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Long-Term Outcomes in Patients with Connective Tissue Disease-Associated Pulmonary Arterial Hypertension in the Modern Treatment Era: Meta-Analyses of Randomized, Controlled Trials and Observational Registries

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Declaration of interests

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Objective

Data on the magnitude of benefit of modern pulmonary arterial hypertension (PAH) therapies in connective tissue disease-associated PAH (CTD-PAH) are limited. We performed meta-analyses of randomized, controlled trials (RCTs) and registries to quantify this benefit (PROSPERO# CRD42020167119).

Methods

PubMed and EMBASE were searched for articles reporting data from RCTs or registries published 1/1/2000–11/25/2019. Eligibility criteria included multicenter studies with ≥30 CTD-PAH patients. RCTs had to evaluate approved PAH therapy and report long-term clinical morbidity/mortality or 6-minute walk distance. Registries had to report survival. Random effects models were used to pool data.

Results

Eleven RCTs (N=4329 n=1267 CTD-PAH) and 19 registries (N=9739; n=4008 CTD-PAH) were included. Investigational therapy produced a 36% reduction in risk of clinical morbidity/mortality events versus control (HR=0.64; 95%CI: 0.54–0.75; *P*<0.001) in all patients and a 36% reduction (HR=0.64; 95% CI: 0.51–0.81; *P*<0.001) in CTD-PAH patients. Survival was lower in CTD-PAH versus all patients (62%, 95% CI: 57%–67% versus 72%, 95% CI: 69%–75% at 3 years). Survival in CTD-PAH patients treated primarily after 2010 was higher than in those treated before (73%, 95% CI: 62%–81% versus 65%, 95% CI: 59%–71% at 3 years).

Conclusions

Modern therapy provides a similar reduction in morbidity/mortality risk in CTD-PAH and the overall PAH population. Risk of death is higher in CTD-PAH than in PAH overall, but survival has improved in the last 10 years, which may be related to increased screening and/or new treatment approaches. Early detection of PAH in patients with CTD and upfront intensive treatment are warranted.

INTRODUCTION

Pulmonary arterial hypertension (PAH) leads to right ventricular dysfunction and failure with a median survival of approximately 3 years from the time of diagnosis (1, 2). Connective tissue disease-associated PAH (CTD-PAH) is historically associated with shortened survival compared to idiopathic PAH (IPAH) (3–6). Early detection of PAH with established methods among patients with CTD, such as systemic sclerosis (SSc) (7), and subsequent early treatment may improve survival outcomes (8). Rheumatologists are in a unique and critical position to identify these patients.

Availability of new and combination therapy approaches targeting multiple pathophysiological pathways have improved outcomes in PAH (9–16). However, trials of PAH therapies generally enroll patients with all PAH etiologies, and trials devoted

solely to CTD-PAH are rare; therefore, the magnitude of treatment effect in CTD-PAH is poorly defined as these patients represent a subgroup in most trials, albeit a large one. Further, data on whether new treatment approaches have resulted in improved survival in CTD-PAH are lacking.

We conducted 2 meta-analyses: we analyzed randomized, controlled trials (RCTs) to evaluate the magnitude of benefit of US Food and Drug Administration (FDA)-approved PAH therapies in patients with CTD-PAH, and we analyzed real-world observational disease registries to evaluate survival outcomes for patients with CTD-PAH as compared to the overall PAH population, and between patients treated mostly before or mostly after 2010. Compared to prior meta-analyses that have evaluated outcomes in RCTs among patients with CTD-PAH (17,18), our RCT meta-analysis provides a more contemporary dataset that includes modern agents and treatment paradigms, as well as a larger sample size. Our second meta-analysis extends these findings by evaluating long-term survival outcomes, an endpoint that is not typically included in RCTs because of their shorter duration. We also investigated survival over time to determine whether the availability of newer therapies and treatment approaches has translated into improved survival in real-world settings.

PATIENTS AND METHODS

These meta-analyses were conducted according to Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (19) with a modification suited to the rare disease state of PAH. Specifically, we conducted a comprehensive literature search instead of a systematic review to identify peer-reviewed reports of RCTs evaluating new therapies and disease registries. We did not expand the search to databases beyond PubMed and Embase, nor did we examine reference lists and non-database sources for additional information because of the very low likelihood of this method yielding additional articles in this rare disease.

The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; #CRD42020167119) (20).

Search strategy and selection criteria

PubMed and Embase (Elsevier) were searched for English-only articles reporting data from RCTs or registries and published between January 1, 2000, and November 25, 2019. Search terms for RCTs were “pulmonary arterial hypertension” in the title AND (randomized OR randomised), restricted to human subjects, in PubMed and (‘pulmonary hypertension’/exp OR ‘pulmonary hypertension’), restricted to phase 3 or 4 randomized, controlled studies, in Embase. Search terms for registries were “pulmonary arterial hypertension” in the title AND (registry OR observation OR consecutive OR multicenter OR multicentre), restricted to human subjects, in PubMed and ‘pulmonary hypertension’ in the title AND (‘observational study’/exp OR ‘observational study’) in Embase.

Studies were included if the RCT or registry was conducted at multiple centers; enrolled adults with World Health Organization (WHO) Group 1 pulmonary hypertension (i.e., PAH) (21); included ≥30 patients with CTD-PAH; provided CTD-PAH subgroup identification with publicly available CTD-PAH–specific outcomes data; enrolled patients in the year 2000 or later; and reported long-term clinical morbidity and/or mortality (median enrollment time of ≥6 months). Only peer-reviewed data were included. Additional inclusion criteria for RCTs were: phase 3 or 4; the evaluated PAH therapy must be currently FDA-approved; ≥3 months’ exposure to study drug for PAH treatment; and time-to-morbidity/mortality, time-to-clinical worsening, or 6-minute walk distance (6MWD), measured 3 to 6 months from baseline, had to have been a defined primary or secondary endpoint.

To minimize the risk of bias in study selection, we utilized strict pre-specified inclusion/exclusion criteria (as noted above). This involved a detailed review of each study design, patient inclusion and exclusion criteria, and definition of study endpoints. Studies not meeting the pre-specified criteria were excluded. In addition, at least 2 reviewers independently verified the studies that were to be included in the analyses, with any disagreements arbitrated by the lead and senior authors.

Publications providing the same data were removed. For multiple publications from 1 study, the most recent publication containing data on the CTD population was utilized. Data from all primary manuscripts of RCTs were included in the analysis for all PAH patients and CTD-PAH patients unless more detailed information for CTD-PAH patients were included in later post hoc analyses. When we extracted data from the post hoc analyses of the CTD-PAH subgroup, we ensured the number of patients in the CTD-PAH subgroup and the statistical analysis method were consistent with data from the primary manuscript. If multiple registries were conducted in 1 country, only studies that did not substantially overlap in enrollment period were included to avoid capturing data from the same patient in multiple registries.

Data were extracted from RCT and registry publications separately by 2 team members (with medical, science, or statistical expertise) under the leadership of statisticians at Actelion Pharmaceuticals. Extracted data were verified by a third team member independently. In the event of a discrepancy, a statistician verified the data prior to final statistical analysis and JH arbitrated any disagreements.

Data were extracted for patients with all PAH etiologies and for CTD-PAH separately. Baseline data extracted for both RCTs and registries were 6MWD, age, sex, WHO functional class (FC), and PAH etiology. Post-baseline data extracted were change from baseline in 6MWD between 3 and 6 months, number of clinical morbidity/mortality events, and hazard ratio (HR) from RCTs; and from registries, survival rates at 1, 2, and 3 years as reported or from Kaplan-Meier curves using a graph digitizer.

Data analysis

The meta-analysis of RCTs evaluated the effect of PAH therapies on time to clinical morbidity and/or mortality in all patients and patients with CTD-PAH, as well as the effect on 6MWD measured between 3 and 6 months after initiation of study treatment. The components of the clinical morbidity/mortality endpoints varied among the studies (Supplementary Table S1). The meta-analysis of registries evaluated survival outcomes in all patients and in patients with CTD-PAH. Analysis populations are defined in Supplementary Table S2.

To assess heterogeneity among studies, we calculated I^2 associated with the fixed effects meta-analysis models. These values indicated high heterogeneity for most analyses using fixed effects models but acceptable I^2 values using random effects meta-analysis models (Supplementary Table S3). Thus, we controlled for heterogeneity by consistently using random effects meta-analysis models to pool results using inverse variance weighting followed by un-weighting by applying a random effects variance component. The overall treatment effect estimate was calculated using the DerSimonian and Laird random effects method (22).

Time-to-event endpoints were estimated using the Kaplan-Meier method. Survival rates at 1-, 2-, and 3 years in registries were extracted from Kaplan-Meier curves and were stratified by study period mostly before or after 2010 to assess the impact of newer treatment approaches. Outcomes were analyzed for the overall PAH population and stratified by disease etiology (all CTD-PAH patients and CTD-PAH subtypes [SSc or systemic lupus erythematosus (SLE), or IPAH]). Registries with ≥50% of the study period in 2010 or later were classified as the after-2010 group.

Sensitivity analyses included analysis of treatment effect in RCTs in IPAH compared with CTD-PAH. In registries, analysis of survival rate in selected studies containing both CTD-PAH and other etiologies was performed to confirm the historical difference between etiologies.

A forest plot showing the effect size and associated variability in each study, as well as the combined effect, was created to examine the consistency of results. If any outliers were apparent, the data extraction was verified from the original source and the units were confirmed to ensure that no unit conversion was necessary. If, after this, an outlier was detected, a sensitivity analysis removing the outlier could be conducted to assess the impact on the overall analysis. However, no such outliers were found in our analysis.

Statistical analyses were performed with Comprehensive Meta-Analysis Version 3 Software (Biostat, Englewood, NJ).

Role of funding source

DK, VM, CZ, JH, SM, GC, and MS contributed to the study design. Employees of the study funder collected (CZ, JH, MS) and analyzed (CZ) the data. All authors had full access to the data, contributed to data interpretation, contributed to manuscript writing, and had final responsibility for the decision to submit for publication.

RESULTS

For RCTs, a total of 801 articles were identified through our comprehensive search strategy (Supplementary Figure S1) and 11 studies were ultimately included in the meta-analysis (Supplementary Table S4). For the primary endpoint, 5 RCTs reported time-to-clinical morbidity/mortality event (as defined in Supplementary Table S1) (12–16,23,24) and 6 RCTs reported change in 6MWD (10,11,25–30). The 11 RCTs enrolled 4329 patients with PAH, including 1267 patients with CTD-PAH (29.3%). Each RCT evaluated the addition of a PAH-specific therapy to a patient's current care, which could have included no PAH-specific treatment, monotherapy, or dual combination therapy.

For registries, a total of 1389 articles were identified through our search (Supplementary Figure S2) and 19 registries were ultimately included in the meta-analysis: 9 enrolled patients with PAH of all etiologies (4,5,31–37) and 10 enrolled only patients with CTD-PAH (Supplementary Table S5) (38–47). The 19 registries enrolled 9739 patients with PAH, including 4008 patients with CTD-PAH (41.2%).

At baseline, patients with CTD-PAH had an older mean age and lower mean 6MWD compared to the overall PAH population in both the RCTs and registries. In RCTs, overall, patients had a mean age of 50 years, 78%–79% were female, and 41%–43%

had FC I–II disease (Table 1). Patients with CTD-PAH had a mean age of 55–56 years versus 50 years among patients of all PAH etiologies (Supplementary Table S6) and had a mean 6MWD of 337–339 m versus 355–357 m among patients of all PAH etiologies (Supplementary Table S7).

In all 16 registries that reported baseline characteristics separately for the CTD-PAH population, patients with CTD-PAH had a mean age of 55 years, 87% were female, 30% had FC I–II disease, and the mean 6MWD was 327 m (Supplementary Table S8). From the 9 registries that enrolled patients with all PAH etiologies, all patients had a mean age of 51 years, 74% were female, 28% had FC I–II disease, and the mean 6MWD was 348 m; and patients with CTD-PAH had a mean age of 56 years, 84% were female, 24% had FC I–II disease, and the mean 6MWD was 328 m (Table 2). Baseline data from registries for the CTD-PAH subgroups treated before and after 2010 are shown in Supplementary Table S9. Baseline data from registries for the CTD-PAH subgroups of SSc and SLE are shown in Supplementary Table S10.

Outcomes from RCTs

The 5 RCTs that reported time-to-clinical morbidity/mortality event as the primary endpoint enrolled 3172 patients (n=941 with CTD-PAH [30%]) (12–16,23,24). Additional PAH therapy resulted in a 36% reduction in risk of morbidity/mortality events compared to control (HR=0.64; 95% CI: 0.54–0.75; *P*<0.001) in the overall PAH population and a 36% reduction (HR=0.64; 95% CI: 0.51–0.81; *P*<0.001) in patients with CTD-PAH (Figure 1).

Additional PAH therapy led to a placebo- or monotherapy-corrected increase in 6MWD of 28.6 m (95% CI: 19.2–38.0; *P*<0.001) in the overall PAH population (Figure 2A). Eight RCTs (N=2874; n=882 with CTD-PAH [31%]) reported this endpoint by CTD-PAH etiology (9–12,15,23–30). Additional PAH therapy led to an increase in 6MWD of 34.6 m (95% CI: 22.1–47.1; *P*<0.001) in the overall PAH population and 20.4 m (95% CI: 10.9–29.9; *P*<0.001) in patients with CTD-PAH (Figure 2B and Figure 2C).

Sensitivity analyses were performed to compare outcomes between patients with CTD-PAH and IPAH among the subset of trials that reported outcomes separately in the IPAH subpopulation. Results from patients with IPAH trended similar to the overall PAH population (HR=0.63; 95% CI: 0.54–0.73; *P*<0.001).

Outcomes from registries

Among 9 registries that included patients with PAH irrespective of etiology (4,5,31,32–37), survival rates in patients with CTD-PAH (n=2113) were lower than in the overall PAH population (N=7829) (Figure 3A).

Among all CTD-PAH patients with available data, including those from both all-PAH and CTD-PAH–specific registries (19 registries; n=3978), survival rates in patients with CTD-PAH treated in registries with ≥50% of the study period during or after 2010 (n=1819) were higher than in those treated in registries with ≥50% of the study period occurring before 2010 (n=2159) (Figure 3B).

Among all patients with CTD-PAH, survival rates were lower for those with SSc (n=1485) (36,38,41,43,44,46,47) compared to those with SLE (n=456) (39,40,42,45) (Figure 3C).

DISCUSSION

Our meta-analysis of RCTs demonstrated that patients with CTD-PAH derive a clinically significant benefit from currently available PAH therapies which, in many patients, comprised the addition of a drug targeting a second or third pathway involved in the pathophysiology of PAH. Our meta-analysis of registries showed that patients with CTD-PAH have a higher risk of death than the overall PAH population; however, survival has improved among the CTD-PAH population treated mostly in the last 10 years compared to earlier patient populations.

Two other relatively recent meta-analyses have also evaluated the benefit of PAH-specific therapy in patients with CTD-PAH (17,18). Rhee and colleagues (17) evaluated individual patient data from 11 RCTs published between 2002 and 2013 (n=2762;

n=827 with CTD-PAH [30%]). Most of the trials (59% of patients) evaluated endothelin receptor antagonists (ERAs). Similar to our 6MWD results, patients with CTD-PAH experienced less benefit than patients with IPAH. The mean placebo-corrected treatment effect in change in 6MWD from baseline to 3 months was 23.1 m (CTD-PAH) versus 40.4 m (IPAH; adjusted treatment effect difference, -17.3 m; 90% CI, -31.3 to -3.3; *P*-value for interaction=0.043). We reported a similar placebo-/monotherapy-corrected change in 6MWD of 20.4 m in patients with CTD-PAH. Our reference population included patients with all PAH etiologies, which may explain the lower benefit of 34.6 m observed in our study compared to those with IPAH reported by Rhee and colleagues (17). However, earlier meta-analyses of 6MWD from RCTs are also conflicting with 1 showing similar benefit in patients with CTD-PAH and PAH of all etiologies (48) and another showing no benefit in patients with CTD-PAH (49). Time-to-clinical worsening was not significantly prolonged among patients with CTD-PAH in the meta-analysis by Rhee and colleagues (17) with an odds ratio of 0.72 (95% CI, 0.45–1.16); whereas we demonstrated a benefit (HR, 0.64; 95% CI, 0.51–0.80). The difference between meta-analyses may result from several factors. We believe that our analysis provides a more precise estimate of treatment effect because we applied more stringent statistical methods to pool the studies. Specifically, we measured the time to a clinical morbidity/mortality event by using the hazard ratio, which averages the treatment effect over the entire study period. Rhee and colleagues measured clinical worsening events using an odds ratio, which is affected by differences in study duration. Further, our study required a median study duration of ≥6 months to capture long-term clinical morbidity and mortality (current standards to assess overall benefit), whereas approximately half of the trials included by Rhee and colleagues (17) were of 12- to 18-weeks duration (i.e., a previous standard to assess PAH therapy efficacy). Finally, we used a more contemporary dataset, which included trials of the most recently available PAH therapies comprising oral ERAs, phosphodiesterase type 5 inhibitors, oral prostacyclin pathway agents, and riociguat, as well as more use of combination therapy. This dataset, thus, more accurately reflects current treatment approaches. This approach also resulted in a larger patient population (1267 CTD-PAH patients from

RCTs compared with 827 in the analysis by Rhee and colleagues), which increases the precision of the statistical estimates.

Pan and colleagues (18) analyzed data extracted from 6 RCTs published between 2011 and 2017 (n=3262; n=963 with CTD-PAH [30%]). These trials evaluated ERAs, tadalafil, selexipag, and riociguat. This meta-analysis aimed to compare combination therapy versus monotherapy; however, background therapy varied among studies and patients within the studies. Among 4 RCTs in the CTD-PAH subset included in the analysis, additional PAH therapy led to a 27% relative risk reduction of clinical worsening (pooled relative risk, 0.73 [95% CI, 0.60–0.89], *P*=0.002). These data are consistent with our finding of a 36% reduction in risk of a clinical morbidity/mortality event in the CTD-PAH population. There were differences in methodology between the 2 analyses. In our study, for clinical relevance, only treatment arms receiving FDA-approved doses were analyzed. Additionally, our meta-analysis includes the more recently published FREEDOM-EV trial (16), which was published after the Pan and colleague's (18) meta-analysis was completed. Pan and colleagues also found no statistically significant benefit in change in 6MWD among patients with CTD-PAH with additional therapy (21.38 m; 95% CI, -20.38 to 63.14; *P*=0.32). This endpoint was derived from 3 RCTs. Our meta-analysis, which included 8 trials for this endpoint, demonstrated a similar numerical benefit for patients with CTD-PAH that was statistically significant (20.4 m; 95% CI, 10.9 to 29.9; *P*<0.001), perhaps reflecting greater statistical power due to increased sample size. Overall, compared to the Pan and colleague's (18) meta-analysis, our study provides an expanded evaluation, including the FREEDOM-EV trial, with an additional meta-analysis of survival in registries because long-term survival outcomes and longitudinal analysis of survival outcomes over decades are inaccessible from RCTs.

Patients with CTD-PAH have a substantial risk of death; however, patients with CTD-PAH who were treated within the last 10 years have numerically higher survival rates than those treated earlier. This difference may be related to increased screening for PAH, especially in SSc. Increased screening leads to earlier diagnosis, which provides the opportunity for earlier management (8) but also introduces lead-time bias (50). If

lead-time bias is present, patients in later registries would be expected to be younger with less severe disease. Our analysis found that in the later registries, patients were older (mean age 57 years vs 54 years), but had less severe disease (as defined by proportion of patients with FC I-II disease, 40% versus 23%, respectively) and greater 6MWD (336 m vs 321 m; Supplemental Table S9). Whether lead-time bias is playing a substantial role in our results cannot be definitively determined from the current analysis.

The difference in survival over time also may reflect the availability of new treatment approaches. The survival improvement is likely underestimated since just 6 registries (32%) enrolled patients in 2015 or later, when all currently available treatments were in use and early combination therapy became more prevalent (5,34,39,41,46,47). More recent data are available from the United Kingdom Pulmonary Hypertension Audit (51). The most recent peer-reviewed published data from this database are included in our meta-analysis (38); however, the latest report available (data from 2009-2019) is not included due to lack of peer review. Published data from 2001–2007 reported 1-, 2-, and 3-year survival rates among patients with SSc-associated PAH of 78%, 58%, and 47%, respectively. Corresponding survival rates from 2009–2019 were 81%, 61%, and 55%, respectively. These data corroborate the improved survival rates observed over time in our meta-analysis. Consistent with clinical observations and published data (6,38,52), our meta-analysis demonstrated that patients with SSc have worse survival rates than those with SLE. It should be noted, however, that patients with SSc in our analysis were older than those with SLE and appeared to have more severe disease as indicated by fewer patients with FC I/II disease and shorter 6MWD (Supplementary Table S10) which likely also contributed to their poorer survival. We were not able to use meta-analysis to compare the treatment effect in RCTs in patients with SSc versus those with SLE since only two RCTs provided sufficient data on patients with SSc (23, 24) and one on patients with SLE (24).

Because all-cause mortality was evaluated, we may be overestimating death due to PAH among patients with CTD-PAH. These patients are older and experience greater comorbidity burden than the overall PAH population. As such, these patients are

possibly frailer and may die from causes other than their PAH. Although registries are subject to bias, these sources of long-term data and larger sample size were deemed important to include in order to provide prolonged survival data unavailable from RCTs. Current guidelines now recommend combination therapy and more intensive therapy regardless of PAH etiology (53), and our meta-analysis of registries provides evidence suggesting that the modern approach to treatment is improving survival in CTD-PAH. Nonetheless, survival remains lower for these patients, highlighting the need for continued research into the best treatment approaches and screening programs to promote early diagnosis and prompt management. Additional avenues for research to improve outcomes in this population include standardized reporting of comorbidities, which can substantially impact outcomes in CTD-PAH, as well as in PAH of other etiologies (54). Identification of comorbidities is further complicated by lack of a consensus definition of significant interstitial lung disease in SSc. An additional area of focus should be standardized reporting of baseline risk profiles, since data suggest that patients with CTD-PAH are at greater risk of death despite a less severe hemodynamic phenotype (5,55). Identification of clinically relevant changes in outcome measures, which may differ among PAH subtypes, would also be helpful. Finally, the era of personalized medicines may enable smaller study sizes and ultimately facilitate the discovery of treatment approaches that show greater benefit within CTD-PAH populations.

A strength of our meta-analyses is the inclusion of only trials evaluating therapies that are approved for PAH treatment. By limiting RCTs to approved therapies, the results better reflect the benefit that can be observed in real-world settings. In addition, our meta-analysis of RCTs assessed the impact of current PAH treatments on morbidity and mortality, as endorsed by the 6th World Symposium on Pulmonary Hypertension (53). A limitation of our meta-analysis of RCTs was that definitions of a clinical morbidity/mortality event varied to a limited extent across studies (Supplementary Table S1). A limitation of our meta-analysis of registries was the limited availability of studies that enrolled patients from 2015 onward to provide a survival estimate consistent with that observed in modern clinical practice. In all analyses, the overall PAH population to which we compared the CTD-PAH population included patients with CTD-PAH because

not all studies provided IPAH-specific data. However, sensitivity analyses of RCTs that provided IPAH-specific data, demonstrated similar trends with IPAH versus CTD-PAH as with all PAH etiologies versus CTD-PAH. An additional limitation is that the extent to which the treatment effect is influenced by different background therapies, potential variability in exposure to therapies, concomitant medications (such as immunosuppressants), as well as different proportions of newly and previously diagnosed patients, in the study populations is unknown. Finally, the diagnosis of PAH was accepted per each study or registry criteria; it is possible that underlying conditions, such as pulmonary veno-occlusive disease and concomitant ILD, were present and to differing degrees among the various studies. A limitation of our search methodology was that we did not search additional databases beyond PubMed and Embase. As noted, however, we do not expect any differences in outcomes as a result of this given the parameters of our meta-analyses, the rarity of this disease state, and the relatively small number of studies reporting data separately for the subset of patients with CTD-PAH.

In conclusion, these complementary meta-analyses of RCTs and observational disease registries demonstrated that patients with CTD-PAH had a similar reduction in the risk of clinical morbidity and mortality events as the overall PAH population with modern PAH treatments. The improvement in 6MWD in patients with CTD-PAH appeared smaller than in those with other types of PAH, perhaps reflecting comorbidities (such as musculoskeletal involvement), independent of their cardiopulmonary capacity. Patients with CTD-PAH have a higher risk of death than the overall PAH population; however, survival has improved among this subgroup treated in the last 10 years compared to earlier cohorts. Patients with SSc have worse survival rates than those with SLE. Given the high risk of mortality in these patients, early detection and upfront aggressive treatment are warranted (56).

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Figure legends

Figure 1. Time to clinical morbidity/mortality event for all patients (left panel) and patients with CTD-PAH (right panel) in randomized, controlled trials that evaluated time-to-clinical morbidity/mortality event as a primary endpoint (5 trials). AMBITION=Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension; CI=confidence interval; CTD-PAH=connective tissue disease-associated pulmonary arterial hypertension; GRIPHON=Prostacyclin (PGI_2) Receptor Agonist in Pulmonary Arterial Hypertension; HR=hazard ratio; SERAPHIN=Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome.

Figure 2. Change in 6MWD for all patients in all randomized, controlled trials (A; 11 trials); for all patients in randomized, controlled trials that reported 6MWD in patients with CTD-PAH (B; 8 trials); and for patients with CTD-PAH (C; 8 trials). *Combined data from ARIES-1 and ARIES-2 presented. 6MWD=6-minute-walk distance; AMBITION=Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension; ARIES=Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies; BREATHE-1=Bosentan Randomized Trial of Endothelin Antagonist Therapy; CI=confidence interval; CTD-PAH=connective tissue disease-associated pulmonary arterial hypertension; GRIPHON=Prostacyclin (PGI_2) Receptor Agonist in Pulmonary Arterial Hypertension; PATENT-1=Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1; PHIRST=Pulmonary Arterial Hypertension and Response to Tadalafil; SERAPHIN=Study with an Endothelin Receptor Antagonist in Pulmonary Arterial

Hypertension to Improve Clinical Outcome; SUPER=Sildenafil Use in Pulmonary Arterial Hypertension.

Figure 3. Survival estimates (A) in patients by PAH etiology among registries in which all PAH etiologies were included (9 registries); (B) in patients with CTD-PAH from all registries (19 registries) by enrollment period; and (C) by CTD subtype from disease-specific registries or registries that included disease-specific outcomes (8 registries for SSc and 4 registries for SLE). Vertical bars represent 95% confidence intervals. CTD=connective tissue disease; CTD-PAH=connective tissue disease-associated pulmonary arterial hypertension; PAH=pulmonary arterial hypertension; SLE=systemic lupus erythematosus; SSc=systemic sclerosis.

Table 1. Baseline characteristics of all patients in randomized, controlled trials

	Investigational Arm				Control Arm			
Study (ref.)	**N**	**Mean Age, y (SD)**	**Female, %**	**FC I–II, %**	**N**	**Mean Age, y (SD)**	**Female, %**	**FC I–II, %**
AMBITION (12)	253	55 (14)	74	30	247	54 (15)	81	32
GRIPHON (15)	574	48 (15)	80	48	582	48 (16)	80	45
SERAPHIN (14)	242	45 (15)	80	50	250	47 (17)	74	52
PHIRST (10)	79	53 (15)	75	35	82	55 (15)	79	29
ARIES-1 (28)	67	49 (16)	79	36	67	48 (16)	88	37
ARIES-2 (28)	63	50 (16)	81	46	65	51 (14)	68	40
PATENT (11)	254	51 (17)	80	45	126	51 (17)	78	51
SUPER-1 (9)	71	48 (15)	79	39	70	49 (17)	81	47
BREATHE-1 (25)	144	49 (16)	79	0	69	47 (16)	78	0
COMPASS-2 (13)	159	53 (15)	79	45	175	55 (16)	73	39
FREEDOM EV (16)	346	46 (16)	80	62	344	45 (15)	78	70
Overall*	**2252**	**50 (SE, 1.1)**	**79**	**41**	**2077**	**50 (SE, 1.2)**	**78**	**43**

*estimated mean and standard error from the random effects model.

AMBITION=Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension; ARIES=Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies; BREATHE-1=Bosentan

Randomized Trial of Endothelin Antagonist Therapy; FC=functional class; GRIPHON=Prostacyclin (PGI_2) Receptor Agonist in Pulmonary Arterial Hypertension; PATENT=Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1; PHIRST=Pulmonary Arterial Hypertension and Response to Tadalafil; ref.=reference; SD=standard deviation; SE=standard error; SERAPHIN=Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome; SUPER=Sildenafil Use in Pulmonary Arterial Hypertension.

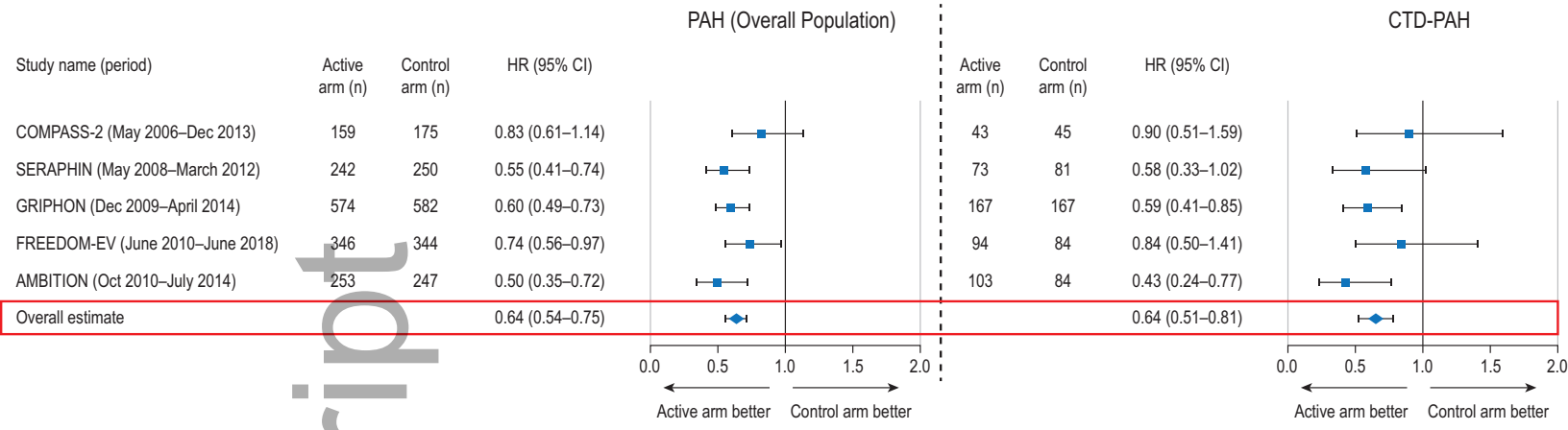
Table 2. Baseline characteristics of patients in registries enrolling patients with PAH irrespective of etiology

	All Patients (n=7844)					Patients with CTD-PAH (n=2113)			
Registry (ref.)	Mean Age, y (SD)	Female, %	FC I–II, %	Mean 6MWD, m (SD)	CTD, %	Mean Age, y (SD)	Female, %	FC I–II, %	Mean 6MWD, m (SD)
REHAP (31)	45 (17)	71	31	363 (120)	18	54 (15)	90	21	309 (115)
PAH-QuERI (32)	55 (16)	77	47	—	29	—	—	—	—
COMPERA (5)	64 (16)	64	11	298 (126)	22	66 (13)	78	11	273 (130)
French PAH Network Registry (4)	50 (15)	66	25	329 (109)	15	56 (15)	80	26	315 (111)
REVEAL (33)	50 (17)	77	—	—	28	—	—	—	—
THALES (34)	46 (17)	77	21	—	22	—	—	—	—
Chinese Registry-PAH (35)	36 (15)	76	46	390 (111)	37	42 (14)	85	45	384 (107)
BPR (36)	59 (17)	77	11	-	42	62 (11)	85	6	—
KORPAH (37)	50 (17)	78	53	363 (116)	58	54 (17)	85	63	358 (114)
Overall*	**51 (SE, 2.7)**	**74**	**28**	**348 (SE, 16.4)**	**29**	**56 (SE, 3.3)**	**84**	**24**	**328 (SE, 20.1)**

*estimated mean and standard error from the random effects model.

— Indicates not reported.

6MWD=6-minute-walk distance; BPR=Bosentan Patient Registry; COMPERA=Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CTD=connective tissue disease; FC=functional class; KORPAH=Korean Registry of Pulmonary Arterial Hypertension; PAH=pulmonary arterial hypertension; PAH-QuERI=Pulmonary Arterial Hypertension-Quality Enhancement Research Initiative; ref.=reference; REHAP=Spanish Registry of Pulmonary Arterial Hypertension; REVEAL=Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management; SD=standard deviation; SE=standard error.



Note: Overall HRs were estimated using random effects models.

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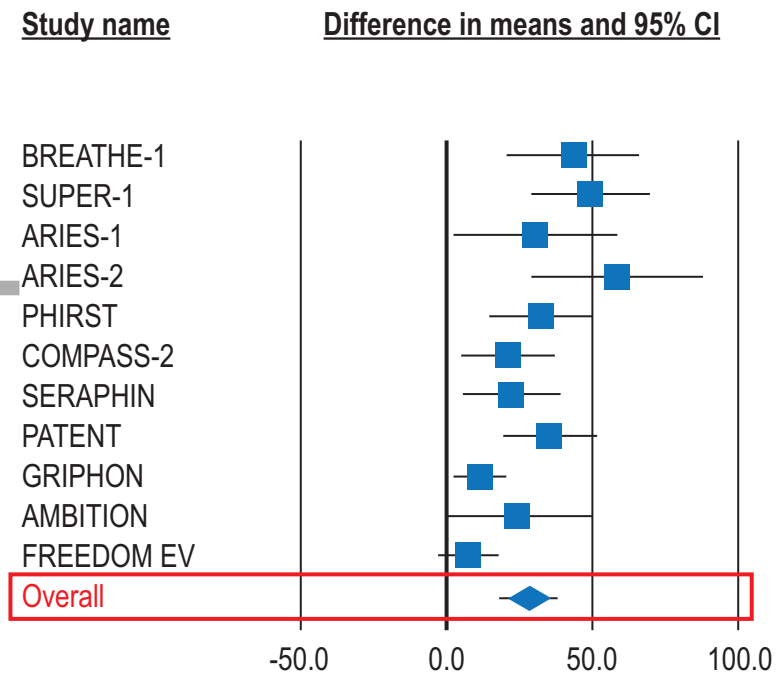
A.



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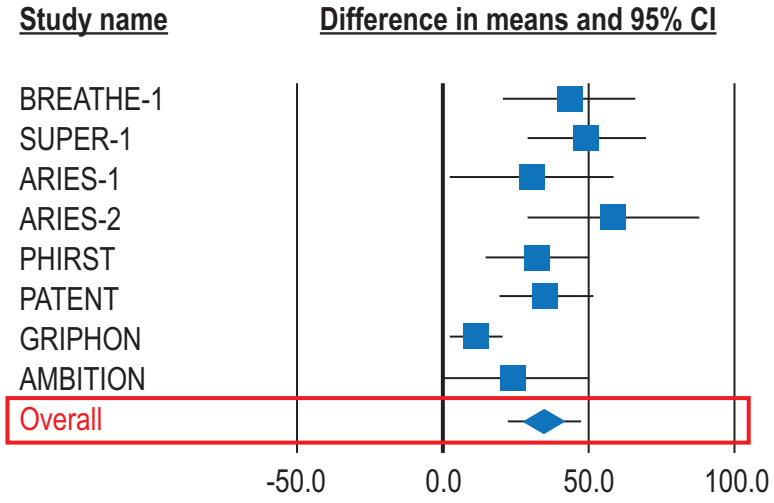

C.