Effect of Chronic Digoxin Use on Mortality and Heart Failure Hospitalization in Pulmonary Arterial Hypertension

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Background

- Pulmonary arterial hypertension (PAH) is a fatal disease that affects the pulmonary vasculature through vasoconstriction and adverse vascular remodeling that obliterates and stiffens the pulmonary vasculature resulting in increased pulmonary artery pressures, pulmonary vascular resistance, and pulmonary vascular stiffness
- The resulting increase in right ventricular (RV) afterload eventually leads to RV dysfunction and failure, which remains the strongest predictor of death
- Digoxin, a cardiac glycoside, provides ionotropic support for patients with ventricular dysfunction
- Furthermore, digoxin use is not without risk as there is an increased risk of mortality among patients using digoxin in an atrial fibrillation population
- Digoxin acutely increases cardiac output in patients with pulmonary arterial hypertension (PAH) and right ventricular failure; however, the effects of chronic digoxin use in PAH are unclear.

Objective

- we aimed to describe patients with PAH treated with chronic digoxin therapy and to examine the association of digoxin use with all-cause mortality and HF-related hospitalization in patients with PAH using the Minnesota Pulmonary Hypertension Repository

Methods

- Data from the Minnesota Pulmonary Hypertension Repository were used.
- It is a single-center registry that enrolls all consecutive patients treated for pulmonary hypertension at the University of Minnesota Pulmonary Hypertension Clinic since March 2014. Patients who were diagnosed before March 2014 were entered retrospectively.
- The median follow-up time was 2.1 (interquartile range, 0.6–5.0) years for the matched cohort

outcomes

- The primary outcome was a composite of all-cause mortality or HF hospitalization.
- The secondary outcomes include: (1) all-cause mortality, (2) HF hospitalization, and (3) composite of all-cause mortality or lung transplantation (transplant-free survival).

Inclusion Criteria

- Adult patients (aged ≥ 18years at the time of enrollment) diagnosed with World Health Organization (WHO) Group I PAH who were enrolled between March 2014 and September 16, 2020.
- In the Minnesota Pulmonary Hypertension Repository, the diagnosis of PAH required the following: (1) a mean pulmonary artery pressure ≥25mmHg at rest up until 2019 and ≥20mmHg at rest since 2019, with a pulmonary capillary wedge pressure of 3 wood units; and (2) the exclusion of other WHO categories of pulmonary hypertension by clinical evaluation and objective tests, including pulmonary function tests and ventilation-perfusion scan.

Exclusion criteria

- Patients with obstructive lung disease diagnosed by reduced expiratory flow rates (forced expiratory volume in 1 second/forced vital capacity <75% predicted), more than mild interstitial lung disease diagnosed by reduced total lung capacity <60%)
- Chronic thromboembolic pulmonary disease were excluded from the study.
- Additionally, patients who were already on chronic digoxin therapy for other medical indications before the diagnosis of PAH were excluded.

Long term PAH Management

- Patients with PAH who responded to acute vasodilator challenge were treated with calcium channel blockers.
- All patients who did not respond to acute vasodilator challenge at the time of diagnosis were treated with monotherapy or combination therapy using phosphodiesterase-5-inhibitors, endothelin receptor antagonists, and prostacyclin analogue, or prostacyclin receptor agonists based on the severity of the disease as recommended.

- Initially, patients with low and intermediate-risk characteristics were treated with monotherapy or sequential combination therapy, but after 2015, a prospective dual therapy approach using a phosphodiesterase-5-inhibitors and an endothelin receptor antagonists was used as clinically indicated.
- Patients with high-risk characteristics were treated from diagnosis with initial combination therapy, including a parenteral prostacyclin. Digoxin and diuretics were used to treat right HF as needed at the discretion of the treating physician. Digoxin was dosed based on a nomogram and levels were checked only if clinically indicated. Patients were followed every 3 to 6 months regularly in the outpatient setting, and more frequently if needed.

Results

- Among 205 patients with PAH in the repository, 32.7% (n=67) were on digoxin. Digoxin was more often prescribed to patients with severe PAH and right ventricular failure.
- After propensity score-matching, 49 patients were digoxin users, and 70 patients were non users; of these 31 (63.3%) in the digoxin group and 41 (58.6%) in non digoxin group met the primary end point during a median follow-up time of 2.1 (0.6–5.0) years.
- Digoxin users had a higher combined all-cause mortality or HF hospitalization (HR, 1.82 [95% CI, 1.11–2.99]), all-cause mortality (HR, 1.92 [95% CI, 1.06–3.49]), HF hospitalization (HR, 1.89 [95% CI, 1.07– 3.35]), and worse transplant-free survival (HR, 2.00 [95% CI, 1.12–3.58]) even after adjusting for patient characteristics and severity of PAH and right ventricular failure.

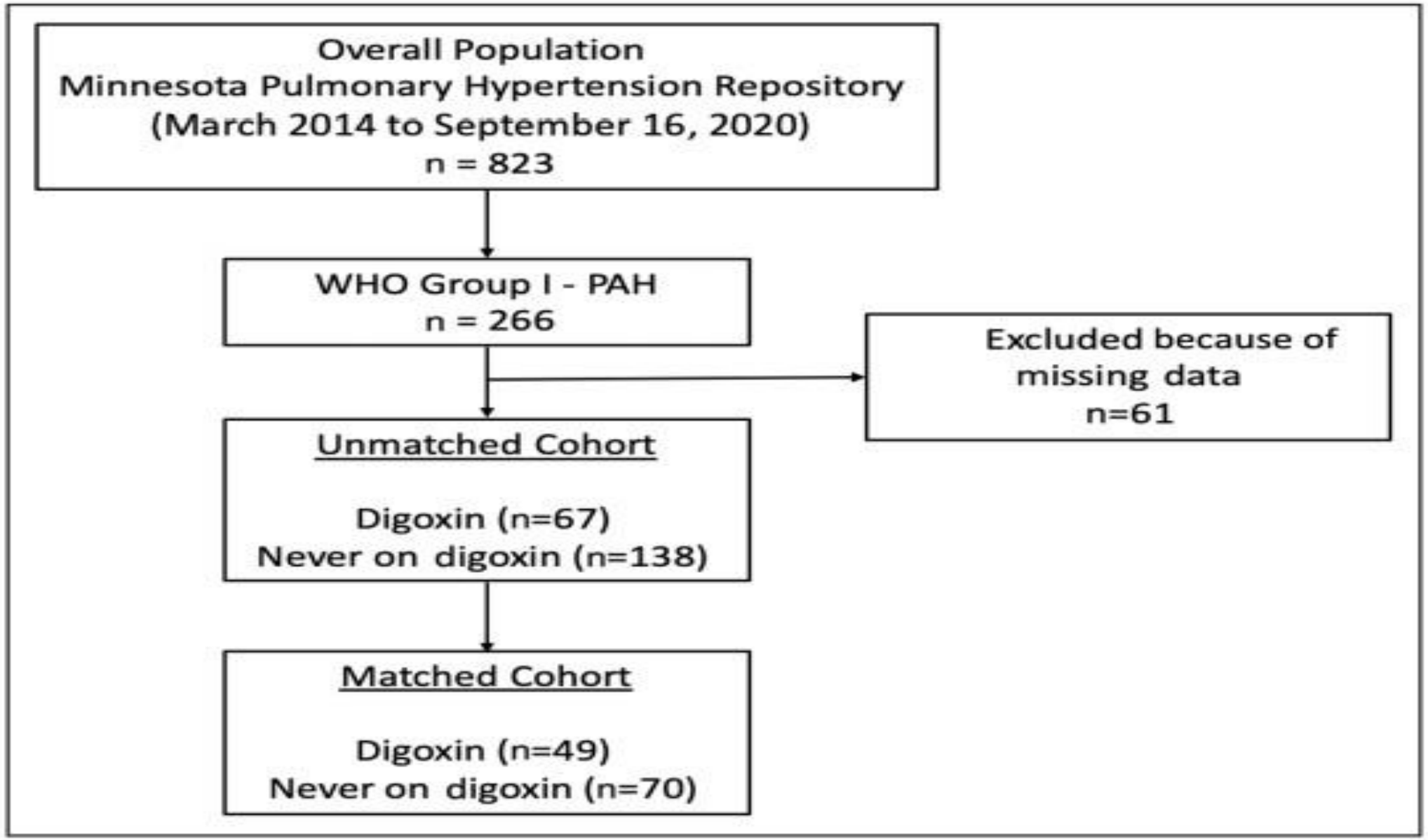

Figure 1. Study flow diagram.
PAH indicates pulmonary arterial hypertension; and WHO, World Health Organization.

Table 1. Baseline Patient Characteristics by Digoxin Use in the Matched Cohort

Characteristic	Matched Cohort			
	Never on digoxin	Digoxin		
	n=70*	n=49*	*P* value	SMD
Age at index‡	54.3±15.3	55.9±16.4	0.590	0.036
Women	53 (75.7%)	37 (75.5%)	0.980	0.005
Race			0.212	0.338
White	51 (72.9%)	39 (79.6%)		
Black	4 (5.7%)	5 (10.2%)		
Other clinical characteristics/unknown	15 (21.4%)	5 (10.2%)		
Body mass index‡, kg/m^2; n=117	29.1±7.2	29.2±9.5	0.949	0.012
WHO functional class, n=100			0.541	0.298
I	2 (3.5%)	2 (4.8%)		
II	9 (15.5%)	4 (9.5%)		
III	41 (70.7%)	28 (66.7%)		
IV	6 (10.3%)	8 (19.1%)		
Etiology			0.838	0.174
Idiopathic	16 (22.9%)	10 (20.4%)		
Heritable	1 (1.4%)	2 (4.1%)		
Anorexigen	5 (7.1%)	3 (6.1%)		
APAH	48 (68.6%)	34 (69.4%)		
Medications at baseline				
Prostacyclin	6 (8.6%)	6 (12.2%)	0.548	0.121
Phosphodiesterase-5 inhibitor	21 (30.0%)	19 (38.8%)	0.319	0.186
Endothelin receptor antagonist	8 (11.4%)	6 (12.2%)	0.892	0.025
Riociguat	0 (0.0%)	1 (2.0%)	0.412	0.204
Warfarin	13 (18.6%)	10 (20.4%)	0.803	0.046
Calcium channel blocker	12 (17.1%)	9 (18.4%)	0.863	0.032
Supplemental oxygen	11 (15.7%)	10 (20.4%)	0.509	0.122

Echocardiography				
LV ejection fraction‡, n=106	61.5±5.8	62.5±5.4	0.387	0.173
RV enlargement, n=109	46 (71.9%)	41 (91.1%)	0.014	0.511
RV enlargement severity, *n = 87*			0.996	0.018
Mild	7 (15.2%)	6 (14.6%)		
Moderate	21 (45.7%)	19 (46.3%)		
Severe	18 (39.1%)	16 (39.0%)		
RV dysfunction (n=108)	40 (61.5%)	33 (76.7%)	0.098	0.334
RV dysfunction severity (n=72)			0.339	0.357
Mild	10 (25.6%)	4 (12.1%)		
Moderate	19 (48.7%)	20 (60.6%)		
Severe	10 (25.6%)	9 (27.3%)		
TAPSE‡, n=73	1.7±0.5	1.7±0.4	0.957	0.013
S'‡, n=49	10.4±2.2	10.7±2.5	0.632	0.138
RV fractional area change‡, n=64	33.4±11.3	33.3±10.2	0.950	0.016
Right heart catheterization				
Mean right atrial pressure, mm Hg‡	9.2±5.1	9.7±4.5	0.566	0.108
Mean PA pressure, mm Hg‡	49.2±14.5	50.1±11.1	0.690	0.076
Pulmonary capillary wedge pressure, mm Hg‡	10.8±4.2	11.4±6.9	0.526	0.114
Mixed venous oxygen saturation, %‡ (n=104)	65.4±8.3	62.0±8.3	0.039	0.415

Characteristic	Matched Cohort			
	Never on digoxin	Digoxin		
	n=70*	n=49*	*P* value	SMD
Cardiac index, L/min per m²‡	2.4±0.83	2.2±0.83	0.273	0.227
Cardiac output, L/min‡	4.4±1.6	4.2±1.8	0.424	0.148
Pulmonary vascular resistance, Wood units‡	10.1±5.8	10.8±5.2	0.487	0.131
Other clinical characteristics				
Six-minute walk test distance, m†, n=68	356 (291–457)	323 (249–406)	0.220	0.306
NT-proBNP, pg/mL†, n=106	531 (218–1842)	2539 (789–6043)	0.001	0.586
GFR (mL/min)†, n=114	75 (56–90)	71 (54–90)	0.596	0.050
Atrial fibrillation	6 (8.6%)	2 (4.1%)	0.468	0.185

APAH indicates associated pulmonary arterial hypertension; GFR, glomerular filtration rate; LV, left ventricular; NT-proBNP, N-terminal pro–brain natriuretic peptide; PA, pulmonary artery; RV, right ventricular; SMD, standardized mean difference; TAPSE, tricuspid annular plane systolic excursion; and WHO, World Health Organization.

*n in the column header indicates the entire sample. The n for each covariate is listed in the row label. Covariates without n specified in row labels had no missing data.

†Reported as median (interquartile range).

‡Reported as mean±SD.

Table 2. Association of Digoxin Users Versus Nonusers With Primary and Secondary Outcomes in Matched Cohort

Outcome	Events		HR (95% CI)
	Digoxin	Nondigoxin	
Primary: all-cause mortality+HF hospitalization	31	41	1.82 (1.11–2.99)
Secondary (1): all-cause mortality	23	26	1.92 (1.06–3.49)
Secondary (2): all-cause mortality+lung transplant	25	27	2.00 (1.12–3.58)
Secondary (3): HF hospitalization	24	30	1.89 (1.07–3.35)

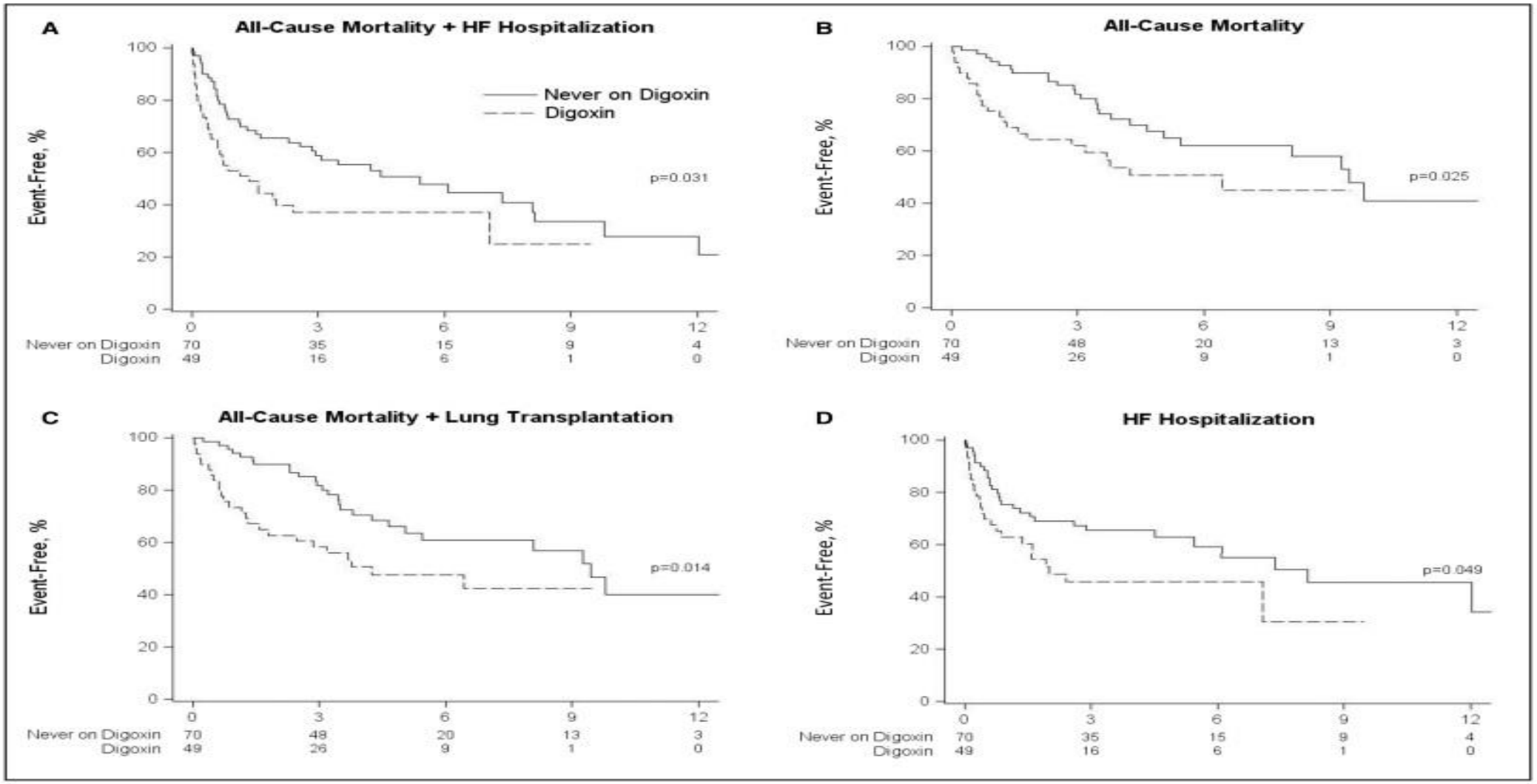

Figure 2. Kaplan–Meier survival estimates stratified by digoxin use status.
A, Primary end point: combined all-cause mortality and HF hospitalization. **B**, Secondary end point: all-cause mortality. **C**, All-cause mortality and lung transplantation (transplant-free survival). **D**, HF hospitalization. HF indicates heart failure.

Table 3. Association of Digoxin Users Versus Nonusers With Primary and Secondary Outcomes in Subgroup With Cardiac Index <2.5 L/min per m^2 or Mean Right Atrial Pressure >8 mm Hg

Outcome	Events		HR (95% CI)
	Digoxin	Nondigoxin	
Primary: all-cause mortality+HF hospitalization	26	30	1.85 (1.07–3.21)
Secondary (1): all-cause mortality	19	18	1.95 (0.99–3.86)
Secondary (2): all-cause mortality+lung transplant	21	19	2.04 (1.06–3.92)
Secondary (3): HF hospitalization	20	20	2.02 (1.07–3.83)

Conclusion

- In conclusion, in this observational study, chronic digoxin therapy in patients with PAH did not reduce all-cause mortality, HF hospitalizations, and lung transplant. Contrary to our initial hypothesis, it was associated with worse outcomes. Future prospective studies should assess the safety and efficacy of chronic digoxin use in PAH.