Use of Selective Serotonin Reuptake Inhibitors and Outcomes in Pulmonary Arterial Hypertension

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Background: Selective serotonin reuptake inhibitors (SSRIs) have been suggested to offer therapeutic benefit in patients with pulmonary arterial hypertension (PAH). We conducted two analyses to explore the association between SSRI use and PAH outcomes using the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry).

Methods: First, new users (SSRI-naïve patients who initiated treatment after enrollment, incident use analysis, $n = 220$) were matched (1:2) with non-SSRI users (nonusers, $n = 440$) by enrollment center, sex, date of most recent visit, age, and 6-min walk distance. Second, a cross-sectional design was used to compare nonusers ($n = 2,463$), high-affinity SSRI users ($n = 430$), and non-high-affinity SSRI users ($n = 125$) at enrollment. Mortality and a composite end point defined by events indicative of clinical worsening were evaluated.

Results: New users had a higher risk of death (unadjusted hazard ratio [HR], 1.74; 95% CI, 1.19-2.54; $P = .004$) and were less likely to be free from the composite end point 2 years after enrollment vs nonusers (25.7% vs 43.2%, respectively; $P < .001$). Similarly, among prevalent SSRI users (patients with a history of SSRI use at enrollment), high-affinity SSRI users were less likely to be free from the composite end point vs nonusers (unadjusted HR, 1.20; 95% CI, 1.07-1.36; $P = .003$). In both analyses, differences in outcome were maintained after adjustment for clinical variables previously associated with PAH outcomes.

Conclusions: In a large population of patients with PAH, incident SSRI use was associated with increased mortality and a greater risk of clinical worsening, although we could not adjust for all potential confounders.

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Abbreviations: 6MWD = 6-minute walk distance; FC = functional class; HR = hazard ratio; NYHA = New York Heart Association; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; REVEAL Registry = Registry to Evaluate Early and Long-term PAH Disease Management; SERT = serotonin transporter; SSRI = selective serotonin reuptake inhibitor

The serotonin hypothesis of pulmonary arterial hypertension (PAH) emerged > 40 years ago and was reemphasized in the 1990s following the association of pulmonary hypertension (PH)¹ with anorexic agents such as aminorex fumarate and fenfluramine.²⁻⁵ Serotonin promotes pulmonary arterial smooth muscle cell and fibroblast proliferation, pulmonary arterial vasoconstriction, and local microthrombosis—all key pathogenic features in PAH. These effects of serotonin are mediated by interactions between serotonin and its transporter and receptors.⁶⁻¹⁰ In particular, the serotonin transporter (SERT) plays a key role in the pathogenesis of experimental PH; in animal models, SERT

overexpression predisposes to the development of PH, whereas pharmacologic blockade of SERT is protective.¹¹⁻¹⁴ In humans, a functional polymorphism in the *SERT* gene correlates with more severe PH associated with COPD.¹⁵

Selective serotonin reuptake inhibitors (SSRIs) act via blockade of SERT, resulting in an extracellular accumulation of serotonin and increased activation of serotonin receptors.¹⁶ SSRIs have been associated with both protection against and regression of PH in animal models, suggesting a possible role in the treatment of PAH in humans.^{1,14,17} Early observational studies have suggested therapeutic efficacy of SSRIs in patients with

PAH.^{18,19} However, maternal SSRI use has been identified as a potential risk factor for the development of persistent PH of the newborn, raising the possibility that SSRI exposure may actually be harmful to human pulmonary vascular development.²⁰ Furthermore, a more recent population-based study in Canada reported a positive association between SSRI use and PAH, which was ascribed to residual confounding.²¹

Considering these inconsistencies, we used the large, multicenter, observational, US-based, longitudinal registry of patients with group I PAH, the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry), to assess the association between SSRI use and outcomes in patients with PAH.

MATERIALS AND METHODS

Patient Population

In the REVEAL Registry, PAH was defined as a mean pulmonary artery pressure > 25 mm Hg at rest or > 30 mm Hg with exercise, pulmonary capillary wedge pressure (PCWP) or left ventricular end-diastolic pressure ≤ 18 mm Hg, and pulmonary vascular resistance ≥ 240 dyne/s/cm⁵. For this analysis, we excluded patients with PCWP or left ventricular end-diastolic pressure > 15 mm Hg and aged ≤ 18 years, with the goal of focusing on adults with PAH. The registry design and baseline characteristics of the enrolled patients have been described previously.^{22,23}

Incident and Prevalent Use Analyses

To detect an association between SSRI use and clinical outcomes, we applied two analytical approaches. In the first (incident use analysis), a nested case-control design was used to match REVEAL Registry patients reporting new SSRI use (new users, or those who started an SSRI after the initial REVEAL Registry enrollment visit) to non-SSRI users. New SSRI (n = 220) and non-SSRI users (n = 440) were matched by a 1:2 ratio by enrollment center, date of most

recent visit, sex, age, and 6-min walk distance (6MWD) at the assessment corresponding to SSRI initiation. In the second approach (prevalent use analysis), a cross-sectional design was used. In this analysis, SSRI use at the time of enrollment served to classify patients into one of three groups: non-SSRI users (n = 2,463), high-affinity SSRI users (n = 430), and non-high-affinity SSRI users (other users; n = 125).

SSRI Classification

SSRIs were classified according to their affinity for SERT.²⁴ High-affinity SSRIs (dissociation constant, K_d < 1 nmol) include paroxetine, escitalopram, sertraline, and fluoxetine.^{25,26} Other SSRIs were those with moderate and low affinity (eg, citalopram, duloxetine, nefazodone, and venlafaxine).

Outcome Measures

Two outcome variables were assessed: (1) mortality from enrollment and (2) a composite clinical end point. The composite end point consisted of major events (death, transplantation, or atrial septostomy), hospitalization, a 15% reduction in 6MWD, and/or worsened New York Heart Association (NYHA) functional class (FC).

Statistical Analyses

Categorical data are presented as percentages and were analyzed using the χ^2 or Fisher exact test where appropriate. Continuous data are summarized as mean ± SD and were analyzed using the student *t* test. Kaplan-Meier estimates and Cox proportional hazards models were used for the outcome analyses. In the incident use analysis, results were adjusted by the most recent PAH group I diagnosis, NYHA FC, and depression at baseline. In the prevalent use analysis the model was adjusted using the REVEAL Registry multivariable prognostic equation.²⁷ *P* < .05 was considered statistically significant.

RESULTS

Patient Characteristics

Of the 3,523 subjects in the REVEAL Registry, 3,018 were included in this study (Fig 1). High-affinity SSRI users were more often women compared with nonusers (*P* < .001), and SSRI users overall were more likely to be white (Table 1). The geographic distribution of patients by enrollment center was similar across all study groups (all *P* > .05) (Table 1). Clinical subtypes of PAH were similarly distributed, with the exception of increased PAH associated with drugs and toxins among other SSRI users compared with non-SSRI users in the prevalent use analysis (*P* < .001). Among those reporting a history of drug or toxin exposure, anorexigens (fenfluramine and its derivatives) or amphetamines were the most common agents used (2.3%-7.2% and 2.1%-4.5%, respectively). New users were more likely to be diagnosed with connective tissue disease associated with PAH compared with matched nonusers (*P* = .034) (Table 1).

Comorbid Conditions

The prevalence of comorbid conditions was similar (with the exception of obstructive airway disease)

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FIGURE 1. STROBE diagram for the incident and prevalent use analysis. New users started SSRIs after enrollment in the REVEAL Registry and were matched with non-SSRI user control subjects. The prevalent use analysis comprised patients who started SSRI at time of enrollment. 6MWD = 6-min walk distance; SSRI = selective serotonin reuptake inhibitor.

between new users and nonusers in the incident use analysis (Table 1). In the prevalent use analysis, however, hypertension, obesity, sleep apnea, and thyroid disease were more frequent in high-affinity SSRI users compared with nonusers (all $P < .05$). Other SSRI users were more likely to have obesity or sleep apnea compared with nonusers (all $P < .05$). As expected, SSRI users had a higher proportion of patients with depression than nonusers in both analyses (37.7%–44.0% vs 6.9%–8.4%, respectively; $P < .001$), although depression was reported in only a minority of SSRI users.

Functional Status and Hemodynamics

In both analyses, SSRI users were more likely to have NYHA FC III/IV at enrollment than nonusers. New users and high-affinity SSRI users had a significantly shorter 6MWD vs matched nonusers or all nonusers (Table 2). There were no significant differences in hemodynamic measurements between new users and nonusers (incident use analysis). In the prevalent use analysis, high-affinity SSRI users had a slightly higher PCWP compared with nonusers (10.0 ± 4.2 vs 9.6 ± 3.8 , $P = .049$). No differences were detected

in mean right atrial pressure, cardiac index, or mixed venous oxygen saturation between SSRI users and nonusers in either analytic approach (Table 2).

PAH-Specific and Other Medications at Enrollment

In the incident use analysis, new users were more likely than nonusers to be receiving an endothelin receptor antagonist (57.5% vs 47.9%, $P = .020$) (Table 3). No differences in the use of prostanoids, phosphodiesterase type 5 inhibitors, diuretics, warfarin, digoxin, thyroid hormone, or supplemental oxygen were detected. In the prevalent use analysis, high-affinity SSRI users were significantly more likely than nonusers to be treated with prostanoids, diuretics, oxygen, and thyroid hormone replacement.

SSRI Use

Patients in the REVEAL Registry used a total of 15 different SSRIs (Table 4). Among new users, escitalopram was used most frequently ($n = 47$, 21.4%), followed by citalopram ($n = 46$, 20.9%) and sertraline ($n = 37$, 16.8%). Among the 555 prevalent SSRI users,

Table 1—Demographic and Clinical Characteristics

Characteristic	Incident Use Analysis, Incident SSRI Use ^a			Prevalent Use Analysis, Prevalent SSRI Use				
	New SSRI Users (n = 220)	Matching Non- SSRI Users (n = 440)	P Value	HA SSRI Users ^b (n = 430)	Other SSRI Users ^c (n = 125)	All Non-SSRI Users (n = 2,463)	P Value ^d	P Value ^e
Age at baseline, y								
Mean ± SD	50.7 ± 15.1	51.6 ± 14.8	.43	54.0 ± 13.2	52.1 ± 12.6	52.3 ± 15.2	.034	.85
Female	183 (83.2)	364 (82.7)	.88	373 (86.7)	104 (83.2)	1,902 (77.2)	< .001	.12
Race								
White	166 (75.5)	297 (67.5)	.081	351 (81.6)	106 (84.8)	1,721 (69.9)	< .001	.003
Black	18 (8.2)	65 (14.8)	...	28 (6.5)	12 (9.6)	356 (14.5)	...	...
Hispanic	22 (10.0)	51 (11.6)	...	36 (8.4)	4 (3.2)	218 (8.9)	...	...
Other	14 (6.4)	27 (6.1)	...	15 (3.5)	3 (2.4)	168 (6.8)	...	...
Time from diagnosis to baseline, mo								
Median	34.2	39.7	.13	25.7	19.5	16.8	< .001	.80
Geographic region ^f								
Midwest	45 (20.5)	91 (20.8)	> .99	102 (23.7)	31 (24.8)	571 (23.2)	.96	.19
Northeast	25 (11.4)	50 (11.4)	...	89 (20.7)	32 (25.6)	537 (21.8)	...	...
South	75 (34.2)	148 (33.8)	...	126 (29.3)	25 (20.0)	709 (28.8)	...	...
West	74 (33.8)	149 (34.0)	...	113 (26.3)	37 (29.6)	641 (26.1)	...	...
Clinical subtype			.74				.74	.02
Idiopathic PAH	84 (38.7)	199 (45.6)	.092	188 (43.7)	51 (40.8)	1,127 (45.8)	.43	.28
Familial PAH	4 (1.8)	12 (2.8)	.48	14 (3.3)	2 (1.6)	66 (2.7)	.50	.46
Associated with PAH ^g			.075				.56	.21
CHD	23 (10.6)	42 (9.6)	.70	37 (8.6)	9 (7.2)	245 (9.9)	.39	.31
CTD	73 (33.6)	112 (25.7)	.034	121 (28.1)	32 (25.6)	637 (25.9)	.32	.95
Drugs/toxins ^h	13 (6.0)	26 (6.0)	.99	25 (5.8)	16 (12.8)	121 (4.9)	.43	< .001
HIV	3 (1.4)	7 (1.6)	> .99	11 (2.6)	3 (2.4)	40 (1.6)	.17	.46
PoPH	11 (5.1)	24 (5.5)	.82	20 (4.7)	5 (4.0)	149 (6.0)	.25	.34
Other	5 (2.3)	14 (3.2)	.52	12 (2.8)	6 (4.8)	65 (2.6)	.86	.15
Pulmonary venoocclusive disease	1 (0.5)	0 (0.0)	.33	2 (0.5)	1 (0.8)	12 (0.5)	> .99	.48
Comorbidities at baseline								
Hypertension ⁱ	97 (44.1)	166 (37.7)	.12	198 (46.0)	53 (42.4)	959 (39.0)	.006	.44
Obese ^j	78 (36.3)	144 (33.6)	.49	162 (38.8)	54 (46.6)	753 (32.3)	.009	.001
CTD ^k	79 (35.9)	139 (31.6)	.27	138 (32.1)	41 (32.8)	707 (28.7)	.16	.33
Clinical depression	83 (37.7)	37 (8.4)	< .001	183 (42.6)	55 (44.0)	171 (6.9)	< .001	< .001
OAD ^l	60 (27.3)	84 (19.1)	.016	110 (25.6)	36 (28.8)	536 (21.8)	.082	.065
Sleep apnea	49 (23.4)	101 (24.5)	.78	108 (26.3)	41 (35.7)	448 (19.4)	.001	< .001
Thyroid disease ^m	57 (25.9)	114 (25.9)	> .99	121 (28.1)	30 (24.0)	504 (20.5)	< .001	.34
Diabetes	29 (13.2)	52 (11.8)	.61	49 (11.4)	20 (16.0)	299 (12.2)	.66	.20

Data are presented as No. (%) unless noted otherwise. CHD = congenital heart disease, CTD = connective tissue disease; HA = high affinity; OAD = obstructive airway disease; PAH = pulmonary arterial hypertension; PoPH = portopulmonary hypertension; SSRI = selective serotonin reuptake inhibitor.

^aNon-SSRI users were matched 2:1 with new SSRI users by enrollment center, sex, date of most recent visit, age, and 6-min walk distance.

^bHA SSRIs include paroxetine, sertraline, fluoxetine, and escitalopram.

^cOther SSRIs include moderate-affinity SSRIs, low-affinity SSRIs, and nonselective serotonin transporter inhibitors.

^dComparison of all non-SSRI users and HA SSRI users.

^eComparison of all non-SSRI users and other SSRI users.

^fThe geographic region is categorized according to the census region and is determined by the state of the site.

^gAssociated PAH subgroups are mutually exclusive according to the following hierarchy: CHD, CTD, PoPH, drugs/toxins, HIV, and other.

^hDrugs and toxins were subclassified (not mutually exclusive) as anorexigens, amphetamines, cocaine, and not identified. The number of patients within each subcategory is listed (respectively) by the analysis. Incident: new SSRI users (5, 6, 0, 2), non-SSRI users (14, 12, 0, 0). Prevalent: HA-SSRI (15, 9, 0, 1), other SSRI users (9, 6, 0, 1), non-SSRI users (62, 52, 6, 5).

ⁱIncludes patients with hypertension and/or patients with reported use of β -blockers.

^jBMI $\geq$ 30 kg/m².

^kCTD is collected on the comorbid condition form and includes scleroderma, CTD, lupus, rheumatoid arthritis, and other CTD.

^lDefined as obstructive lung disease, reactive airway disease, and COPD.

^mIncludes patients with hyperthyroidism/hypothyroidism and/or patients with reported use of synthetic thyroid replacement treatment of hypothyroidism.

Table 2—Functional and Hemodynamic Variables

Characteristic	Incident Use Analysis, Incident SSRI Use ^a			Prevalent Use Analysis, Prevalent SSRI Use				
	New SSRI Users (n = 220)	Matching Non-SSRI Users (n = 440)	P Value	HA SSRI Users ^b (n = 430)	Other SSRI Users ^c (n = 125)	All Non-SSRI Users (n = 2,463)	P Value ^d	P Value ^e
Baseline NYHA FC, No. (%)								
I	5 (2.4)	36 (8.6)	.001	12 (3.1)	4 (3.5)	173 (7.8)	.001	.16
II	80 (37.7)	182 (43.2)	...	123 (31.9)	34 (30.1)	781 (35.4)	...	...
III	108 (50.9)	184 (43.7)	...	217 (56.4)	66 (58.4)	1,106 (50.1)	...	...
IV	19 (9.0)	19 (4.5)	...	33 (8.6)	9 (8.0)	149 (6.7)	...	...
Baseline 6MWD, m								
Median	354.0	386.0	.009	350.5	341.4	374.9	.005	.30
Hemodynamics, Mean ± SD (No.)								
mPAP, mm Hg	48.9 ± 14.7 (219)	49.7 ± 14.2 (439)	.52	48.4 ± 13.9 (426)	46.5 ± 14.1 (125)	49.6 ± 14.2 (2,431)	.10	.017
PCWP, mm Hg	9.5 ± 4.5 (218)	10.0 ± 4.3 (436)	.12	10.0 ± 4.2 (424)	9.9 ± 4.5 (124)	9.6 ± 3.8 (2,404)	.049	.32
mRAP, mm Hg	8.5 ± 5.2 (205)	8.7 ± 5.2 (417)	.59	9.1 ± 5.2 (397)	9.4 ± 5.2 (118)	8.9 ± 5.5 (2,241)	.43	.33
PVRI, Wood units	17.9 ± 10.0 (193)	18.4 ± 10.9 (375)	.55	17.8 ± 10.6 (357)	16.5 ± 9.3 (105)	18.9 ± 10.6 (2,029)	.086	.025
Fick or thermodilution cardiac index, L/min m ²	2.5 ± 0.8 (194)	2.5 ± 0.9 (378)	.99	2.5 ± 0.8 (359)	2.5 ± 0.7 (106)	2.5 ± 0.9 (2,048)	.58	.59
SvO ₂ , %	64.3 ± 10.3 (149)	64.2 ± 9.7 (310)	.96	64.0 ± 9.6 (269)	63.3 ± 9.5 (84)	63.9 ± 9.8 (1,491)	.93	.56

For incident SSRI use, baseline is defined as the assessment during which new users initiate an SSRI and the assessment used to match non-SSRI users with the new SSRI users. 6MWD = 6-min walk distance; FC = functional class; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; NYHA = New York Heart Association; PVRI = pulmonary vascular resistance index; SvO₂ = mixed venous oxygen saturation. See Table 1 legend for expansion of other abbreviation.

^aNon-SSRI users were matched 2:1 with new SSRI users by enrollment center, sex, date of most recent visit, age, and 6MWD.

^bHA SSRIs include paroxetine, sertraline, fluoxetine, and escitalopram.

^cOther SSRIs include moderate-affinity SSRIs, low-affinity SSRIs, and non-selective serotonin transporter inhibitors.

^dComparison of all non-SSRI users and HA SSRI users.

^eComparison of all non-SSRI users and other SSRI users.

most (n = 430) were using a high-affinity SSRI, such as sertraline (n = 131, 30.5%) or fluoxetine (n = 109, 25.3%). A small group of patients was using multiple SSRIs: three patients in the incident and 16 in the prevalent use analysis.

Unadjusted Outcomes: Mortality and Composite End Point

Kaplan-Meier survival estimates revealed that new users had significantly worse survival and were less likely to be free from the composite end point compared with matched nonusers at 2 years after enrollment (82.7% ± 2.6% vs 88.7% ± 1.5%, respectively, $P = .004$; and 25.7% ± 3.0% vs 43.2% ± 2.4%, $P < .001$) (Figs 2A, 2B). In an unadjusted Cox proportional hazard model, new users demonstrated a significantly increased risk of death (hazard ratio [HR], 1.74; 95% CI, 1.19-2.54; $P < .004$) and a greater risk of clinical worsening (HR, 1.57; 95% CI, 1.30-1.91; $P < .001$) compared with matched control subjects. In the prevalent use analysis, irrespective of SSRI affinity, there were no differences in 2-year survival from the time of enrollment between nonusers and SSRI users (Fig 3A); however, the unadjusted Cox proportional hazard model showed that high-affinity SSRI users had a worse freedom from the composite end point compared with

nonusers (HR, 1.20; 95% CI, 1.07-1.36; $P = .003$) (data not shown).

Adjusted Outcomes

After adjustment for group I subtype, NYHA FC, and depression at baseline in the incident use analysis, new SSRI use was associated with an increased risk of death (HR, 1.56; $P = .030$) and a greater risk of achieving the composite end point (HR, 1.48; $P < .001$) compared with matched control subjects (Figs 4, 5). In the prevalent use analysis, after adjustment for terms comprising the REVEAL Registry prognostic equation,²⁷ SSRI use was not associated with mortality ($P > .05$), and high-affinity SSRI use was associated with a greater risk of achieving the composite end point compared with nonusers (HR, 1.18; $P = .008$; data not shown). Depression was not associated with mortality or clinical worsening in the incident use analysis (Figs 4, 5).

DISCUSSION

In this large, contemporary cohort of patients with PAH, our incident use analysis showed that SSRI use was associated with a greater risk of death and clinical worsening during a 2-year follow-up period from enrollment. In the prevalent use analysis, high-affinity

Table 3—Most Recent PAH-Specific Medications and Concomitant Medications at Baseline by SSRI Use

Characteristic, No. (%)	Incident Use Analysis, Incident SSRI Use ^a			Prevalent Use Analysis, Prevalent SSRI Use				
	New SSRI Users (n = 220)	Matching Non- SSRI Users (n = 440)	P Value	HA SSRI Users ^b (n = 430)	Other SSRI Users ^c (n = 125)	All Non-SSRI Users (n = 2,463)	P Value ^d	P Value ^e
PAH-specific medications								
ERA	126 (57.5)	207 (47.9)	.020	192 (45.1)	54 (43.2)	1,003 (41.2)	.13	.66
PDE-5 inhibitor	138 (63.0)	244 (56.5)	.11	205 (48.1)	52 (41.6)	1,125 (46.2)	.46	.31
Any prostanoid	109 (49.8)	186 (43.1)	.10	190 (44.6)	46 (36.8)	894 (36.7)	.002	.98
Concomitant medications								
Diuretic	152 (69.1)	298 (67.7)	.72	317 (73.7)	82 (65.6)	1,617 (65.7)	.001	> .99
Warfarin	110 (50.0)	221 (50.2)	.96	215 (50.0)	51 (40.8)	1,211 (49.2)	.75	.068
Oxygen	87 (39.5)	161 (36.6)	.46	200 (46.5)	57 (45.6)	924 (37.5)	< .001	.069
Digoxin	60 (27.3)	126 (28.6)	.71	115 (26.7)	32 (25.6)	605 (24.6)	.33	.79
Thyroid replacement	46 (20.9)	95 (21.6)	.84	119 (27.7)	24 (19.2)	472 (19.2)	< .001	> .99

For the new SSRI starts, “baseline” is defined at the assessment during which new users initiate an SSRI and the assessment used to match the non-SSRI users to the new SSRI users. For the enrollment SSRI usage, “baseline” is defined as study enrollment. “Most recent” is defined as the baseline value, if available; otherwise the last available value prior to and closest to the baseline assessment. Any prostanoid = IV epoprostenol, IV treprostinil, subcutaneous treprostinil, inhaled iloprost, inhaled treprostinil, and oral treprostinil; ERA = endothelin receptor antagonist, including bosentan, sitaxsentan, and ambrisentan; PDE-5 inhibitor = phosphodiesterase type 5 inhibitor, including sildenafil and tadalafil. See Table 1 legend for expansion of other abbreviations.

^aMatching non-SSRI users were matched 2:1 to new SSRI users by exact center and sex, and closest visit date, age, and 6MWD.

^bHA SSRI includes paroxetine, sertraline, fluoxetine, and escitalopram.

^cOther SSRI includes moderate-affinity SSRI, low-affinity SSRI, and noncategorized SSRI.

^dComparing all non-SSRI users and HA SSRI users.

^eComparing all non-SSRI users and other SSRI users.

SSRI users had a similar survival but accelerated clinical worsening compared with nonusers. These findings were maintained despite adjustment for potentially confounding variables.

Our data also demonstrate that patients who were using an SSRI had a worse NYHA FC and a shorter 6MWD at baseline compared with nonusers. In addition, a larger proportion of SSRI users were receiv-

ing PAH-specific medications, including endothelin receptor antagonists and prostanoids, compared with nonusers. These data suggest that SSRI users had more severe PAH than nonusers. Alternatively, the functional capacity of these patients could have been affected by the presence of depression, consistent with the results of a previous study indicating a trend toward worse baseline 6MWD and a higher FC in patients

Table 4—SSRI Use at Baseline

Characteristic, No. (mean ± SD)	Incident Use, Analysis Incident SSRI Use ^a	Prevalent Use, Analysis Prevalent SSRI Use	
	New SSRI Users (n = 220)	HA SSRI Users ^b (n = 430)	Other SSRI Users ^c (n = 125)
Escitalopram	47 (21.4)	101 (23.5)	0 (0.0)
Sertraline	37 (16.8)	131 (30.5)	0 (0.0)
Fluoxetine	32 (14.5)	109 (25.3)	0 (0.0)
Paroxetine	19 (8.6)	91 (21.2)	0 (0.0)
Citalopram	46 (20.9)	1 (0.2)	67 (53.6)
Duloxetine	17 (7.7)	3 (0.7)	26 (20.8)
Nefazodone	1 (0.5)	0 (0.0)	3 (2.4)
Fluvoxamine	0 (0.0)	1 (0.2)	0 (0.0)
Other ^d	24 (10.9)	7 (1.6)	32 (25.6)

For the new SSRI starts, “baseline” is defined at the assessment during which new users initiate an SSRI, and the assessment used to match the non-SSRI users to the new SSRI users. SSRI use was not mutually exclusive, and more than one SSRI could be counted per subject. A total of 16 (incident use) and three (prevalent use) subjects reported multiple SSRI use. A total of 15 different SSRIs were reported used by REVEAL Registry subjects. See Table 1 legend for expansion of abbreviation.

^aMatching non-SSRI users were matched 2:1 to new SSRI users by exact center and sex, and closest visit date, age, and 6MWD.

^bHA SSRIs include paroxetine, sertraline, fluoxetine, and escitalopram.

^cOther SSRI users reported use of non-HA SSRIs including moderate-affinity, low-affinity, and noncategorized SSRIs.

^dOther SSRIs reported were amitriptyline, bupropion, desvenlafaxine, doxepin, mirtazapine, trazodone, and venlafaxine.

FIGURE 2. A, Kaplan-Meier estimates of 2-year survival in new SSRI users vs non-SSRI users (incident use analysis). New users had a worse survival compared with matched non-SSRI users ($82.7\% \pm 2.6\%$ vs $88.7\% \pm 1.5\%$, respectively; $P = .004$). B, Kaplan-Meier estimates of 2-y freedom from the composite end point in new SSRI users vs non-SSRI users (incident use analysis). Fewer new SSRI users remained free from the composite end point vs matched nonusers ($25.7\% \pm 3.0\%$ vs $43.2\% \pm 2.4\%$, respectively; $P < .001$). The composite end point included major events (death, transplantation, or atrial septostomy), hospitalization, a 15% reduction in 6MWD, and/or worsened New York Heart Association functional class. See Figure 1 legend for expansion of abbreviations.

with symptoms suggestive of major depression.²⁸ However, our data demonstrate that pulmonary hemodynamics were comparable between SSRI users and nonusers in the incident use analysis. In the prevalent use analysis, PCWP was only slightly higher among high-affinity SSRI users compared with nonusers, and this difference is not considered clinically relevant. Discrepancies between hemodynamics and other indicators of severity raise the possibility that other factors like depression, obesity, or SSRI use may supplant the predictive value of baseline pulmonary hemodynamics.

Our findings are inconsistent with several previous reports. In a single-center, retrospective study of 84 patients with PAH, Kawut and colleagues¹⁸ found that 13 patients with PAH who were exposed to high-affinity SSRIs showed a tendency toward a reduced risk of death (HR, 0.53; 95% CI, 0.07-3.9; $P = .53$). More recently, using a combined retrospective and prospective database from Chicago that dates back to the 1980s, Shah and colleagues¹⁹ reported that SSRI use conferred a survival advantage in both group I PAH and non-group I PH patients (HR, 0.35; 95% CI, 0.14-0.87; $P = .023$). Interestingly, among incident SSRI

FIGURE 3. A, Kaplan-Meier estimates of 2-year survival in HA-SSRI, other SSRI, and non-SSRI users (prevalent use analysis). Similar survival was observed in the HA-SSRI group vs non-SSRI users ($77.0\% \pm 2.1\%$ vs $81.7\% \pm 0.8\%$, respectively; $P = .13$) and in other SSRI users vs non-SSRI users ($81.2\% \pm 3.8\%$ vs $81.7\% \pm 0.8\%$, respectively; $P = .96$). B, Kaplan-Meier estimates of 2-y freedom from the composite end point in HA-SSRI, other SSRI, and non-SSRI users (prevalent use analysis). Fewer HA-SSRI users compared with non-SSRI users remained free from the composite end point ($32.0\% \pm 2.3\%$ vs $39.2\% \pm 1.0\%$, respectively; $P = .003$). Other SSRI users and non-SSRI users reached the composite end point at a similar rate ($40.7\% \pm 4.7\%$ vs $39.2\% \pm 1.0\%$, respectively; $P = .87$). The composite end point included major events (death, transplantation, or atrial septostomy), hospitalization, a 15% reduction in 6MWD, and/or worsened New York Heart Association functional class. HA = high affinity. See Figure 1 legend for expansion of other abbreviations.

users in that cohort, a nonsignificant trend toward improved survival was observed ($P = .089$). Compared with these studies, the present analysis provides greater statistical power because of the larger patient population, as well as a contemporary therapeutic background upon which to examine the association between PAH and SSRI use. For example, approximately one-half of the patients using SSRIs in the REVEAL Registry were also taking prostanoids, compared with none in the Chicago cohort.¹⁹

Our findings are concordant with a retrospective, population-based study examining the relationship between SSRIs and PAH in the Canadian health-care system.²⁰ In that study, 460 patients with PAH (defined as patients who received one or more prescriptions for a PAH-specific medication) were matched with 4,536 control subjects, and SSRI use was associated with an increased risk of PAH requiring pharmacologic treatment (adjusted OR, 1.55). The authors concluded

FIGURE 4. Forest plot of adjusted HRs of survival showing decreased and increased risk of death in new SSRI users vs non-SSRI users (incident use analysis). APAH = associated with pulmonary arterial hypertension; CTD = connective tissue disease; FC = functional class; HR = hazard ratio; IPAH = idiopathic pulmonary arterial hypertension; NYHA = New York Heart Association; PoPH = portopulmonary hypertension. See Figure 1 legend for expansion of other abbreviation.

that SSRIs are not protective against PAH and speculated that the association between SSRIs and PAH was likely the result of residual confounders, such as depression and anxiety.²¹

Studies of the REVEAL Registry have shown that depression is common in patients with PAH, significantly exceeding the prevalence in the general population (25% vs 6.7%, respectively).²² In addition, a

FIGURE 5. Forest plot of adjusted HRs of composite end points showing decreased and increased risk of clinical worsening in new SSRI users vs non-SSRI users (incident use analysis). The composite end point included major events (death, transplantation, or atrial septostomy), hospitalization, a 15% reduction in 6MWD, and/or worsened NYHA FC. See Figure 1 and 4 legends for expansion of abbreviations.

previous study using a validated tool to assess the prevalence of depressive symptoms in PAH found that 15% and 55% of patients with PAH have symptoms suggestive of major depressive disorder and depression, respectively.²⁸ We were surprised to find that clinical depression was reported in only approximately 40% of SSRI users in the present study, raising the possibility that depression was underreported. Furthermore, SSRI use was more prevalent in white than in nonwhite women, which is consistent with patterns of SSRI use in non-PAH populations in the United States.²⁹

Although it was not associated with mortality or a worse outcome in the incident use analysis, depression may have counteracted favorable effects associated with SSRIs. Depression is a well-established risk factor for heart failure and the progression of established atherosclerotic disease^{30,31} related to behaviors that impact health, particularly physical inactivity.³² Considering that patients with PAH with depression have higher brain natriuretic peptide levels and a trend toward shorter 6MWDs than patients with PAH without depression, the potential negative impact of depression on functional status and other outcomes in PAH could be substantial. In addition, depression may contribute directly to the pathogenesis and progression of PAH. Both depression and PAH are characterized by increased levels of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor- α , which could reflect a mechanistic link between these two disease processes.³³⁻³⁵ These findings are provocative, but whether there is a causal relationship between depression and the progression of PAH cannot be determined based on the present results. Alternatively, alleviation of depression could have a beneficial effect on outcomes in PAH that is independent of any impact on pathogenic mechanisms; however, we were not able to evaluate any effect of SSRIs on depression in the present study.

Several aspects of our study limit our ability to definitively explore the relationship between PAH, SSRI use, depression, and serotonin biology. First, a longitudinal observational cohort study precludes conclusions about causality; we are limited to demonstrating associations. Also, SSRI-user groups had a greater number of comorbidities compared with nonusers, raising the concern that adjustments for residual (cryptic) group confounders were inadequate. In particular, the possibility of underreporting of depression would impede our ability to adjust for this potentially deleterious confounder. In addition, we were unable to incorporate into our model longitudinal changes in BMI; however, we acknowledge that weight gain could impact both functional status and outcomes in these patients.³⁶ Finally, considering the posited contribution of excessive serotonin to the pathogenesis of PH, it would be interesting to examine potential interactions between

SSRIs and other serotonergic drugs or exposures, such as anorexigens. Although an association was observed between anorexigen exposure and PAH in other SSRI users in the prevalent analysis, an evaluation of this interaction was precluded by the infrequency of exposures and lack of detail regarding the exposure intensity. Despite these limitations, the much larger size of the REVEAL Registry database, its established validity as a resource for defining contemporary PAH epidemiology, and our ability to identify a sizable control population strengthen the present observations compared with previous cohorts.

In conclusion, among patients enrolled in the REVEAL Registry, incident SSRI use was associated with greater mortality and worse clinical outcomes, and prevalent SSRI use was associated with similar outcomes compared with nonusers. These data contradict prior cohort studies demonstrating an association between improved survival and SSRI use. Furthermore, SSRI users in the present analysis had significantly worse NYHA FC and 6MWD at enrollment and higher rates of depression, which indicates a possible role for depression or other confounders, such as obesity, in the course of PAH. Further prospective, randomized, and observational studies with more detailed analyses of PAH-associated depression and obesity will be necessary to better delineate these relationships.

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Additional information: The e-Appendix can be found in the "Supplemental Materials" area of the online article.

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