PULMONARY ARTERIAL HYPERTENSION-TARGETED THERAPIES IN PATIENTS WITH CONNECTIVE TISSUE DISEASE-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

Zaw Zaw HTUN[1,2], Siriluck MANAPUNSOPEE[1,2], Prapaporn PORNSURIYASAK[2], Kunlawat THADANIPON[2], Amarit TANSAWET[3], and Ammarin THAKKINSTIAN[2]

1 Master of Science Program in Medical Epidemiology (International Program), Faculty of Medicine Ramathibodi Hospital, Faculty of Public Health, and Faculty of Tropical Medicine, Mahidol University, Thailand; zzawhtoon@gmail.com
2 Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand; siriluck.map@student.mahidol.ac.th (S.M.); prapaporn.por@mahidol.ac.th (P.P.); kunlawat.tha@mahidol.ac.th (K.T); ammarin.tha@mahidol.ac.th (A.Th)
3 Department of Research and Medical Innovation, Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, Thailand; amarit@nmu.ac.th

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ABSTRACT

Connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) is the most severe form and has the lowest survival rates among all pulmonary arterial hypertension (PAH) subgroups. However, no consensus exists on the most effective therapy in reducing the risk of clinical worsening for this patient population. This systematic review and network meta-analysis aimed to identify the most effective PAH-targeted treatment for CTD-PAH patients. Seven randomized controlled trials consisting of 1,042 patients were identified by MEDLINE, Scopus, and ClinicalTrials.gov. Combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 inhibitor (PDE5i) significantly reduced the risk of clinical worsening compared to placebo (hazard ratio, 0.31; 95% confidence interval, 0.13 to 0.74). Moreover, combination therapy ranked highest for reducing the clinical worsening, followed by PDE5i and ERA monotherapies. Based on these findings, combination therapy is the preferred treatment for patients with CTD-PAH. These findings provide valuable insights into clinical decision-making and help tailor therapies for this patient group, who may have diverse treatment responses compared to those with idiopathic PAH.

Keywords: Systematic Review, Network Meta-analysis, Connective Tissue Diseases, Pulmonary Arterial Hypertension, Targeted Therapies

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INTRODUCTION

Connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) is a subtype of pulmonary arterial hypertension (PAH). It is the second most prevalent type, following idiopathic PAH (IPAH) and affects 15 to 25% of people with PAH (Ruopp & Cockrill, 2022). Systemic sclerosis (SSc) has the highest prevalence of PAH among connective tissue diseases (CTDs), with PAH occurring in 8 to 12% of patients with SSc. The prevalence of PAH is estimated to be less than 4% in systemic lupus erythematosus (SLE) and less than 1% in other CTDs (Vonk et al., 2021). Among all PAH subtypes, CTD-PAH is the most severe form and has the lowest survival rates. The 3-year survival rate for CTD-PAH patients is 62% (95% confidence interval [CI], 57% to 67%), compared to 72% (95% CI, 69% to 75%) in the overall PAH patient population (Chung et al., 2010; Khanna et al., 2021). In the United States (US), CTD-PAH patients have a lower one-year survival (86% vs. 93%; $P < 0.001$) and a lower rate of freedom from hospitalization (67% vs. 73%; $P = 0.03$) compared to the IPAH patients (Chung et al., 2010).

Endothelin receptor antagonists (ERAs), phosphodiesterase 5 inhibitors (PDE5i), soluble guanylate cyclase (sGC) stimulators, prostacyclin analogs (PA), and prostacyclin receptor agonists (PRA) are the targeted drug treatments for PAH (Humbert et al., 2023; Pitre et al., 2022). Sotatercept, a first-in-class activin signaling inhibitor, was recently approved by the US Food and Drug Administration (Kang, 2024). The 5-year survival rate of patients with PAH has improved from 34% in 1991 to over 60% in 2015 with the advancement in PAH-targeted therapies (Ruopp & Cockrill, 2022). However, patients with CTD-PAH tend to have a poorer response to PAH-targeted therapies than those with IPAH, particularly in terms of improving the six-minute walk distance (6MWD) and reducing the risk of clinical worsening (Rhee et al., 2015). The underlying pathophysiology of CTD-PAH could be attributed to these differences in treatment response.

To date, seven systematic reviews and meta-analyses have investigated PAH-targeted therapies among patients with CTD-PAH. However, they have several limitations. Some studies were conducted over a decade ago, and new randomized controlled trials (RCTs) have been conducted since then (Avouac et al., 2008; Kuwana et al., 2013), some did not include clinical worsening as an efficacy outcome measure (Avouac et al., 2008; Kuwana et al., 2013; Lei et al., 2021), while others failed to assess all available and updated PAH-targeted treatments (Lei et al., 2021; Pan et al., 2018; Shivakumar et al., 2020). Although a recent systematic review and meta-analysis (Erdogan et al., 2024) evaluated the efficacy of PAH-targeted therapies in CTD-PAH patients, the most recently approved drug was not included, and the most effective treatment regimen has not yet determined. These limitations underscore the need for a network meta-analysis (NMA), in which both direct and indirect comparisons of multiple treatments can be performed. It also provides a ranking to estimate the probability of being the most effective treatment among various treatment regimens. Furthermore, RCTs that primarily focus on the CTD-PAH patients are limited; most analyses for this patient group come from subgroup analyses in the RCTs conducted on the overall PAH populations. In addition, only a limited number of RCTs have conducted head-to-head comparisons of PAH-targeted therapies. As a result, there remains a gap of knowledge to make a consensus on the most effective PAH-targeted treatment for CTD-PAH patients.

Therefore, this study aimed to evaluate the efficacy of PAH-targeted therapies and estimate the most effective treatment for patients with CTD-PAH using a systematic review and NMA. Understanding the optimal treatment regimens for CTD-PAH could enhance clinical decision-making and help tailor therapies for this specific patient group.

LITERATURE REVIEWS

Pulmonary hypertension (PH) is a life-threatening disorder characterized by a marked remodeling of pulmonary vasculature, coupled with a progressive rise in the pulmonary vascular load and subsequent pressure load on the right ventricle, resulting in hypertrophy, remodeling, and failure of the right ventricle (Pitre et al., 2022; Ruopp & Cockrill, 2022). It involves multiple clinical conditions, which may be associated with various cardiovascular and respiratory diseases. It is defined by a mean pulmonary artery pressure (mPAP) of more than 20 mmHg at rest. PAH is one of the five groups of PH. It is mainly diagnosed by clinical suspicion of PH and confirmed by right heart catheterization (RHC) as a gold standard test, followed by identifying the underlying conditions as the etiology of PAH. If the cause of the disease cannot be identified, IPAH is considered. PAH is diagnosed by RHC, in which it can be defined if mPAP is > 20 mmHg, pulmonary vascular resistance (PVR) is ≥3 WU and pulmonary artery wedge pressure is ≤15 mmHg. PAH is subdivided into IPAH, heritable PAH, PAH with venous/capillary involvement, persistent PH of the newborn, and associated with drugs and toxins, CTDs, HIV infection, portal hypertension, and congenital heart disease, etc. (Humbert et al., 2023; Ruopp & Cockrill, 2022). CTD, such as SSc, SLE, mixed connective tissue disease, and, rarely, idiopathic inflammatory myopathies and Sjögren's syndrome, are associated with PAH (Pitre et al., 2022; Ruopp & Cockrill, 2022).

CTD-PAH affects 15 to 25% of people with PAH and is the second most prevalent type of PAH, following IPAH (Ruopp & Cockrill, 2022). CTD-PAH predominantly affects females, with a female-to-male ratio of 4:1, and the mean age at diagnosis is over 50 years (Humbert et al., 2023). PAH occurring in 8-12% of patients with SSc, which is the highest prevalence among CTDs. The exact prevalence of PAH in other CTD-PAH remains unclear due to the absence of routine screening in these patient groups, however, the prevalence of PAH is estimated to be <4% in SLE and <1% in other CTDs (Vonk et al., 2021).

Five classes of medication have been developed for the treatment of PAH, and they target three classical pathways of PAH pathophysiology: the endothelin pathway, the nitric oxide/cyclic guanosine monophosphate pathway, and the prostacyclin pathway. ERAs (Ambrisentan, Bosentan, Macitentan), PDE5i (Sildenafil and Tadalafil), sGC (Riociguat), PA (Epoprostenol, Treprostinil, Iloprost and Beraprost), and PRA (Selexipag), are the targeted drug treatments of PAH (Humbert et al., 2023; Pitre et al., 2022). Recently, Sotatercept, a first-in-class activin signalling inhibitor, has been approved by the US Food and Drug Administration for the treatment of adults with PAH due to pulmonary artery vasculopathy, which includes IPAH, heritable PAH, CTD-PAH and PAH associated with corrected congenital shunts (Kang, 2024).

PAH-targeted therapies have been shown to improve different outcome measures in patients with CTD-PAH, such as 6MWD, World Health Organization functional class (WHO FC) and hemodynamic parameters (i.e., mPAP, PVR, right atrial pressure (RAP), and cardiac index (CI)), compared to the placebo group (Erdogan et al., 2024). They were also associated with a reduction in clinical worsening, ranging from 36 to 39% in CTD-PAH patients receiving any PAH-targeted medications compared to those receiving placebo (Erdogan et al., 2024; Khanna et al., 2021). Moreover, the combination of PAH-targeted therapies significantly reduced the risk of clinical worsening events by 27% compared to monotherapy (Pan et al., 2018).

In the Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial (PATENT)-1 study, Riociguat demonstrated an improvement in 6MWD in patients with CTD-PAH at 12-week follow-up, compared to placebo (least squares mean treatment difference, 28 m; 95% CI, -4 to 61). It also led to improvements in WHO FC, PVR and CI. In the open-label, long-term extension study PATENT-2, where all patients received Riociguat for CTH-PAH, clinical worsening occurred in 29% of patients, with the 2-year survival rate of 93% (Humbert et al., 2017). The GRIPHON trial compared Selexipag with placebo and found a 41% reduction in the risk of morbidity/mortality events in CTD-PAH patients (hazard ratio [HR], 0.59; 95%

CI, 0.41 to 0.85). It also showed improvement in 6MWD (treatment effect, 12 m; 95% CI, 4 to 27) and N-terminal prohormone B-type natriuretic peptide (NT-proBNP) (treatment effect, -140; 95% CI, -265 to -51) compared to placebo (Gaine et al., 2017). In addition, initial combination therapy with Ambrisentan and Tadalafil reduced the clinical worsening by 57% (HR, 0.43; 95% CI, 0.24 to 0.77) compared to pooled monotherapy of Ambrisentan and Tadalafil (Coghlan et al., 2017). Recently, in a multicenter, phase 3 trial among patients with PAH, add-on Sotatercept improved 6MWD from baseline to week 24 (treatment effect, 40.8 m; 95% CI, 27.5 to 54.1; $P < 0.001$), PVR, NT-proBNP, and WHO FC, compared to standard treatments including monotherapy, double therapy, triple therapy and parenteral prostacyclin. There was also an 84% reduction in the risk of death or nonfatal clinical worsening event (HR, 0.16; 95% CI, 0.08 to 0.35; $P < 0.001$) in the Sotatercept group (Hoeper et al., 2023).

RESEARCH METHODOLOGY

This study is a systematic review and NMA conducted according to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) (Hutton et al., 2015) and registered in PROSPERO (CRD42024587178). All available studies were searched from inception to 6 September 2024. They are identified from MEDLINE via PubMed, and Scopus. The relevant unpublished and ongoing studies were searched from ClinicalTrials.gov. Reference lists of selected articles and previous systematic reviews were also reviewed. Eligible studies were selected based on the following criteria. The population of interest was adults diagnosed with CTD-PAH. The interventions were various PAH-targeted therapies (such as ERA, PDE5i, sGC, PA/PRA, and Sotatercept), administered either as monotherapy or in combination therapy, compared to placebo or other PAH-targeted therapies. The outcome of interest was the time to clinical worsening. RCTs and post-hoc studies of the primary RCTs that reported results of CTD-PAH patients were selected. Due to the limited number of primary studies on the CTD-PAH group, the search was extended to include the overall PAH population. Data were then extracted from the subgroup or post-hoc analyses in addition to the studies directly focusing on CTD-PAH. Studies were excluded if there were insufficient data for pooling after three attempts at contacting the authors every two weeks.

Intervention and the outcome of interests

The following medications were considered in this study: ERA (Ambrisentan, Bosentan, Macitentan), PDE5i (Sildenafil, Tadalafil), sGC (Riociguat), PA/PRA (Epoprostenol, Treprostinil, Iloprost, Beraprost, Selexipag), and Sotatercept. These PAH-targeted therapies were evaluated both as monotherapy and in combination therapy. This study exclusively focused on standard dose of PAH-targeted therapies. The outcome was the time to clinical worsening. The definition of clinical worsening varies slightly across RCTs, but it is generally defined as the first occurrence of all-cause death, hospitalization due to pulmonary hypertension, lung transplantation, atrial septostomy or initiation of parenteral prostanoids therapy.

Data extraction and quality assessment

Data was extracted independently by two reviewers (Z.Z.H. and S.M.) using a data extraction form. Extracted data includes general characteristics (study setting, country, number of patients, and treatment duration), patient characteristics (age, gender, etiology of CTD-PAH, 6MWD at baseline, WHO FC at baseline, time since PAH diagnosis, and baseline PAH medications), PAH medications (dose, and route of administration), and outcome measures. For studies that did not report HR directly, it was extracted from the Kaplan-Meier curve using WebPlotDigitizer (Rohatgi, 2024). The quality of RCTs was assessed using Revised Cochrane Risk of Bias tool (RoB 2) (Sterne et al., 2019).

Statistical analysis

PAH-targeted therapies were pooled according to drug classes using direct and indirect evidence across a network of studies. The two-stage NMA was applied for analysis. In the first stage, regression analysis was applied to estimate the relative treatment effects (ln[HR]) along with their variance-covariance for each study, using placebo as a reference treatment. In the second stage, a multivariate meta-analysis was applied to pool the relative treatment effects across studies. A league table was constructed to summarize the relative treatment effects from multiple treatment comparisons. The probability of being the best treatment was assessed using the surface under the cumulative ranking curve (SUCRA) and a rankogram, where the minimum value of SUCRA was considered the best ranking for reducing the risk of clinical worsening. The predictive interval plot was used to estimate the future treatment effect of each treatment regimen after accounting for uncertainty in the NMA. Transitivity was explored according to the covariables (mean age, percentage of females, percentage of SSc patients, mean duration since PAH diagnosis, percentage of WHO FC at baseline, mean of 6MWD at baseline, percentage of baseline PAH medications, and treatment duration). The inconsistency assumption for NMA was checked using a design-by-treatment model. Publication bias in the NMA was assessed using the comparison-adjusted funnel plot and Egger's test. STATA version 18.0 was used for data analysis, and a two-sided p-value of less than 0.05 was considered statistically significant.

RESEARCH RESULTS

Studies were identified from MEDLINE via PubMed (N=839), Scopus (N=3107), and ClinicalTrials.gov (N=71). After removing the duplicate records and assessing eligibility according to the PRISMA guidelines, seven RCTs with 1,042 patients were included in this systematic review and NMA for the clinical worsening outcome. The percentage of low risk was 30% in the ROB 2 assessment. The mean age ranged from 45.2 to 58.2 years, with the percentage of females between 75.7% and 90.0%. The treatment duration of the studies varies from 12 weeks to 36 months. Characteristics of included studies are described in Table 1 and a network map of the outcome is shown in Figure 1.

Table 1 Characteristics of included studies

Author	Interventions	n	Treatment duration (Weeks)	Mean age (years)	Female (%)	SSc (%)	Time since PAH diagnosis (Mean, months)	Background PAH Medication (%)	WHO FC (III & higher) (%)	6MWD (Mean, meters)
Denton CP, 2006	Bosentan vs. Placebo	66	16	55.0	83.3	78.8	22.5	0.0	100.0	328.3
Pulido T, 2013	Macitentan vs. Placebo	154	156	45.6	76.5	NA	32.4	63.7	47.5	360.0
McLaughlin V, 2015	Bosentan+Sildenafil vs. Sildenafil	88	16	53.9	75.7	NA	25.7	0.0	58.1	360.3
Gaine S, 2017	Selexipag vs. Placebo	334	26	52.3	90.0	NA	19.8	76.6	53.0	344.3
Coghlan J, 2017	Ambrisentan+Tadalafil vs. Ambrisentan/Tadalafil	187	24	58.2	88.2	63.1	0.7†	0.0	74.3	326.2
Galie N, 2017	Tadalafil vs. Placebo	35	16	56.5	87.5	NA	NA	55.4	64.3	328.9
White RJ, 2020	Treprostinil vs. Placebo	178	12	45.2	78.8	NA	6.4†	100.0	34.0	395.7

† Median, NA not available

The relative treatment effect, HRs (95% CI), for clinical worsening outcome were pooled using the two-stage NMA. The results of all possible pairwise comparisons among PAH-targeted

therapies are presented in Table 2. The combination therapy of ERA and PDE5i was associated with a 69% reduction in the risk of clinical worsening (HR, 0.31; 95% CI, 0.13 to 0.74) compared to placebo. Moreover, oral PA/PRA significantly reduced the risk of clinical worsening (HR, 0.66; 95% CI, 0.44 to 0.98). Although PDE5i or ERA monotherapies were associated with a reduced risk of clinical worsening, the results were not statistically significant. The inconsistency assumption was checked using the design-by-treatment method, which showed no evidence of inconsistency ($\chi 2 = 3.33$; $P = 0.1892$). Therefore, the consistency model was used for analysis.

Among PAH-targeted therapies, the combination of ERA and PDE5i ranked first for reducing the risk of clinical worsening based on SUCRA, followed by PDE5i monotherapy and ERA monotherapy. A predictive interval plot was constructed to estimate the expected range of treatment effects in future studies while accounting for uncertainty. The combination therapy had a 95% predictive interval (0.00 to 128.52), considerably wider than the 95% CI, indicating potential variability in treatment effects across different settings. A comparison-adjusted funnel plot demonstrated a symmetrical distribution, and the Egger's test showed no significant asymmetry (P = 0.913), indicating the absence of substantial publication bias.

Table 2 Pooled HRs (95% CI) for clinical worsening in all possible pairwise comparisons estimated from NMA

Reference treatment	**HR (95% CI)**				
	Placebo	**ERA+PDE5i**	**Oral PA/PRA**	**PDE5i**	**ERA**
Placebo	2.9, 0.0	**0.31* (0.13,0.74)**	**0.66* (0.44,0.98)**	0.49 (0.19,1.23)	0.60 (0.35,1.05)
ERA+PDE5i	**3.22* (1.35,7.65)**	96.7, 89.6	2.12 (0.83,5.45)	1.56 (0.96,2.54)	1.94 (0.93,4.08)
Oral PA/PRA	**1.52* (1.02,2.25)**	0.47 (0.18,1.21)	42.1, 4.4	0.74 (0.27,1.99)	0.92 (0.46,1.81)
PDE5i	2.06 (0.82,5.21)	0.64 (0.39,1.04)	1.36 (0.50,3.68)	60.0, 3.2	1.25 (0.54,2.87)
ERA	1.65 (0.96,2.87)	0.51 (0.25,1.08)	1.09 (0.55,2.16)	0.80 (0.35,1.85)	48.2, 2.8

Columns are compared to rows. Each off-diagonal cell (white) contains a HR (95% CI). Each diagonal cell (grey) contains SUCRA (first value) and a percentage probability of being the best treatment of each regimen (second value). The asterisk (*) indicates statistically significant comparisons

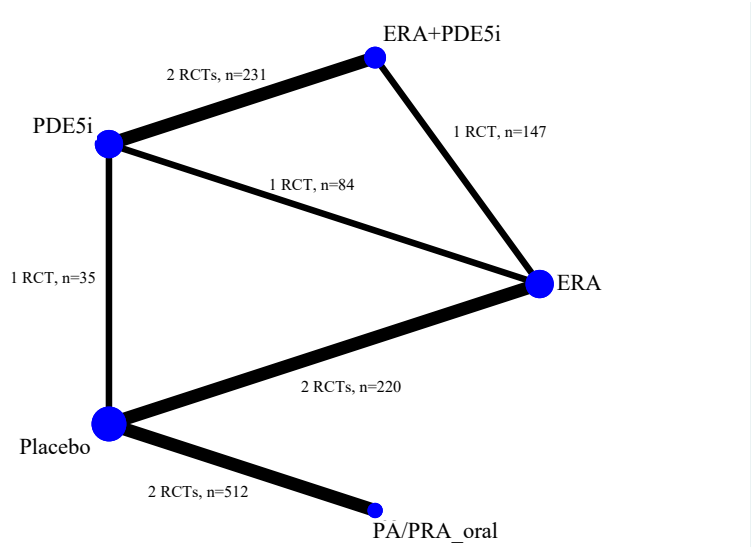

Figure 1 Network map comparing all PAH-targeted therapies for clinical worsening.

DISCUSSION & CONCLUSION

Seven RCTs involving 1,042 patients were identified and analyzed using a systematic review and NMA to pool the HRs (95% CI) for clinical worsening outcome. The study evaluated all available PAH-targeted therapies, including ERA (Ambrisentan, Bosentan, Macitentan), PDE5i (Sildenafil, Tadalafil), PA/PRA (Selexipag, oral Treprostinil), and combination therapies (Ambrisentan plus Tadalafil, Bosentan plus Sildenafil).

All PAH-targeted therapies reduced the risk of clinical worsening compared to placebo. However, combination therapy (ERA plus PDE5i) and oral PA/PRA showed statistically significant reductions, whereas ERA monotherapy demonstrated only a marginal effect. Previous systematic reviews and direct meta-analyses reported pooled treatment effects for all available PAH-targeted therapies, with reductions in the risk of clinical worsening by 36% (Khanna et al., 2021) and 39% (Erdogan et al., 2024). Our findings from the NMA further demonstrated that the risk of clinical worsening was reduced by 40 to 50% with ERA or PDE5i monotherapy, and by 69% with combination therapy. These findings reinforce the efficacy of PAH-targeted therapies in patients with CTD-PAH.

Notably, treatment with oral PA/PRA reduced the risk to a lesser extent by 34%, which may be influenced by the high proportion (88%) of patients receiving baseline PAH medications, potentially contributing to a ceiling effect on the add-on treatment. Additionally, this trial included fewer patients with WHO FC III or higher, which may further influence the observed outcomes. Our findings regarding ERA treatment were consistent with a prior systematic review and meta-analysis. ERA monotherapy from two RCTs with 373 CTD-PAH patients reduced the risk of composite clinical failure endpoints by 23% compared to placebo, albeit non-statistically significant. By contrast, the combination therapy with ERA and PDE5i from three RCTs with 452 patients provided a significantly greater reduction in composite clinical failure endpoints by 50% compared to monotherapy (Shivakumar et al., 2020).

Based on SUCRA, the combination therapy ranked as the most effective regimen for reducing the risk of clinical worsening, followed by PDE5i monotherapy and ERA monotherapy. These findings emphasize the importance of considering combination therapy as the preferred treatment for patients with CTD-PAH.

To our knowledge, this is the first NMA updating the efficacy of PAH-targeted therapies specifically focusing on patients with CTD-PAH. This study provides a comprehensive assessment of relative treatment effects by incorporating both direct and indirect comparison and identifies the most effective regimen for this patient group. However, this study had some

limitations. Despite efforts to include all PAH-targeted therapies, studies evaluating the efficacy of sGC and Sotatercept on clinical worsening outcomes in patients with CTD-PAH reported the results in the open-label extension period of the trials, introducing a potential bias in assessing the treatment response. Hence, we excluded these studies from the analysis due to potential bias in assessing treatment response.

Concerning the transitivity assumption, there is a variability in trial duration, ranging from 12 to 156 weeks, as well as differences in patient characteristics between treatment comparisons across the studies such as time since PAH diagnosis, background PAH medications, CTD subtypes, and outcome definitions. These differences may contribute to the heterogeneity among the studies. Furthermore, differences in the approach to combination therapies (i.e., initial combination or add-on combination at the time of clinical worsening) may affect the outcome.

In addition, CTD-PAH cases in these studies were mostly SSc, with only a small number of other CTDs. It may, however, be difficult to resolve this issue with the limited number of studies on the CTD-PAH population. Therefore, clinicians should interpret these findings with caution, as they may not be generalizable across all CTD-PAH subtypes. All these limitations allow for further research to address unmet needs in the choice of combination therapy among available PAH drug classes and understanding variations in treatment responses among different CTD subtypes.

In conclusion, a combination of PAH-targeted therapy may confer a preferable regimen in patients with CTD-PAH, as it effectively reduces the risk of clinical worsening. These findings provide valuable insights into clinical decision-making and help tailor therapies for this patient group, who may have diverse treatment responses compared to those with IPAH.

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