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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

Dinesh Khanna,[1] (ID) Carol Zhao,[2] Rajan Saggar,[3] (ID) Stephen C. Mathai,[4] Lorinda Chung,[5] J. Gerry Coghlan,[6] Mehul Shah,[2] John Hartney,[2] and Vallerie McLaughlin[1]

Objective. Data on the magnitude of benefit of modern therapies for pulmonary arterial hypertension (PAH) in connective tissue disease (CTD)–associated PAH are limited. In this study, we performed meta-analyses of randomized, controlled trials (RCTs) and registries to quantify the benefit of these modern therapies in patients with CTD-PAH.

Methods. The PubMed and Embase databases were searched for articles reporting data from RCTs or registries published between January 1, 2000 and November 25, 2019. Eligibility criteria included multicenter studies with ≥30 CTD-PAH patients. For an RCT to be included, the trial had to evaluate an approved PAH therapy, and long-term risks of clinical morbidity and mortality or 6-minute walk distance had to be reported. For a registry to be included, survival rates had to be reported. Random-effects models were used to pool the data.

Results. Eleven RCTs (total of 4,329 patients; 1,267 with CTD-PAH) and 19 registries (total of 9,739 patients; 4,008 with CTD-PAH) were included. Investigational therapy resulted in a 36% reduction in the risk of clinical morbidity/mortality events both in the overall PAH population (hazard ratio [HR] 0.64, 95% confidence interval [95% CI] 0.54, 0.75; $P < 0.001$) and in CTD-PAH patients (HR 0.64, 95% CI 0.51, 0.81; $P < 0.001$) as compared to control subjects. The survival rate was lower in CTD-PAH patients compared to all PAH patients (survival rate 62%, 95% CI 57, 67% versus 72%, 95% CI 69, 75% at 3 years). The survival rate in CTD-PAH patients treated primarily after 2010 was higher than that in CTD-PAH patients treated before 2010 (survival rate 73%, 95% CI 62, 81% versus 65%, 95% CI 59, 71% at 3 years).

Conclusion. Modern therapy provides a similar reduction in morbidity/mortality risk in patients with CTD-PAH when compared to the PAH population overall. Risk of death is higher in CTD-PAH patients than in those with 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 up-front intensive treatment are warranted.

INTRODUCTION

Pulmonary arterial hypertension (PAH) leads to right ventricular dysfunction and failure, with a median survival of ~3 years from the time of diagnosis (1,2). Connective tissue disease (CTD)–associated PAH is historically associated with shortened survival compared to idiopathic PAH (IPAH) (3–6). Early detection of PAH with established methods among patients with CTDs, such as those with 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 pathophysiologic pathways have led to improved outcomes in PAH (9–16). However, trials of PAH therapies generally enroll patients with different etiologies of PAH, and trials devoted solely to those with 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. Furthermore, data on whether new treatment approaches have resulted in improved survival in CTD-PAH are lacking.

For the present study, we conducted 2 meta-analyses. In one meta-analysis, 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. In the other meta-analysis, we analyzed real-world observational disease registries to compare survival outcomes between patients with CTD-PAH and the overall PAH population, and between patients treated mostly before 2010 and those treated 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 data set 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 end point 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

Study design. These meta-analyses were conducted in accordance with the 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 registration no. 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. Specific parameters (search terms, Boolean operators, and filters) were applied. To identify RCTs, we searched in PubMed for the term "pulmonary arterial hypertension" in the title along with "AND (randomized OR randomised)" and restricted the search to human subjects; in Embase, we searched for "('pulmonary hypertension'/exp OR 'pulmonary hypertension')" and restricted the search to phase III or phase IV RCTs. To identify registries, we searched in PubMed for the term "pulmonary arterial hypertension" in the title along with "AND (registry OR observation OR consecutive OR multicenter OR multicentre)" and restricted the search to human subjects; in Embase, we searched for "pulmonary hypertension" in the title along with "AND ('observational study'/exp OR 'observational study')."

RCTs and registries had to meet the following inclusion criteria. 1) The RCT or registry was conducted at multiple centers. 2) Enrolled patients were adult patients with World Health Organization (WHO) group 1 pulmonary hypertension (i.e., PAH) (21). 3) The RCT or registry included ≥30 patients with CTD-PAH. 4) Publicly available CTD-PAH–specific outcomes data were provided for the CTD-PAH subgroup. 5) Enrollment of patients began in 2000 or later. 6) Long-term incidence rates of clinical morbidity and/or mortality were reported (median enrollment time ≥6 months).

Only peer-reviewed data were included. Additional inclusion criteria for RCTs were as follows: the RCT was a phase III or phase IV study; the evaluated PAH therapy had received current approval from the FDA; patients were exposed to the study drug for PAH treatment for at least 3 months; and one of the defined primary or secondary end points was time to clinical morbidity/mortality, time to clinical worsening, or 6-minute walk distance (6MWD) measured 3–6 months from baseline.

To minimize the risk of bias in study selection, we utilized the above-noted strict prespecified inclusion/exclusion criteria. This involved a detailed review of each study design, patient inclusion and exclusion criteria, and definition of study end points. Studies not meeting the prespecified 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 author (DK) and senior author (VM).

Publications providing the same data from the same RCT or registry were removed. For multiple publications from a single study, the most recent publication containing data on the CTD-PAH population was utilized. Data from all primary reports of RCTs were included in the analyses of 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 that the number of patients in the CTD-PAH subgroup and the statistical analysis method were consistent with that described in the primary report. If multiple registries were conducted in a single 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 the final statistical analysis, and one of the authors (JH) arbitrated any disagreements.

Data were extracted separately for patients with any of the PAH etiologies and for patients with CTD-PAH. Baseline data extracted for both RCTs and registries were the 6MWD, age, sex, WHO functional class, and PAH etiology. Data extracted after baseline were the change in the 6MWD from baseline to between 3 and 6 months, number of clinical morbidity/mortality events, and hazard ratio (HR) (with 95% confidence interval [95% CI]) for the long-term risk of morbidity/mortality in RCTs. In addition, data from the registries included the survival rates at 1, 2, and 3 years, as reported in the registry or as determined from Kaplan-Meier survival curves using a graph digitizer.

Statistical analysis. The meta-analysis of RCTs evaluated the effect of PAH therapies on time to clinical morbidity and/or mortality in all patients and in patients with CTD-PAH, as well as the effect on the 6MWD measured between 3 and 6 months after initiation of study treatment. The components of the clinical morbidity/mortality end points varied among the studies (see Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract). The meta-analysis of registries evaluated survival outcomes in all patients and in patients with CTD-PAH. Analysis populations are defined in Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract.

To assess heterogeneity among studies, we calculated the I^2 value associated with the fixed-effects meta-analysis models. These values indicated that most analyses using fixed-effects models had high heterogeneity, whereas analyses using random-effects meta-analysis models had I^2 values that were considered to be within the acceptable range of heterogeneity (I^2 lower than 50%) (see Supplementary Table 3, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract). Thus, we controlled for heterogeneity among studies by consistently using random-effects meta-analysis models to pool results, using inverse variance weighting followed by unweighting with application of

a random-effects variance component. The overall treatment effect estimate was calculated using the DerSimonian and Laird random-effects method (22).

Time-to-event end points were estimated using the Kaplan-Meier method. Survival rates at 1, 2, and 3 years in the 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 patients with IPAH compared to patients with CTD-PAH. In the 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 using Comprehensive Meta-Analysis version 3 software (Biostat).

RESULTS

Study and patient characteristics. With regard to RCTs, a total of 801 articles were identified through our comprehensive search strategy (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract) and 11 studies were ultimately included in the meta-analysis (as listed in Supplementary Table 4 on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract). Among those that met the criteria for one of the defined primary end points, 5 RCTs reported time to clinical morbidity/mortality events (12–16,23,24) (specifically defined in Supplementary Table 1 [http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract]), and 6 RCTs reported change in the 6MWD (10,11,25–30). The 11 RCTs enrolled a total of 4,329 patients with PAH, including 1,267 patients with CTD-PAH (29.3%). Each RCT evaluated the addition of a PAH-specific therapy to a patient's current care, so that patients were stratified according to whether they received no PAH-specific treatment, monotherapy, or dual combination therapy.

With regard to observational registries, a total of 1,389 articles were identified through our search (see Supplementary Figure 2,

Table 1. Baseline characteristics of all patients with PAH in the randomized, controlled trials*

	Investigational treatment group				Control group			
Study (ref.)	No. of patients	Age, mean ± SD years	Female, %	WHO functional class I–II, %	No. of subjects	Age, mean ± SD years	Female, %	WHO functional class 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
All studies	2,252	50 ± 1.1†	79	41	2,077	50 ± 1.2†	78	43

* PAH = pulmonary arterial hypertension; WHO = World Health Organization; AMBITION = Ambrisentan plus Tadalafil in PAH; GRIPHON = Prostacyclin Receptor Agonist (Prostaglandin I₂) in PAH; SERAPHIN = Study with an Endothelin Receptor Antagonist in PAH to Improve Clinical Outcome; PHIRST = PAH and Response to Tadalafil; ARIES = Randomized, Double-blind, Placebo-controlled, Multicenter, Efficacy Study of Ambrisentan for PAH (1 and 2); PATENT = PAH Soluble Guanylate Cyclase–Stimulator Trial 1; SUPER-1 = Sildenafil Use in PAH; BREATHE-1 = Bosentan Randomized Trial of Endothelin Antagonist Therapy; COMPASS-2 = Combination of Bosentan and Sildenafil Versus Sildenafil Monotherapy on PAH; FREEDOM-EV = International, Multicenter, Randomized, Double-blind, Placebo-controlled Event-driven Trial of Oral Treprostinil in Subjects with PAH.
† Values are the estimated mean ± SEM from the random-effects model.

available on the *Arthritis & Rheumatology* website at http://online library.wiley.com/doi/10.1002/art.41669/abstract) and 19 registries were ultimately included in the meta-analysis (as listed in Supplementary Table 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41669/ abstract): in 9 of the registries, patients with PAH of all etiologies were enrolled (4,5,31–37), and in 10 registries, only patients with CTD-PAH were enrolled (38–47). The 19 registries enrolled 9,739 patients with PAH, including 4,008 patients with CTD-PAH (41.2%).

At baseline both in the RCTs and in the registries, patients with CTD-PAH were older and had a lower mean 6MWD compared

to the overall PAH population. In RCTs, patients with PAH of any etiology had a mean age of 50 years, 78–79% were female, and 41–43% had WHO functional class I or II disease (Table 1). Patients with CTD-PAH in the RCTs had a mean age of 55–56 years, compared to a mean age of 50 years among patients of all PAH etiologies, and had a mean 6MWD of 337–339 meters, compared to a mean 6MWD of 355–357 meters among patients of all PAH etiologies (see Supplementary Tables 6 and 7 on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/ doi/10.1002/art.41669/abstract).

In all 16 registries in which baseline characteristics were reported separately for the CTD-PAH population, patients with

Table 2. Baseline characteristics of the registry patients with PAH of any etiology and patients with CTD-PAH*

	All patients (n = 7,844)					Patients with CTD-PAH (n = 2,113)			
Registry (ref.)	Age, mean ± SD years	Female, %	WHO functional class I–II, %	6MWD, mean ± SD meters	CTD, %	Age, mean ± SD years	Female, %	WHO functional class I–II, %	6MWD, mean ± SD meters
REHAP (31)	45 ± 17	71	31	363 ± 120	18	54 ± 15	90	21	309 ± 115
PAH-QuERI (32)	55 ± 16	77	47	NR	29	NR	NR	NR	NR
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	NR	NR	28	NR	NR	NR	NR
Turkish registry (34)	46 ± 17	77	21	NR	22	NR	NR	NR	NR
Chinese Registry-PAH (35)	36 ± 15	76	46	390 ± 111	37	42 ± 14	85	45	384 ± 107
BPR (36)	59 ± 17	77	11	NR	42	62 ± 11	85	6	NR
KORPAH (37)	50 ± 17	78	53	363 ± 116	58	54 ± 17	85	63	358 ± 114
All registries	51 ± 2.7†	74	28	348 ± 16.4†	29	56 ± 3.3†	84	24	328 ± 20.1†

* PAH = pulmonary arterial hypertension; CTD-PAH = connective tissue disease–associated PAH; WHO = World Health Organization; 6MWD = 6-minute walk distance; REHAP = Spanish Registry of PAH; PAH-QuERI = PAH Quality Enhancement Research Initiative; NR = not reported; COMPERA = Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; REVEAL = Registry to Evaluate Early and Long-term PAH Disease Management; BPR = Bosentan Patient Registry; KORPAH = Korean Registry of PAH.
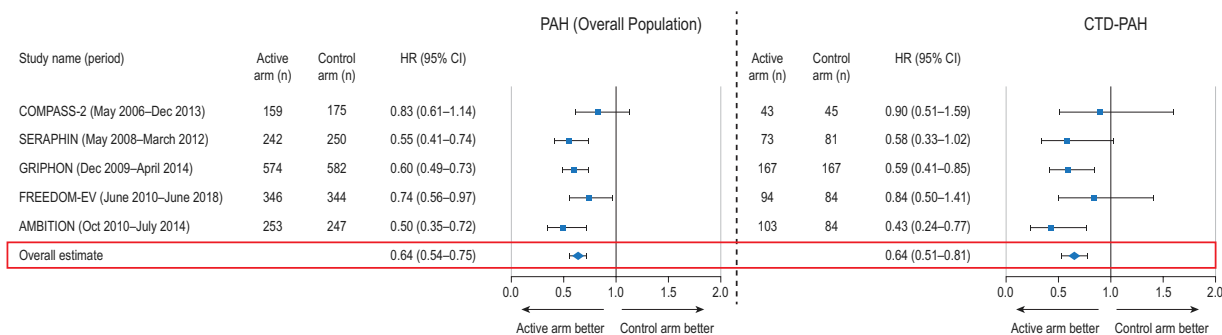† Values are the estimated mean ± SEM from the random-effects model.

Figure 1. Time to clinical morbidity/mortality event for all patients with pulmonary arterial hypertension (PAH) (left) and patients with connective tissue disease (CTD)–associated PAH (right) in randomized, controlled trials that evaluated time to clinical morbidity/mortality event as a primary end point (5 trials). Results are depicted as forest plots, showing the hazard ratio (HR) with 95% confidence interval (95% CI) in the active treatment group relative to the control group. Overall HRs were estimated using random-effects models. COMPASS-2 = Combination of Bosentan and Sildenafil Versus Sildenafil Monotherapy on PAH; SERAPHIN = Study with an Endothelin Receptor Antagonist in PAH to Improve Clinical Outcome; GRIPHON = Prostacyclin Receptor Agonist (Prostaglandin I$_2$) in PAH; FREEDOM-EV = International, Multicenter, Randomized, Double-blind, Placebo-controlled Event-driven Trial of Oral Treprostinil in Subjects with PAH; AMBITION = Ambrisentan plus Tadalafil in PAH.

CTD-PAH had a mean age of 55 years, 87% were female, 30% had WHO functional class I or II disease, and the mean 6MWD was 327 meters (see Supplementary Table 8 on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract). In the 9 registries in which patients with all PAH etiologies were enrolled, the patients had a mean age of 51 years, 74% were female, 28% had WHO functional class I or II disease, and the mean 6MWD was 348 meters. Patients with CTD-PAH in these 9 registries had a mean age of 56 years, 84% were female, 24% had WHO functional class I or II disease, and the mean 6MWD was 328 meters (Table 2). Baseline data from the registries for the CTD-PAH subgroups treated before 2010 and those treated after 2010 are shown in Supplementary Table 9, and baseline data from the registries for the CTD-PAH subgroups of SSc and SLE are shown in Supplementary Table 10 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract).

Outcomes from RCTs. Among the 5 RCTs in which time to clinical morbidity/mortality events was reported as the primary end point, 3,172 patients were enrolled (941 with CTD-PAH [30%]) (12–16,23,24). Additional PAH therapy resulted in a 36% reduction in the risk of morbidity/mortality events in the overall PAH population compared to that in control subjects (HR 0.64, 95% CI 0.54, 0.75; *P* < 0.001), and a 36% reduction in the risk of morbidity/mortality events in patients with CTD-PAH compared to controls (HR 0.64, 95% CI 0.51, 0.81; *P* < 0.001) (Figure 1).

In the overall PAH population, additional PAH therapy led to a placebo- or monotherapy-corrected increase in the 6MWD (mean increase of 28.6 meters, 95% CI 19.2, 38.0; *P* < 0.001) (Figure 2A). In 8 RCTs (total of 2,874 patients; 882 with CTD-PAH [31%]), this end point was reported according to CTD-PAH etiology (9–12,15,23–30). Additional PAH therapy led to an increase

in the 6MWD in the overall PAH population (mean increase of 34.6 meters, 95% CI 22.1, 47.1; *P* < 0.001) and in patients with CTD-PAH (mean increase of 20.4 meters, 95% CI 10.9, 29.9; *P* < 0.001) (Figures 2B and C).

Sensitivity analyses were performed to compare outcomes between patients with CTD-PAH and patients with IPAH among the subset of trials in which outcomes were reported separately in the IPAH subpopulation. Results from patients with IPAH trended similar to those in the overall PAH population (HR for risk of morbidity/mortality events 0.63, 95% CI 0.54, 0.73; *P* < 0.001).

Outcomes from registries. Among the 9 registries in which patients with PAH were included irrespective of etiology (4,5,31,32–37), survival rates in the 2,113 patients with CTD-PAH were lower than in the 7,829 patients in the overall PAH population (Figure 3A).

Among all CTD-PAH patients with available data, including those from both the all-PAH registries and the CTD-PAH–specific registries (19 registries, 3,978 patients), survival rates in patients with CTD-PAH in the registries in which treatment was received within ≥50% of the study period during or after 2010 (n = 1,819) were higher than in patients with CTD-PAH in the registries in which treatment was received within ≥50% of the study period occurring before 2010 (n = 2,159) (Figure 3B).

Among all patients with CTD-PAH, survival rates were lower for those with SSc (n = 1,485) (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, comprises the addition of a drug targeting a second or third pathway involved in the
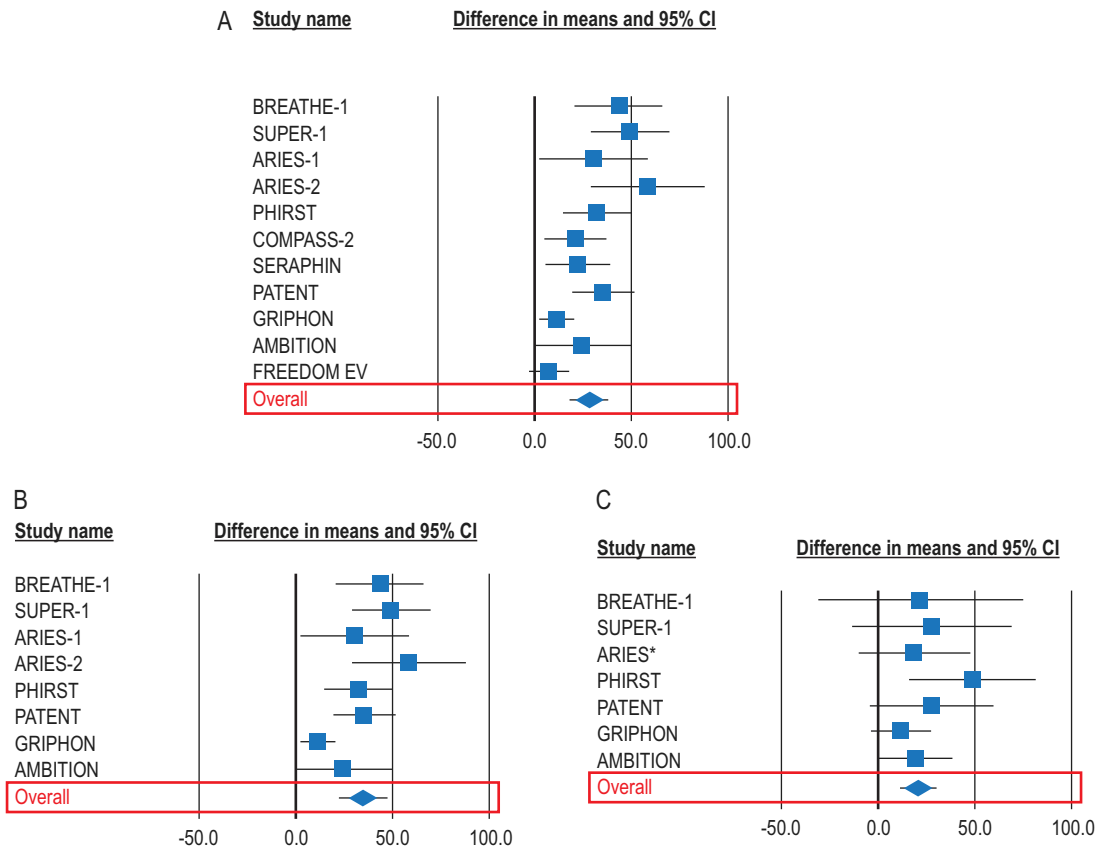
Figure 2. Change in the 6-minute walk distance (6MWD) for all patients with pulmonary arterial hypertension (PAH) of any etiology in all randomized, controlled trials (RCTs) (11 trials) (**A**), for all patients in RCTs that reported 6MWD in patients with connective tissue disease (CTD)–associated PAH (8 trials) (**B**), and for patients with CTD-PAH (8 trials) (**C**). Results are depicted as forest plots, showing the mean change in the 6MWD from baseline to between 3 and 6 months, with 95% confidence interval (95% CI). *Combined data from the Randomized, Double-blind, Placebo-controlled, Multicenter, Efficacy Study of Ambrisentan for PAH 1 and 2 (ARIES-1 and ARIES-2, respectively). BREATHE-1 = Bosentan Randomized Trial of Endothelin Antagonist Therapy; SUPER-1 = Sildenafil Use in PAH; PHIRST = PAH and Response to Tadalafil; COMPASS-2 = Combination of Bosentan and Sildenafil Versus Sildenafil Monotherapy on PAH; SERAPHIN = Study with an Endothelin Receptor Antagonist in PAH to Improve Clinical Outcome; PATENT = PAH Soluble Guanylate Cyclase–Stimulator Trial 1; GRIPHON = Prostacyclin Receptor Agonist (Prostaglandin I2) in PAH; AMBITION = Ambrisentan plus Tadalafil in PAH; FREEDOM-EV = International, Multicenter, Randomized, Double-blind, Placebo-controlled Event-driven Trial of Oral Treprostinil in Subjects with PAH.

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 (total of 2,762 patients; 827 with CTD-PAH [30%]). Most of the trials (59% of patients) evaluated endothelin receptor antagonists (ERAs). Similar to our findings based on the 6MWD, patients with CTD-PAH experienced less benefit than patients with IPAH. The mean placebo-corrected treatment effect, measured as the change in 6MWD from baseline to 3 months, was 23.1 meters in patients with CTD-PAH versus 40.4 meters in patients with

IPAH (adjusted treatment effect difference −17.3 meters, 90% CI −31.3, −3.3; *P* for interaction = 0.043). We reported a similar placebo- or monotherapy-corrected mean change in the 6MWD of 20.4 meters in patients with CTD-PAH. Our reference population included patients with all PAH etiologies, which may explain the lower benefit (difference of 34.6 meters for the change in the 6MWD) observed in our study compared to that observed in patients with IPAH reported by Rhee and colleagues (17). However, earlier meta-analyses of RCTs reporting change in the 6MWD are also conflicting, with one study showing a similar treatment benefit between patients with CTD-PAH and those with PAH of all etiologies (48) and another showing no treatment 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), as the odds ratio for the likelihood of a longer time to clinical worsening was 0.72
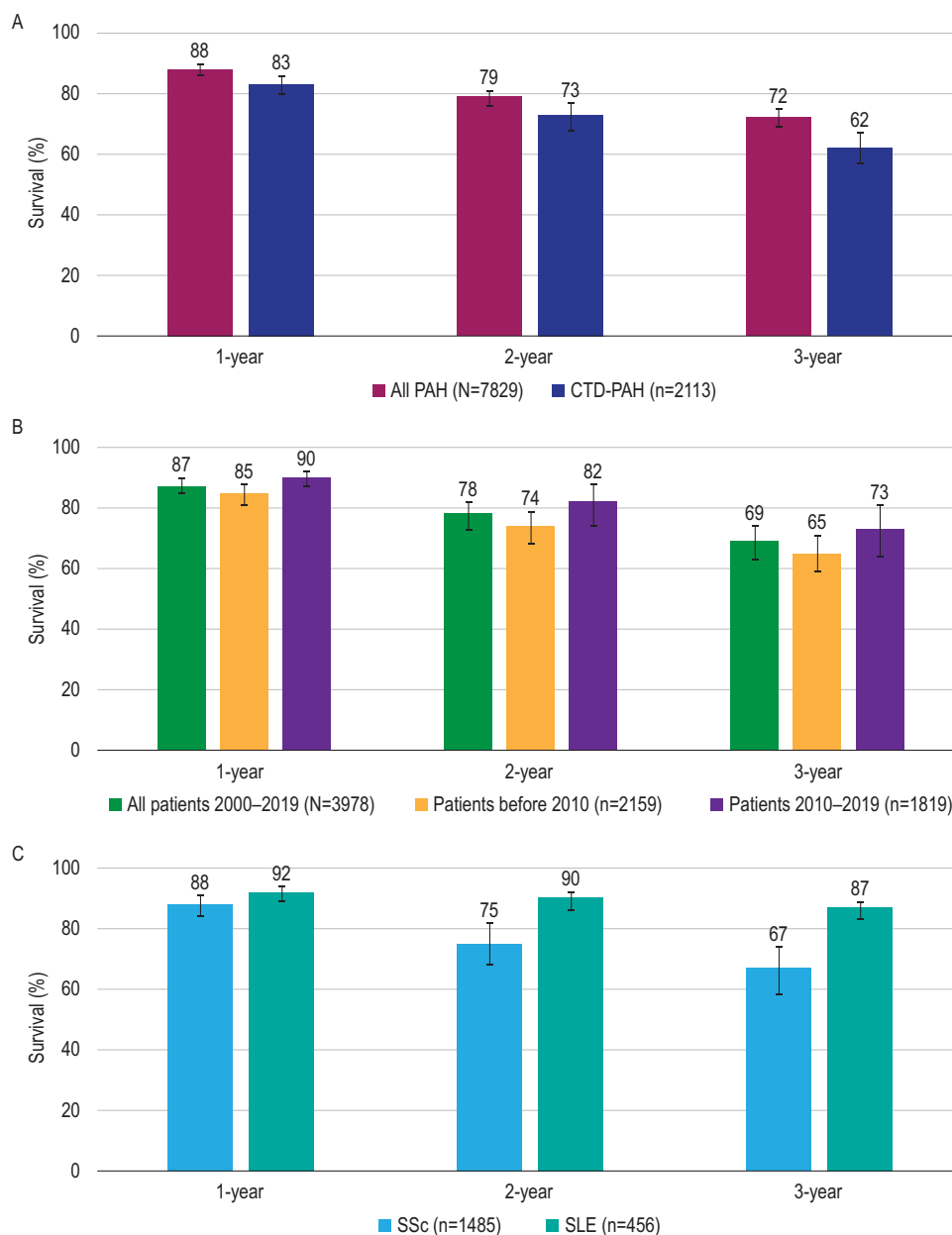
Figure 3. Survival estimates at 1 year, 2 years, and 3 years in all patients with pulmonary arterial hypertension (PAH) and patients with connective tissue disease (CTD)–associated PAH from the registries in which all PAH etiologies were included (9 registries) (**A**), in patients with CTD–associated PAH from all registries (19 registries) by enrollment period (**B**), and by CTD subtype from disease-specific registries or registries that included disease-specific outcomes (8 registries for systemic sclerosis [SSc] and 4 registries for systemic lupus erythematosus [SLE]) (**C**). Results are shown as the survival rates with 95% confidence intervals.

(95% CI 0.45, 1.16), whereas we demonstrated a reduction in the risk of a morbidity/mortality event with PAH-specific therapy (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 HR, 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 ~50% of the trials included in the meta-analysis by Rhee and colleagues (17) were of 12 weeks to 18 weeks in duration (i.e., a previous standard to assess PAH therapy efficacy). Finally, we used a more contemporary data set, 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 data set, thus, more accurately reflects current treatment approaches. This approach also resulted in a larger patient population (1,267 CTD-PAH patients from RCTs, compared to 827 patients 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 (total of 3,262 patients; 963 with CTD-PAH [30%]). These trials evaluated ERAs, tadalafil, selexipag, and riociguat. This meta-analysis aimed to compare combination therapy to 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% reduction in relative risk for 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 those treatment groups receiving FDA-approved doses were analyzed. Additionally, our meta-analysis included the more recently published FREEDOM-EV trial (International, Multicenter, Randomized, Double-blind, Placebo-controlled Event-driven Trial of Oral Treprostinil in Subjects with PAH) (16), the results of which were published after completion of the meta-analysis by Pan and colleagues (18). Pan and colleagues also found no statistically significant benefit from additional therapy in terms of improvement in the 6MWD among patients with CTD-PAH (mean change 21.38 meters, 95% CI −20.38, 63.14; $P = 0.32$). This end point was derived from 3 RCTs. Our meta-analysis, which included 8 trials in which this end point was evaluated, demonstrated a similar benefit (measured numerically as change in the 6MWD) that was statistically significant in patients with CTD-PAH (mean change 20.4 meters, 95% CI 10.9, 29.9; $P < 0.001$), perhaps reflecting greater statistical power due to increased sample size. Overall, compared to the meta-analysis by Pan and colleagues (18), our study provides an expanded evaluation, including the FREEDOM-EV trial, with an additional meta-analysis of survival rates in registries, because data on long-term survival outcomes and longitudinal analysis of survival outcomes over decades cannot be feasibly obtained 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 those with 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 and to have less severe disease. Our analysis found that in the later registries, patients were older than those in the earlier registries (mean age 57 years versus 54 years), but had less severe disease (as defined by the proportion of patients with WHO functional class I or II disease) (40% versus 23%) and had a higher 6MWD (336 meters versus 321 meters) (see Supplementary Table 9, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract). 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 improvement in survival 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 (38) are included in our meta-analysis; 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 WHO functional class I or II disease and a shorter 6MWD (see Supplementary Table 10, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract), which likely also contributed to their poorer survival. We were not able to use meta-analysis to compare the treatment effect in RCTs between patients with SSc and those with SLE since only 2 RCTs provided sufficient data on patients with SSc (23,24) and only 1 provided sufficient data on patients with SLE (24).

Because all-cause mortality was evaluated, we may have overestimated the incidence of death due to PAH among patients with CTD-PAH. These patients were older and experienced a greater comorbidity burden compared to the overall PAH population. As such, these patients were possibly frailer and may have died from causes other than 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 focuses on 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 the lack of a consensus definition for 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 medicine may enable smaller study sizes and, ultimately, facilitate the discovery of treatment approaches that would yield a 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 the RCTs to only those with 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 (as listed in Supplementary Table 1 [http://onlinelibrary.wiley.com/doi/10.1002/art.41669/abstract]) varied to a limited extent across studies.

A limitation of our meta-analysis of registries was the limited availability of studies that enrolled patients from 2015 onward, which would 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 in patients with IPAH compared to those with CTD-PAH as had been observed for the comparison between all PAH etiologies and CTD-PAH.

An additional limitation is that it is unknown to what extent 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. Finally, the diagnosis of PAH was accepted on the basis of the criteria used in each study or registry; it is possible that underlying conditions, such as pulmonary veno-occlusive disease and concomitant interstitial lung disease, 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 with modern PAH treatments, patients with CTD-PAH had a similar reduction in the risk of clinical morbidity and mortality events when compared to the overall PAH population. The improvement in the 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 up-front aggressive treatment are warranted (56).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Khanna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Khanna, Zhao, Mathai, Coghlan, Shah, Hartney, McLaughlin.
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