole population. Thus, in a population with 80% on combination therapy and 36% on triple therapy – there is no evidence that escalation of treatment is disproportionately disadvantageous in the SSc cohort (Table 4).

Concluding remarks: current approaches for PAH-SSc

SSc PAH patients remain complex and we do not have all the answers yet. What is clear is that in those with true PAH-SSc an aggressive approach with early combination therapy is the required standard of care. This is in line with current evidence-based treatment recommendations[27] and represents a meaningful advance in treatment for SSc in general that can be expected to improve disease outcome and survival. Less clear is how we estimate the relative contributions of cardiac, pulmonary and musculoskeletal co-morbidity. Further in managing such patients we must always be cognisant of the role of the auto-immune system, which drives the vasculopathy and can cause deterioration or crises entirely independent of the cardio-pulmonary axis.

Acknowledgements.

This work has been undertaken by Dr JG Coghlan & Prof C Denton. No direct or indirect financial support has been provided. However, Dr Coghlan & Prof Denton have both

performed consultancy work for, received grants from, and honoraria from Actelion Ltd and GSK both of whose products and studies are extensively reviewed.

Figure legends

Figure 1. Meta-analysis of pulmonary hypertension trials including PAH-CTD and PAH-SSc
Comparison of short term gains in six-minute walk distance suggest comparable absolute treatment effect for PAH-SSc but this does not reach statistical significance, most likely due to greater variability and small number of cases. For clinical worsening, the reduction in hazard ration is comparable for PAH-SSc and iPAH. Modified from Rhee et al (ref 10). CW – clinical worsening; Hosp – hospitalisation, Rx – treatment, Tx transplantation, RVF – right ventricular failure

Figure 2. A comprehensive diagnostic algorithm for PAH-SSc
All cases of suspected PH should be evaluated and associated lung fibrosis or cardiac causes of PH excluded. Features of other causes such as PVOD and CTEPH also require exclusion While the principle for the evaluation of SScPAH is identical to that of IPAH, the likelihood of co-existent lung or heart involvement is much greater. Some abnormality of the heart or lung is present in the majority of patients. The issue is not generally exclusion of lung or heart disease, but determining whether the abnormality observed is sufficient to explain the haemodynamic abnormality found. For lung disease < 20% volume of fibrosis or less than 5% emphysema is unlikely to cause precapillary PH in Systemic sclerosis patients. For heart disease, even minor abnormalities should cause suspicion that demonstration of a wedge of < 15 mmHg is not sufficient to make a diagnosis of precapillary PH, thus LVEDP and CMR should be considered. Finally, if more than a single CT feature of PVOD (septal lines, lymphadenopathy or centrilobular nodules) are identified, there is a significant risk of pulmonary oedema with advanced therapies.
LVEF – left ventricular ejection fraction; LA – left atrium; MAPSE – mitral annular plane systolic elevation; LVEPD – left ventricular end diastolic pressure; CMR – cardiac magnetic resonance.

Figure 3. Comparison of IPAH groupings and connective tissue disease (CTD) populations.
Forest plot summarising overall treatment effect on hazard ratio for event driven long term trials including combination PAH therapy in SSc. For the licensed dose of macitentan and in selexipag and ambition study effect was similar fr the PAH-CTD and iPAH subjects. The trials

had different primary end points, slightly different definitions of the IPAH groupings, different proportions of the various CTD populations and in the case of the ambition trial an incident population, so the trials should not be compared to each other, however presentation in a single Forest plot allows visual appreciation of the relative impact of different aggressiveness of the treatment regime with relative outcomes between the IPAH and CTD groups. HR – hazard ratios for morbidity or mortality/ clinical failure outcomes relative to placebo groups. For each study, the IPAH group is the upper of the two hazard ratios shown. Numbers of patients followed by numbers with events is shown for the active comparator group and placebo for each study.

References

[1]Galiè N, Barbera JA, Frost AE, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. N Engl J Med 2015; 373(9):834-844.

[2] Coghlan JG, Galie N, Barbera JA, 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(7):1219-1227.

.

[3] Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galie N, Ghofrani HA, Hoeper MM, Lang IM, Preiss R, Rubin LJ, Di Scala L, Tapson V, Adzerikho I, Liu J, Moiseeva O, Zeng X, Simonneau G, McLaughlin VV. Selexipag for the Treatment of Pulmonary Arterial Hypertension. *N Engl J Med* 2015; 373: 2522-2533.

[4] Pulido T, Adzerikho I, Channick R, Delcroix M, Galiè N, Ghofrani A, Jansa P, Jing Z-C, Le Brun F, Mehta S, Mittelholzer C, Perchenet L, Sastry BK, Sitbon O, Souza R, Torbicki A, Zeng X, Rubin L, Simonneau G. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 809-818.

[5] Hassoun PM, Zamanian RT, Damico R, et al. Ambrisentan and Tadalafil Up-front Combination Therapy in Scleroderma-associated Pulmonary Arterial Hypertension. Am J Respir Crit Care Med. 2015;192(9):1102-10.

[6] Rhee RL, Gabler NB, Sangani S, Praestgaard A, Merkel PA, Kawut SM. Comparison of Treatment Response in Idiopathic and Connective Tissue Disease-associated Pulmonary Arterial Hypertension. *Am J Respir Crit Care Med* 2015; 192: 1111-1117.

[7] Cool CD, Kennedy D, Voelkel NF, et al. Pathogenesis and evolution of plexiform lesions in pulmonary hypertension associated with scleroderma and human immunodeficiency virus infection. Hum Pathol. 1997;28:434–42

[8] 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 control trial. Ann Intern Med 2000;132:425-34.

[9] Avouac J, Wipff J, Kahan A, Allanore Y. Effects of oral treatments on exercise capacity in systemic sclerosis related pulmonary arterial hypertension: a meta-analysis of randomised controlled trials. Ann Rheum Dis. 2008 Jun;67(6):808-14.

[10] Rhee RL, Gabler NB, Praestgaard A, Merkel PA, Kawut SM. Adverse Events in Connective Tissue Disease-Associated Pulmonary Arterial Hypertension. Arthritis Rheumatol. 2015; 67: 2457- 65

[11] Coghlan JG: Complex challenges in Pulmonary Hypertension. In Scleroderma: From pathogenesis to management. In Ed. Varga J; Denton P; Wigley FM Part VII; 2012 Ch 38: 447 – 462.

[12] Fox BD, Shimony A, Langleben D, Hirsch A, Rudski L, Schlesinger R, Eisenberg MJ, Joyal D, Hudson M, Boutet K, Serban A, Masetto A, Baron M. High prevalence of occult left heart disease in **scleroderma**-pulmonary hypertension. *Eur Respir J* 2013; **42**: 1083-91

[13] Lefevre G, Dauchet L, Hachulla E, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. *Arthritis Rheum* 2013;65(9):2412-2423.

[14] Gunther S, Jaïs X, Maitre S, Bérezné A, Dorfmüller P, Seferian A, Savale L, Mercier O, Fadel E, Sitbon O, Mouthon L, Simonneau G, Humbert M, Montani D. Computed tomography findings of pulmonary venoocclusive disease in scleroderma patients presenting with precapillary pulmonary hypertension. *Arthritis Rheumatol* 2012; 64: 2995-3005

[15] Sobanski V, Giovannelli J, Lynch BM, Schreiber BE, Nihtyanova SI, Harvey J, Handler CE, Denton CP, Coghlan JG. Characteristics and Survival of Anti-U1 RNP Antibody-Positive Patients With Connective Tissue Disease-Associated Pulmonary Arterial Hypertension. Arthritis Rheumatol. 2016; 68: 484-93.

[16] Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, Grünig E, Staehler G, Rosenkranz S, Halank M, Held M, Lange TJ, Behr J, Klose H, Claussen M, Ewert R, Opitz CF, Vizza CD, Scelsi L, Vonk-Noordegraaf A, Kaemmerer H, Gibbs JS, Coghlan G, Pepke-Zaba J, Schulz U, Gorenflo M, Pittrow D, Hoeper MM. Anticoagulation and Survival in Pulmonary Arterial Hypertension: Results from the COMPERA Registry. Circulation. 2014 Jan 7;129(1):57-65.

[17] Ramjug S, Hussain N, Hurdman J, Billings C, Charalampopoulos A, Elliot CA, Kiely DG, Sabroe I, Rajaram S, Swift AJ, Condliffe R. Idiopathic and Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: A Comparison of Demographic, Hemodynamic, and MRI Characteristics and Outcomes. Chest. 2017;152 :92-102.

[18] Condliffe R, Kiely DG, Peacock AJ, et al Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med. 2009; 179(2):151-7.

[19] Lefevre G, Dauchet L, Hachulla E, Montani D, Sobanski V, Lambert M, et al. Survival and prognostic factors in systemic sclerosis-associated pulmonary hypertension: a systematic review and meta-analysis. Arthritis Rheum. 2013;65(9):2412-23.

[20] Ling Y, Johnson M, Kiely D et al. 'Idiopathic' pulmonary arterial hypertension with preserved lung function but co-existing parenchymal abnormalities: Response to treatment and survival. Eur Respir J 2012 40: 371

[21] Bourji K, Keleman B, Mathai S et al Poor survival in patients with scleroderma and

pulmonary hypertension due to heart failure with
preserved ejection fraction. Pulm Circ. 2017 Jun; 7(2): 409–420.

[22] Guazzi M, Naeije R. Pulmonary Hypertension in Heart Failure: Pathophysiology, Pathobiology, and Emerging Clinical Perspectives. J Am Coll Cardiol. 2017; 69(13):1718-1734.

[23] Coghlan G. Does left heart disease cause most systemic sclerosis associated pulmonary hypertension? Eur Respir J. 2013 Oct;42(4):888-90.

[24] Connolly M, Abdullah S, Ridout D, Schreiber B, Haddock J, Coghlan JG. Prognostic significance of CT criteria for pulmonary veno-occlusive disease in systemic sclerosis-pulmonary arterial hypertension. Rheumatology 2017 (in Press).

[25] McLaughlin V, Channick RN, Ghofrani HA, Lemarié JC, Naeije R, Packer M, Souza R, Tapson VF, Tolson J, Al Hiti H, Meyer G, Hoeper MM. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. Eur Respir J. 2015 Aug;46(2):405-13.

[26] Gaine S, Chin K, Coghlan G, Channick R, Di Scala L, Galiè N, Ghofrani HA, Lang IM, McLaughlin V, Preiss R, Rubin LJ, Simonneau G, Sitbon O, Tapson VF, Hoeper MM. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. Eur Respir J. 2017 Aug 17;50(2). pii: 1602493. doi: 10.1183/13993003.02493-2016.

[27] Galiè N, Humbert M, Vachiery JL, 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 Heart J. 2016 Jan 1;37(1):67-119.

[28]Chung L, Farber HW, Benza R, Miller DP, Parsons L, Hassoun PM, McGoon M, Nicolls MR, Zamanian RT. Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. Chest. 2014;146:1494-1504.

Table 1: Patient disposition and CTD subgroups in combination therapy trials for PAH

Study	IPAH group	CTD PAH	SScPAH	SLE PAH	Combination Rx
Compass-2 [18]	226	88	38	?	100% v 0%
Seraphin [4] 3mg & 10mg	449	225	116	66	64%
Ambition [1]	279	187	118	17	100% v 0%
Griphon [3]	712	334	170	82	80%

Table 2 Comparison of clinical and demographic features of clinical trial and registry cohorts

Parameter	Ambition [2]	REVEAL[28]	UK national registry[19]	RFH registry[16]	Compera[17]
Age (years)	58	61.8±11	63.9±10.5	63±11	67 (59.5-74)
Sex (F %)	85	88.5	82	85	84
FC I or II /III/IV (%)	23/77/0	25/60/15	16/68/16	21/79 (III+IV)	14/72/14
TLC (% pred)	90	82.7±18.4	NR	NR (FVC 94%)	NR
FEV1 (% pred)	86	73.4±16.4%	NR	NR	NR
mPAP (mm Hg)	44	44.6±11.8	42±17	40±12	41±11
PVR (dynes.sec.cm^{-5})	670	9.6±5.3	715±597	607±417	697±385
PCW (mm Hg)	8.5	9.1±3.5	NR	10±3	9.3±3.3

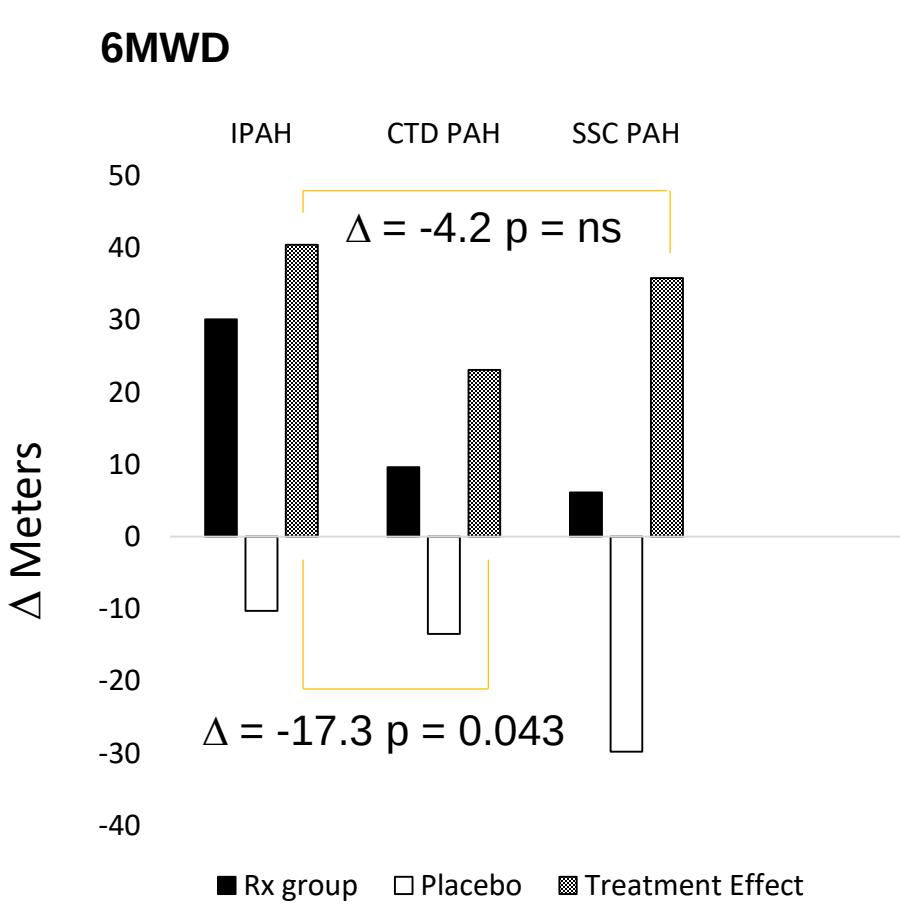
Table 3 Summary of outcome data from the Ambition trial

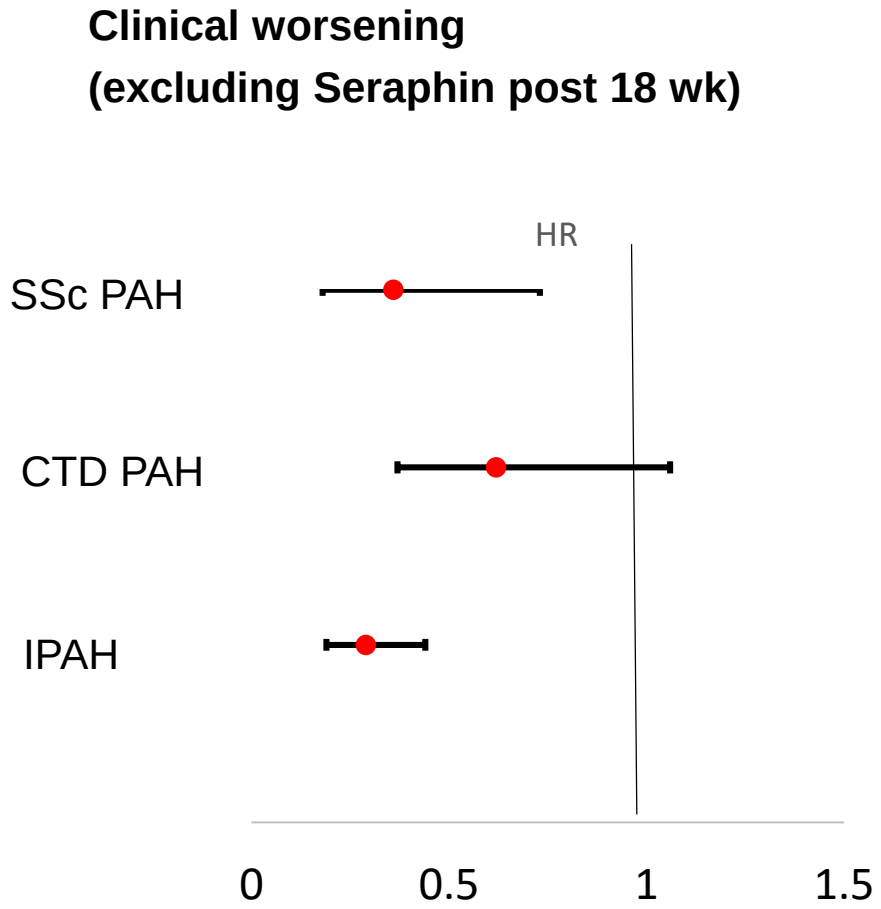
Parameter	Combination iPAH/HPAH	Monotherapy iPAH/HPAH	HR	Combination PAH-SSc	Monotherapy PAH-SSc	HR
Primary EP reached	19%	32%	0.51 (0.31-0.83)	21%	40%	0.44 (0.22-0.89)
Hospitalisation for PAH	8%	18%	0.41 (0.2–0.82)	8%	19%	0.36 (0.13-1.04)
Δ6MWD @ 24wk (m)	+52.5	+26.6		+40.9m	+12.2m	
ΔNTproBNP	-71.2%	-50%	-42.5 (-54.6;-27)	-62.8%	-38.4%	-36.9 (-59.3;-10.2)
Satisfactory clinical outcome	40%	28%	1.7 (1.04-2.9)	31%	29%	1.1 (0.47-2.6)
15% fall in 6MWD	24%	32%		31%	44%	
SAE rate	33%	38%		44%	49%	
AE resulting in discontinuation	11%	10%		14%	13%	

Table 4 Summary of outcome data from the Griphon clinical trial

	Griphon Trial		PAH-SSc Subgroup	
	Placebo N=582	Selexipag N=574	Placebo N=93	Selexipag N=77
Primary composite endpoint of morbidity/mortality up to the end of treatment	Number of patients (%)		Number of patients (%)	
All events	242 (41.6)	155 (27)	46 (49.5)	25 (32.5)
Hospitalisation for worsening of PAH	123 (21.1)	86 (15)	22 (23.7)	10 (13.0)
Disease progression	100 (17.2)	38 (6.6)	18 (19.4)	8 (10.4)
Death from any cause	18 (3.1)	28 (4.9)	1 (1.1)	4 (5.2)
Initiation of parenteral prostanoid therapy or long-term O_2 therapy for worsening PAH	13 (2.2)	10 (1.7)	5 (5.4)	2 (2.6)
Need for lung transplantation or BAS for worsening of PAH	2(0.3)	1 (0.2)	0	1 (1.3)
Secondary endpoint of all-cause death up to the end of the study	Number of patients (%)		Number of patients (%)	
Death from any cause	137 (23.5)	102 (17.8)	22 (23.7)	17 (22.1)

Figure 1 Meta-analysis of pulmonary hypertension trials including PAH-CTD and PAH-SSc





CW = hosp for PAH; Rescue Rx; Lung Tx Septostomy; RVF; Death

Figure 2. A comprehensive diagnostic algorithm for PAH-SSc

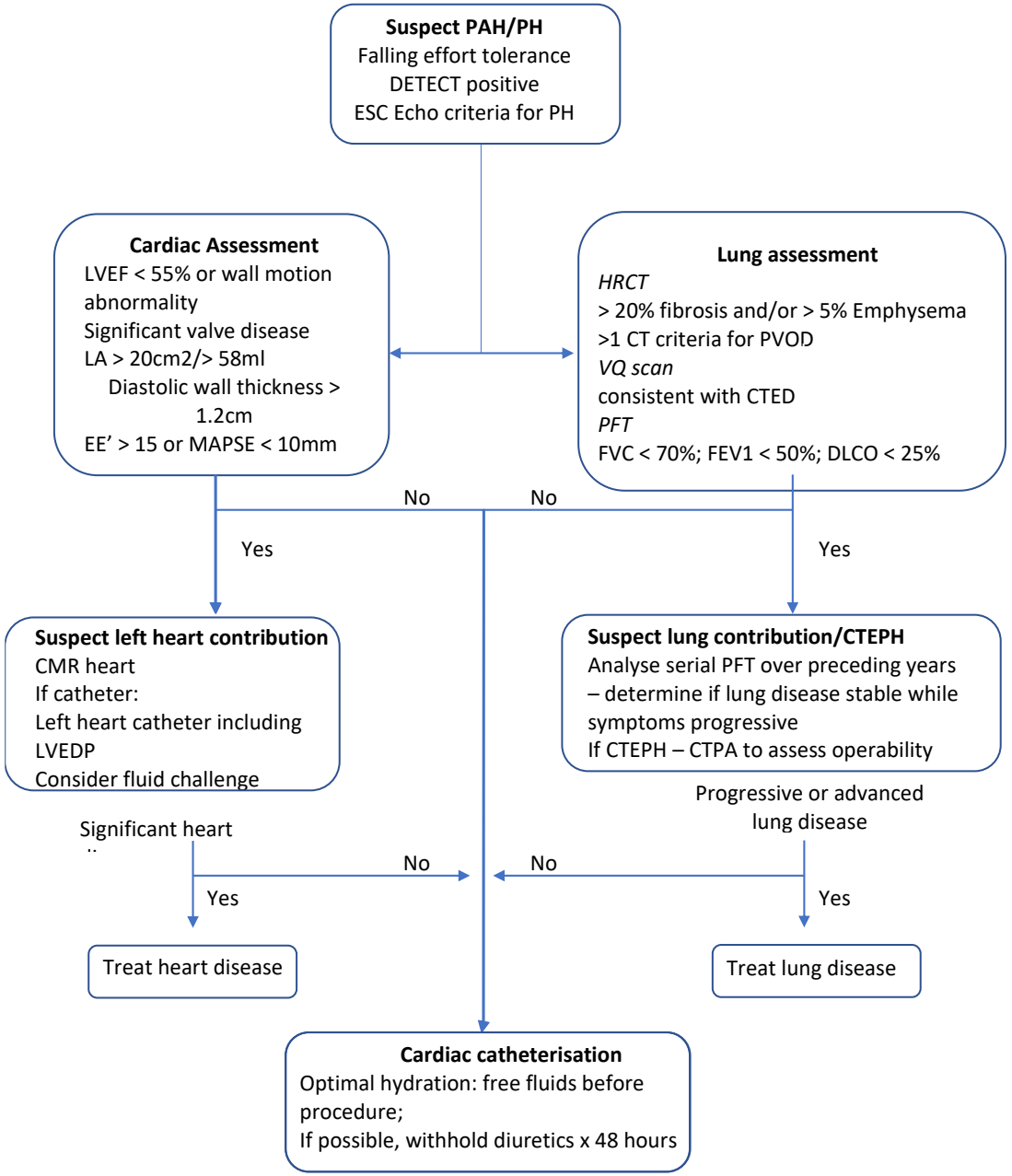


Figure 3. Comparison of IPAH groupings and connective tissue disease (CTD) populations.

		Active Comparator group	Placebo
Compass 2	IPAH/FPAH/Drug & Toxin	107/44	119/60
	CTD PAH	43/22	45/26
Seraphin 3mg	IPAH/Other	162/42	140/75
	CTD PAH	70/26	82/31
Seraphin 10mg	IPAH/Other	147/52	140/75
	CTD PAH	73/20	82/31
Griphon	IPAH/HPAH/Drug & Toxin	347/98	365/156
	CTD PAH	167/48	167/73
Ambition	IPAH/HPAH	134/25	145/46
	CTD PAH	103/20	30/84