β-Blocker Therapy Is Not Associated With Adverse Outcomes in Patients With Pulmonary Arterial Hypertension

A Propensity Score Analysis

Thenappan Thenappan, MD; Samit S. Roy, MSPH; Sue Duval, PhD; Cherylanne Glassner-Kolmin, BS, MPH; Mardi Gomberg-Maitland, MD, MSc

Background—The safety of β-blockers in patients with isolated right ventricular failure because of pulmonary arterial hypertension (PAH) is unclear.

Methods and Results—We studied 564 PAH patients (total cohort) referred to our center from 1982 to 2013. Propensity score-matching was used to match pairs of PAH patients with and without β-blocker use (matched cohort). We compared all-cause mortality between the groups in the total cohort and the matched cohort using bootstrap validation, Kaplan–Meier, and Cox proportional hazard analyses. Seventy-one of the 564 patients in the total cohort were on β-blockers. They were older, had higher prevalence of comorbidities, and were more often on diuretics, digoxin, and angiotensin converting enzyme inhibitors. The severity of PAH and right ventricular failure was similar between those with and without β-blocker use. After propensity matching, 63 patients with β-blocker use were compared with 51 patients without β-blocker use. During a median follow-up time of 4.8 years, there were 339 (60%) deaths in the total cohort and 70 deaths (61%) in the matched cohort. There was no difference in absolute mortality between those with and without β-blockers (P=0.71). β-Blocker use was not associated with increased all-cause mortality in the total cohort after adjusting for propensity score (adjusted hazard ratio, 1.0; 95% confidence interval, 0.7–1.5) and in the matched cohort (hazard ratio, 1.2; 95% confidence interval, 0.8–2.0).

Conclusions—There was no statistically significant difference in long-term mortality between propensity score-matched pairs of PAH patients with and without β-blocker use. These findings need further validation in prospective clinical trials. **(*Circ Heart Fail*. 2014;7:903-910.)**

Key Words: adrenergic blockers ■ heart failure ■ pulmonary hypertension ■ right ventricle

Pulmonary arterial hypertension (PAH) is a debilitating disease characterized by progressive narrowing of the resistance pulmonary arteries, ultimately leading to right ventricular failure (RVF) and death.[1] Despite progress in understanding the pathogenesis and treatment of PAH, incident cases continue to have a 1-year mortality rate of ≈15%.[2–4] Initially, the right ventricle hypertrophies in PAH as an adaptive response to the increased afterload with preserved contractile function. As the disease progresses, the right ventricle dilates because of maladaptive remodeling and eventually fails.[5] Long-term outcomes in PAH are largely determined by the response of the right ventricle to the increased afterload.[5] Right ventricular (RV) function is the major determinant of functional capacity and survival in patients with PAH.[2–4,6,7]

Clinical Perspective on p 910

Increased cardiac adrenergic drive leads to left ventricular dilation, remodeling, and eventually failure in patients with left ventricular systolic dysfunction.[8] Pharmacological blockade of the β-adrenergic receptor with β-blockers is one of the main treatment strategies in left ventricular systolic dysfunction.[9] Multiple large, randomized, double-blind, controlled trials have demonstrated that long-term β-blockade therapy in left ventricular systolic dysfunction improves cardiac function and reduces maladaptive ventricular remodeling and sudden arrhythmias, ultimately leading to improved quality of life and survival.[10–12]

The safety and efficacy of β-blocker therapy in isolated RVF associated with PAH is unclear. There is a theoretical concern for worsening RVF with β-blockers in patients with PAH, as they are highly dependent on the heart rate to maintain their cardiac output (CO).[13] However, preclinical animal studies have demonstrated increased survival with β-blocker therapy in experimental PAH.[14–16] Currently, β-blockers are often used to treat concomitant cardiovascular disease in PAH patients. Human studies have reported conflicting results with respect to the safety and efficacy of β-blockers in patients with PAH.[17,18]

Thus, in this study, we sought to determine the association between β-blocker therapy and long-term adverse outcomes in patients with PAH in our Pulmonary Hypertension Connections (PHC) registry.

Received May 8, 2014; accepted September 23, 2014.

From the Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis (T.T., S.S.R., S.D.); and Section of Cardiology, Department of Medicine, University of Chicago, IL (C.G.-K., M.G.-M.).

Correspondence to Thenappan Thenappan, MD, Section of Advanced Heart Failure and Pulmonary Hypertension, Cardiovascular Division, University of Minnesota Medical School, 420 Delaware Street SE, MMC 508, Minneapolis, MN 55455. E-mail tthenapp@umn.edu

Circ Heart Fail **is available at http://circheartfailure.ahajournals.org** **DOI: 10.1161/CIRCHEARTFAILURE.114.001429**

Methods

Study Population

We studied patients in the PHC registry, which was initiated in March 2004. This database has been described in detail previously.[19] Briefly, the PHC registry was created as a customized patient database to longitudinally collect specific variables on all patients evaluated at a single United States practice at 3 different university hospitals (University of Illinois at Chicago, Rush University Medical Center, and University of Chicago Medical Center) beginning in 1982 and ongoing. Five physicians acquired all the clinical data. Data were collected by a chart review and entered using an Internet-based electronic data capture system. Patients were entered retrospectively from 1982 to February 2004 and prospectively from March 2004. The recruitment period for the current analysis ended in November 2013. Data entry occurred after the complete initial evaluation. For all variables, outliers were verified by a chart review to minimize data entry errors. The investigators collected mortality data after all other data had already been entered. Therefore, clinical data entry was performed blinded to eventual outcome. All new patients gave informed consent for participation in the registry during the initial evaluation. Prospective and established patients actively followed gave informed consent. The PHC received institutional review board approvals for enrollment of subjects.

From the PHC registry, we identified all adult subjects with PAH aged 18 years or older at the time of referral (n=718). PAH was defined per the current guidelines as mean pulmonary artery pressure ≥25 mm Hg at rest, pulmonary capillary wedge pressure of ≤15 mm Hg, and pulmonary vascular resistance (PVR) >3 Wood units. As per the World Health Organization clinical classification of pulmonary hypertension,[20] patients were excluded if they had pulmonary venous hypertension diagnosed by pulmonary capillary wedge pressure >15 mm Hg; obstructive lung disease diagnosed by reduced expiratory flow rates (forced expiratory volume in 1 second/forced vital capacity <70% predicted); more than mild interstitial lung disease diagnosed by typical appearance on computed tomography or total lung capacity <60% predicted; chronic pulmonary thromboembolic disease diagnosed by ventilation perfusion (V/Q) scan (other than normal or low probability), contrast-enhanced chest computed tomography, or pulmonary angiography if necessary; and pulmonary hypertension associated with sarcoidosis and other infiltrative diseases. Of the 718 patients with PAH, we excluded 154 patients in whom either we could not determine β-blocker use at the time of initial evaluation or those with incomplete data. The remaining 564 patients formed our total cohort.

Variables

The following baseline variables at the time of referral were analyzed for characterization of clinical phenotype: demographic data, comorbid conditions, World Health Organization functional class, baseline medications patients were taking at the time of enrollment in the PHC registry, and exercise treadmill testing using the Naughton–Balke protocol as a measure of exercise capacity.[21] We analyzed the baseline echocardiographic and invasive hemodynamics obtained by right heart catheterization for characterization of the severity of PAH and RV function. The echocardiographic variables analyzed include presence of right atrial enlargement, presence of right ventricular hypertrophy, degree of right ventricular dysfunction (mild, moderate, and severe), tricuspid regurgitation jet velocity, presence of left atrial enlargement, left atrial dimension, left ventricular posterior and septal wall thickness, and left ventricular ejection fraction. The hemodynamic variables analyzed include mean right atrial pressure, right ventricular systolic and diastolic pressure, systolic, diastolic, and mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure, CO, pulmonary artery saturation, and PVR.

Long-Term Management

All patients who responded to acute vasodilator challenge were treated with calcium-channel blockers. Initially, a positive response was defined as a 20% decrease in mPAP with an increase in CO; as of 2005, positive vasodilator response was defined as a decrease in mPAP >10 mm Hg and to <40 mm Hg, with unchanged or increased CO.[22] Patients who did not respond to the acute vasodilator challenge received either monotherapy or combination therapy with endothelin antagonists, phosphodiesterase inhibitors, or prostacyclins, based on the severity of symptoms.[23] All patients without contraindications were started on anticoagulation with warfarin to achieve a target international normalized ratio of 2–3.[23] Patients with an arterial oxygen saturation of <90%, either at rest or during exercise, were prescribed supplemental nasal oxygen. In addition, patients received diuretics and digoxin as needed to treat symptoms of RVF.[23] Patients who were on β-blockers for other indications at the time of initial evaluation were continued on it unless they had cardiogenic shock. Patients were followed closely every 6 to 12 months on an outpatient basis and more frequently if medically necessary.

Mortality

The primary outcome was all-cause mortality. Vital statistics were obtained for all patients by chart review and Social Security Death Index. For each death, the date of death was collected. In patients who were not identified as deceased using the Social Security Death Index, it was possible to establish vital status by chart review.

Statistical Analysis

All continuous variables are expressed as mean±standard deviation and categorical variables as frequency (percentage) unless otherwise noted. We compared the baseline demographic, clinical, echocardiographic, and hemodynamic characteristics of the total study cohort, stratified by β-blocker use. Continuous variables were analyzed using either a *t* test or Wilcoxon rank-sum test, and categorical variables were compared using χ^2 or Fisher exact test where appropriate.

To reduce the effect of confounding caused by differences in baseline demographic, clinical, echocardiographic, and hemodynamic characteristics between PAH patients with and without β-blocker use, we used propensity score matching in combination with Cox regression modeling. A propensity score was estimated for each patient using a logistic regression model in which the dependent variable was β-blocker use and the covariates were age, sex, World Health Organization functional class, pathogenesis of pulmonary hypertension, history of hypertension, coronary artery disease, diabetes mellitus, history of obesity, end-stage renal disease, use of calcium-channel blockers, digoxin, aspirin, diuretics, angiotensin-converting enzyme inhibitor, right and left atrial enlargement and right ventricular hypertrophy by echocardiogram, invasive hemodynamic variables, including mean right atrial pressure, mPAP, pulmonary capillary wedge pressure, CO, and PVR. Patients were matched on estimated propensity scores, with replacement, using a nearest neighbor approach. A maximum caliper width =0.2 of the pooled standard deviation of the logit of the propensity score [caliper=0.03] was used, as previously suggested.[24]

We calculated the mean bias between the 2 treatment groups in 2 steps. First we calculated the bias for each covariate before and after matching between those treated with β-blockers and those not treated with β- blockers. Each bias was calculated as the standardized difference of the mean for continuous variables or standardized difference of the prevalence for categorical variables. We then took the arithmetic mean of the absolute standardized differences calculated to generate the mean bias.

Absolute difference in mortality between those with and without β-blocker use in the propensity score–matched cohort was compared using bootstrapped estimates with 1000 replications. We generated bootstrap estimates by sampling with replacement over 1000 repetitions from the matched sample after the study design as described previously.[25] This nonparametric method is based on the assumption that our sample is representative of the population. By resampling our cohort with replacement in the matched sample, we generated 1000 unique samples. The reported estimates reflect the average treatment effect on the treated of β-blockers on mortality over these 1000 samples.

Next, mortality was compared between those with and without β-blocker use in the total cohort and the propensity-matched cohort, using Kaplan–Meier analysis and the log-rank test. The date of initial right heart catheterization was used as the date of entry into the study. Patients were censored at the time of death or when lost to follow up.

To further assess the effect of β-blocker use on all-cause mortality, Cox proportional hazard models were constructed, unadjusted, and adjusted for propensity score in the total cohort and in the matched cohort. To determine whether the use of β-blockers were protective mainly in patients for whom other neurohormonal and renin–angiotensin–aldosterone axis modifying therapies were coadministered, we compared the survival between those with and without β-blocker use in PAH patients who were on diuretics, aldosterone antagonists, or angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (n=280). We tested the proportional hazards assumption by conducting individual likelihood ratio tests for each predictor. For each covariate, we created time-dependent covariates in the form of an interaction term, with the covariate being tested and a log-transformed function of time. We then serially tested each time-dependent covariate using a likelihood ratio test for significance at the 90% level of confidence.

All statistical analyses were performed using Stata (version 13, StataCorp LP, College Station, TX). The authors had full access to the data and take responsibility for their integrity. All authors have read and agree to the article as written.

Results

Baseline Characteristics of the Unmatched Total Cohort

Of the total 564 patients, 71(13%) were on β-blocker therapy and 493 (87%) were not on β-blocker therapy at the time of initial evaluation. Figure 1 displays the name and the frequency of various β-blockers received by the PAH patients in our registry. Table 1 compares the baseline demographic and clinical characteristics between those with and without β-blocker use. PAH patients with β-blocker use were more likely to be older, more often had connective tissue associated and portopulmonary PAH, and less often had idiopathic, familial, and anorexigen-associated PAH. PAH patients receiving β-blockers also had higher prevalence of hypertension, obesity, and coronary artery disease. PAH patients with β-blocker use were more likely to be on angiotensin-converting enzyme inhibitor, diuretics, and aspirin, and less likely to be on digoxin. There was no significant difference in the use of PAH-specific medications at the time of initial evaluation. The severity of pulmonary hypertension and right ventricular dysfunction, measured by baseline echocardiographic and hemodynamic characteristics, were not different between those with and without β-blocker use (Table 2).

Propensity Score

Table 3 lists the odds ratio of the baseline characteristics that were independently associated with the use of β-blockers in patients with PAH. Hypertension, obesity, diuretic use, warfarin use, and higher PA systolic pressure were independently associated with increased use of β-blockers. However, idiopathic PAH, anorexigen-associated PAH, connective tissue disease–associated PAH, digoxin use, endothelin receptor antagonist use, and calcium-channel blockers use were independently associated with decreased use of β-blockers.

Of the 71 PAH patients with β-blocker use, 63 had an estimated propensity score that matched within the 0.03 caliper to 51 PAH patients without β-blockers use. Matching resulted in a reduction in mean bias from 19.4%±16.9% in the total cohort to 7.9%±6.6% in the matched cohort. The standardized bias was <10% for all variables. After matching, there were no significant differences in baseline demographic, clinical, echocardiographic, and hemodynamic characteristics between those with and without β-blocker use (Table 1 and 2). Although the registry from which we collected this data spanned the period from 1982 to 2013, the patients

Table 1. Baseline Clinical Characteristics by β-Blocker Use in the Total and Propensity-Matched Cohort

	β-Blocker					
	Total Cohort			Matched Cohort		
Characteristics	Yes (N=71)	No (N=493)	*P* Value	Yes (N=63)	No (N=51)	*P* Value
Age, y	59±14	55±14	0.02	58±14	59±15	0.63
Female, n (%)	54 (76)	400 (81)	0.34	48 (76)	39 (77)	0.43
Pathogenesis, n (%)			0.01			0.91
Idiopathic	23 (33)	227 (46)		21 (33)	15 (29)	
CTD	24 (34)	155 (31)		23 (37)	17 (33)	
CHD	6 (9)	36 (7)		5 (8)	7 (14)	
Portopulmonary	15 (21)	37 (8)		11 (17.5)	9 (18)	
Anorexigen	1 (1)	20 (4)		1 (1.5)	0 (0)	
Familial	1 (1)	16 (3)		1 (1.5)	2 (4)	
Others	1 (1)	2 (1)		1 (1.5)	1 (2)	
WHO FC III/IV	58 (82)	428 (87)	0.24	53 (84)	43 (84)	0.97
Hypertension	48 (68)	141 (29)	<0.001	40 (64)	30 (59)	0.61
Diabetes mellitus	7 (10)	36 (7)	0.45	7 (11)	7 (14)	0.67
History of obesity	27 (38)	87 (18)	<0.001	21 (33)	14 (28)	0.50
CAD	9 (13)	25 (5)	0.012	7 (11)	6 (12)	0.91
ESRD	1 (1.4)	2 (0.4)	0.28	1 (1.6)	0	1
Medications,* n (%)						
Digoxin	4 (6)	79 (16)	0.019	4 (6)	3 (6)	0.62
CCB	19 (27)	168 (34)	0.22	18 (29)	15 (29)	0.92
Warfarin	23 (32)	138 (28)	0.44	18 (29)	17 (33)	0.58
ACE/ARB	20 (28)	59 (12)	<0.001	19 (30)	15 (29)	0.93
Aspirin	18 (25)	69 (14)	0.013	17 (27)	15 (29)	0.77
Diuretics	42 (59)	196 (40)	0.002	36 (57)	26 (51)	0.51
PDE-5-Inhibitors	4 (6)	22 (5)	0.66	3 (5)	4 (8)	0.70
ETR Blockers	3 (4)	29 (6)	0.57	3 (5)	5 (10)	0.46
Prostacyclin	1 (1)	15 (3)	0.44	1 (2)	1 (2)	0.88

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium-channel blocker; CHD, congenital heart disease; CTD, connective tissue disease; ESRD, end stage renal disease; ETR, endothelin receptor; PDE, phosphodiesterase; and WHO, World Health Organization.

*Baseline medications taken by the patients at the time of enrollment in the Pulmonary Hypertension Connections (PHC) registry.

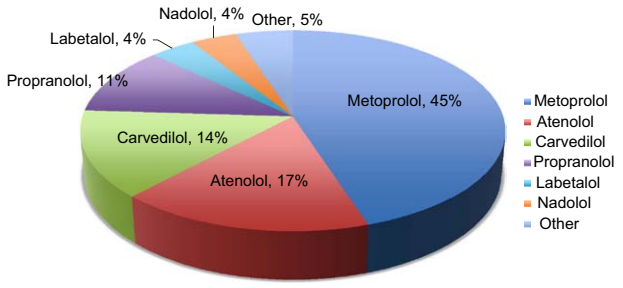

Figure 1. Name and frequency of β-blockers used at baseline.

Table 2. Baseline Echocardiographic and Hemodynamic Characteristics by β-Blocker Use in the Total and Propensity-Matched Cohort

	β-Blocker					
	Total Cohort			Matched Cohort		
Characteristics	Yes (N=71)	No (N=493)	*P* Value	Yes (N=63)	No (N=51)	*P* Value
Echocardiography						
RA enlargement, n (%)	65 (92)	432 (88)	0.34	58 (92)	47 (92)	0.99
RV hypertrophy, n (%)	29 (41)	178 (36)	0.44	25 (40)	24 (47)	0.43
RV Function, n (%)			0.91			0.62
Normal	9 (14.3)	69 (17.4)		9 (16.4)	6 (15.8)	
Mildly reduced	7 (11.1)	49 (12.4)		4 (7.3)	6 (15.8)	
Moderately reduced	24 (38.1)	141 (35.6)		22 (40.0)	15 (39.5)	
Severely reduced	23 (36.5)	137 (34.6)		20 (36.4)	11 (29.0)	
Tricuspid regurgitation jet velocity, m/sec	3.8±1.0 (n=42)	4.1±0.9 (n=266)	0.22	3.9±1.1 (n=38)	4.2±0.9 (n=30)	0.20
Right-left atrial shunt, n (%)	12 (16.9)	74 (15)	0.68	10 (15.9)	9 (17.7)	0.80
LA enlargement, n (%)	18 (25)	91 (19)	0.17	15 (24)	12 (24)	0.97
LA size, mm	36.2±9.6 (n=30)	35.3±6.1 (n=271)	0.34	35.8±9.3 (n=28)	35.9±5.8 (n=22)	0.68
LV posterior wall thickness, mm	10.0±2.5 (n=58)	9.8±1.9 (n=352)	0.83	10.1±2.4 (n=52)	9.9±2.0 (n=35)	0.68
LV septal wall thickness, mm	10.6±3.2 (n=57)	10.1±2.2 (n=352)	0.70	10.8±3.3 (n=52)	10.0±1.9 (n=35)	0.51
LV ejection fraction, %	62±8 (n=46)	61±9 (n=282)	0.55	62±9 (n=42)	62±9 (n=35)	0.92
Treadmill Exercise Testing						
Exercise capacity, metabolic equivalents	3.4±1.4 (n=35)	3.9±2.1 (n=298)	0.37	3.4±1.4 (n=30)	4.1±2.5 (n=29)	0.43
O2 saturation at rest	95±4 (n=40)	95±5 (n=294)	0.12	94.4±4 (n=33)	96.1±2.7 (n=33)	0.11
O2 saturation postexercise	87±9 (n=40)	87±11 (n=283)	0.81	87±9 (n=34)	90±8 (n=33)	0.10
Hemodynamics						
Mean RA pressure, mm Hg	10±6	10±6	0.92	10±6	9±6	0.81
RV systolic pressure, mm Hg	83±21	83±19	0.73	83±20	81±22	0.51
RV diastolic pressure, mm Hg	13±6	14±7	0.33	13±7	13±7	0.56
PA systolic pressure, mm Hg	82±18	82±21	0.91	83±19	81±21	0.69
PA diastolic pressure, mm Hg	35±10	36±12	0.22	35±10	35±11	0.99
Mean PA pressure, mm Hg	50±12	51±14	0.25	50±12	50±14	0.99
PCWP, mm Hg	11±4	10±4	0.13	11±4	11±5	0.88
Cardiac output, l/min	4.3±1.8	4.3±1.7	0.87	4.4±1.9	4.5±2.0	0.81
PA saturation, %	61±9	60±12	0.52	60±10	60±12	0.95
PVR, WU	10.7±6.7	11.5±6.7	0.32	11.1±6.9	11.2±7.3	0.79

LA indicates left atrium; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA, right atrium; RV, right ventricle; and WU, wood units.

comprising our propensity score–matched cohort were all referred between the years 1993 and 2013.

Mortality

The median follow up time of the study cohort was 4.8 years (25th–75th percentile: 1.7–10.2 years). Over the course of follow up, 60% (339/564) of patients died in the total cohort. Among patients without β-blocker use, 60% (294/493) died and 63% (45/71) of those with β-blocker use died. In the propensity score–matched cohort, 57% (29/51) of patients without β-blocker use and 65% (41/63) of patients with β-blocker use died. Using bootstrap analysis with 1000 repetitions, we estimated that the mortality among patients taking β-blockers was 7 (95% confidence interval [CI], −30 to 44–) percentage points higher than the mortality among patients not taking β-blockers, but this was not statistically significant (*P*=0.71).

Using Kaplan–Meier and Cox regression, in the total cohort, β-blocker use was associated with increased all-cause mortality in the unadjusted model (hazard ration [HR] 1.4; 95% CI, 1.1–2.0), but was no longer significant after adjustment with the propensity score (HR 1.0; 95% CI, 0.7–1.5; Figure 2 and Table 4). In contrast to the total cohort, in the matched cohort, β-blocker use was not associated with increased all-cause mortality (HR 1.2; 95% CI, 0.8–2.0; Figure 3 and Table 4). Table 3 summarizes the results of the Cox proportional hazards analysis in both cohorts. There was

Table 3. Adjusted Odds Ratios for Baseline Characteristics Independently Associated With β-Blocker Use in Patients With PAH

Characteristics	Odds Ratio (95% CI)	*P* Value
Idiopathic PAH	0.1 (0.03–0.5)	0.002
Connective tissue disease	0.2 (0.05–0.7)	0.011
Anorexigen use	0.04 (0.003–0.5)	0.003
Hypertension	6.6 (3.1–14.1)	<0.001
History of obesity	3.3 (1.6–7.0)	0.001
Digoxin	0.2 (0.06–0.7)	0.008
Calcium channel blockers	0.4 (0.21–0.9)	0.02
Warfarin	3.2 (1.5–6.7)	0.002
Diuretics	2.3 (1.2–4.4)	<0.001
ETR blockers	0.2 (0.04–0.9)	0.037
Systolic PA pressure	1.1 (1.0–1.1)	0.041

CI indicates confidence interval; ETR, endothelin receptor antagonist; PA, pulmonary artery; and PAH, pulmonary arterial hypertension.

no difference in survival between those with (n=53) and without (n=227) β-blocker use when we restricted our analysis to only those who were on diuretics, aldosterone antagonists, or angiotensin-converting enzyme inhibitor/angiotensin receptor blockers (HR adjusted for propensity score, 0.97; 95% CI, 0.63–1.49; Figure 4).

Patients were enrolled in the PHC registry over a substantial period of time (1982–2013), which could have potentially introduced a bias caused by difference in practice patterns. Thus, we did a post hoc analysis of our matched sample to determine the difference in referral dates between our matched patients. The median difference in referral dates between matches was 1812 days (4.96 years). The smallest difference was 11 days and the largest was 6763 days. We then excluded matches where referral dates were >5 years apart (median difference in date of referral between the study cohorts) and subsequently excluded 31/63 (49%) pairs in our matched sample. Similar to our total matched cohort, in this cohort also there was no difference in survival by Kaplan–Meier analysis between those with and without β-blocker use (Figure 5), and

Table 4. Cox Regression Models for All-Cause Mortality by β-Blocker Use

Analysis	Mortality Events/Total, % (β-Blocker Use) Yes	No	HR (95% CI)	*P* Value
Total Cohort				
Unadjusted	45/71 (63%)	294/493 (60%)	1.4 (1.1–2.0)	0.03
Adjusted with propensity score	45/71 (63%)	294/493 (60%)	1.0 (0.7–1.5)	0.86
Matched cohort	41/63 (65%)	29/51 (57%)	1.2 (0.8–2.0)	0.42

CI indicates confidence interval; and HR, hazard ratio.

β-blocker use was not associated with a statistically significant increase in mortality (HR adjusted for propensity score, 1.59; 95% CI, 0.80–3.17).

Discussion

In this study of a well-characterized, large cohort of PAH patients, we found that β-blocker use is not uncommon in PAH patients, despite severe pulmonary hemodynamics. Despite severe PAH and right ventricular dysfunction, there was no statistically significant difference in long-term all-cause mortality between propensity score–matched pairs of PAH patients with and without β-blocker use.

The suggestion that β-blockers may have deleterious effects and are contraindicated in patients with PAH[13,17] is based on the concept that the contractile reserve of the pressure-overloaded RV is significantly reduced in PAH, requiring patients to be dependent on their heart rate to maintain CO. In support of this, Provencher et al reported that withdrawal of β-blockers improved exercise capacity and right heart hemodynamics in 10 patients with portopulmonary hypertension who were receiving β-blockers for esophageal variceal bleeding prophylaxis.[17] Compared with baseline, 9 out of the 10 patients had an increase in 6 minute walking distance and CO with a reduction in PVR 2 months after withdrawal of β-blockers. The increase in CO was driven solely by an increase in heart rate with no significant change in stroke volume.

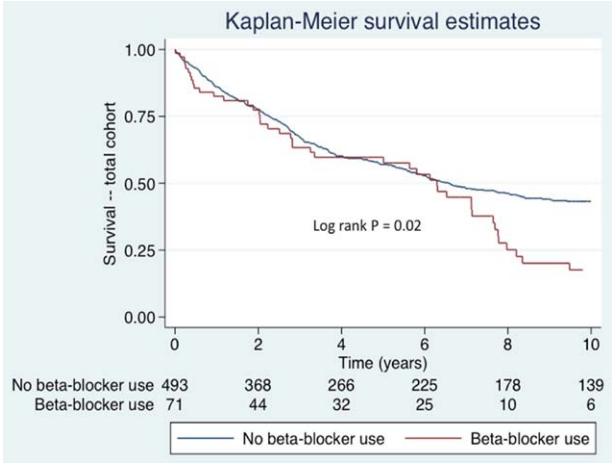

Figure 2. Comparison of Kaplan–Meier survival by β-blocker use in the total cohort.

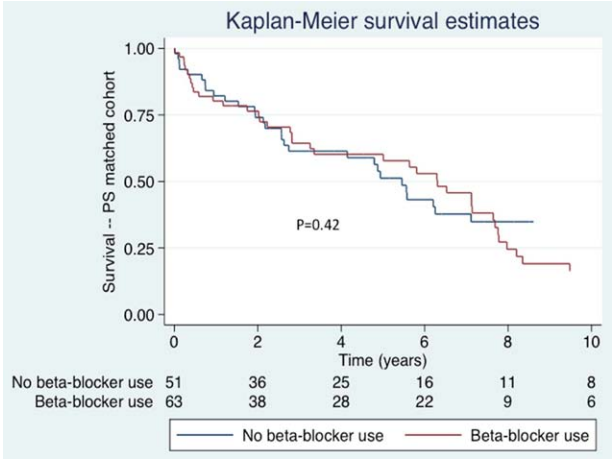

Figure 3. Comparison of Kaplan–Meier survival by β-blocker use in the propensity score–matched cohort. PS indicates propensity score–matched cohort.

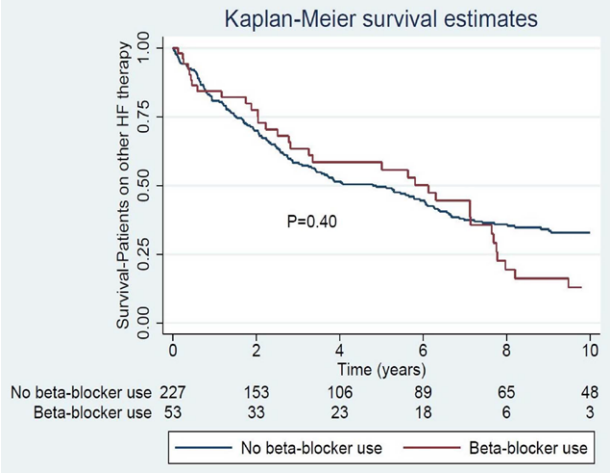

Figure 4. Comparison of Kaplan–Meier survival by β-blocker use in pulmonary arterial hypertension patients on other conventional heart failure therapy. HF indicates heart failure; other conventional HF therapy includes diuretics, aldosterone antagonists, or angiotensin-converting enzyme inhibitor/angiotensin receptor blockers.

This small study questioned the utility of β-blockers in this specific PAH population; however, it was small and lacked a sensitivity analysis with a long-term comparison between those who continued β-blocker use and those who discontinued it. In the short term, it is not surprising that the heart rate increased with improvement in exercise capacity after withdrawal of β-blockers because PAH patients are highly heart rate–dependent. Moreover, 8 of the 10 patients in this study were receiving the first generation, nonselective β-blocker propranolol that perhaps has a greater bronchial and myocardial depressive effect than the currently available selective β-blockers.[26,27]

Contrary to these findings, preclinical animal experiments and human data seem to suggest that β-blockers may be beneficial in PAH-induced isolated RVF by inhibiting neurohormonal activation.[14,15,28] A small cohort study evaluated PAH patients with and without β-blocker therapy at presentation and found no detrimental effect of β-blockers on clinical, functional, or hemodynamic outcomes.[18] After a median follow-up of 20 months, there was a similar decrease in mPAP and PVR between the 2 groups, but there was a small increase in cardiac index in those using β-blockers. There was no statistically significant difference in all-cause mortality, PAH-related hospitalizations, or worsening of RVF between those who were taking or were not taking β-blockers. However, this study did not adjust for the difference in baseline characteristics between those with and without β-blocker use.

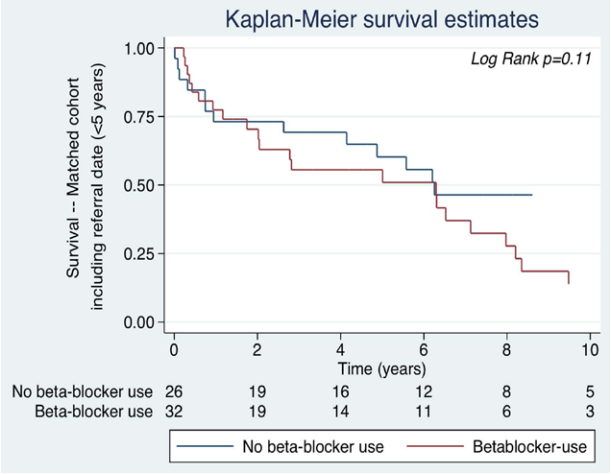

Figure 5. Comparison of Kaplan–Meier survival by β-blocker use in the propensity score–matched cohort after adjusting for date of referral.

Our study confirms these clinical findings in a large well-characterized cohort of patients with severe PAH with long-term follow up (median follow up time, 4.7 years). Additionally, we used propensity score matching in combination with Cox regression modeling to reduce confounding caused by differences in baseline demographic, clinical, echocardiographic, and hemodynamic characteristics between PAH patients with and without β-blocker use. Although there was a crude difference in survival between those with and without β-blocker in the total unmatched cohort, this difference was no longer significant after adjusting for the propensity score. Moreover, β-blocker use was not associated with increased all-cause mortality in the propensity score–matched cohort. We also did not observe difference in mortality between those with and without β-blocker use even when we restricted our analysis to only those on other conventional heart failure therapy.

In our registry, 13% (71/564) of PAH patients were on β-blockers for treatment of concomitant cardiovascular disease. Using multivariable logistic regression, we found that the odds ratio for β-blocker use is significantly higher in PAH patients with coexisting history of hypertension, obesity, diuretic use, warfarin use, and higher pulmonary artery systolic pressure on right heart catheterization. The exact mechanism behind the association between β-blocker use and warfarin use is not clear. Only 8 out of the 564 patients were in atrial fibrillation at the time of initial enrollment in our registry. In our experience, once given a diagnosis of PAH, the medication is often started for this indication before referral to a tertiary PAH center. However, it is possible that some patients were on warfarin for paroxysmal atrial fibrillation at the time of referral to our center. Our registry does not capture the intent of therapy initiation. It also seems that presence of concomitant cardiovascular disease have outweighed the theoretical risk associated with β-blocker therapy and resulted in its use in PAH patients.

This study has several limitations that merit discussion. First, many of the patients diagnosed before 2004 were entered retrospectively, which has inherent limitations. This is a single center study and the results may not be generalizable. We collected data only on the use of β-blockers at baseline; thus, we could not calculate exposure time for β-blockers. However, it is our practice to continue β-blockers in PAH patients who were receiving it for other indications unless they have hypotension or acute decompensated RVF. Second, we did not collect complete exercise testing data to determine whether there was any difference in heart rate and CO response to exercise between PAH patients with and without β-blocker use. However, there was no significant difference in change in oxygen saturation with exercise (surrogate marker of RV reserve) between the 2 groups. Third, we did not collect the details of

the cause of death other than whether it was PAH related or not. Hence, we could not determine whether there was any difference in mortality specifically related to RVF between those with and without β-blocker use. Fourth, although the 2 groups were matched using estimated propensity scores, we cannot completely exclude residual confounding factors that might have influenced the results. Finally, although the low sample size after propensity score matching decreases the power for our study, to the best of our knowledge, this is the largest reported cohort of PAH patients with and without β-blockers use. A noninferiority study design might have provided more power to demonstrate that β-blocker use is not statistically associated with increased mortality in PAH. Nonetheless, we used a superiority design because of lack of an *active* control group for comparison to PAH patients taking β-blockers and because of the lack of previous published estimates of mortality in patients with PAH with which to choose a noninferiority margin. The estimates presented here should help inform future studies in selecting an appropriate noninferiority margin a priori. Hence, our analysis is only hypothesis generating, and β-blockers should not be used in PAH patients based solely on these results.

In conclusion, β-blockers are often used in patients with severe PAH for other existing illness in the PHC registry. β-blockers use is not associated with statistically significant increase in long-term all-cause mortality using propensity score matching analysis. Prospective clinical trials that assess the safety and efficacy of β-adrenergic receptor antagonists in PAH are needed in the future.

Acknowledgments

We thank Dr John E. Connett, PhD, Professor, Division of Biostatistics, School of Public Health, University of Minnesota for advice on the statistical methodology.

Sources of Funding

This study is supported by funding from the Lillehei Heart Institute, Minneapolis, Minnesota.

Disclosures

Thenappan Thenappan has received honoraria for continuing medical education (CME) from Medscape. Actelion, Gilead, Medtronic, Novartis, Lung Biotechnology, and Reata have provided funding to the University of Chicago to support Dr Gomberg-Maitland's conduct of clinical trials. Dr Gomberg-Maitland has served as a consultant for Actelion, Gilead, Medtronic, Bellerophon (formerly known as Ikaria), and United Therapeutics as a member of steering committees and Data Safety Monitoring Board/event committees. She has received honoraria for CME from Medscape and AB Comm. The other authors report no conflicts.

References

1. Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med*. 2004;351:1655–1665.
2. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, Frost A, Barst RJ, Badesch DB, Elliott CG, Liou TG, McGoon MD. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation*. 2010;122:164–172.
3. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaïci A, Weitzenblum E, Cordier JF, Chabot F, Dromer C, Pison C, Reynaud-Gaubert M, Haloun A, Laurent M, Hachulla E, Cottin V, Degano B, Jaïs X, Montani D, Souza R, Simonneau G. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. *Circulation*. 2010;122:156–163.
4. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. *Eur Respir J*. 2010;35:1079–1087.
5. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, Naeije R, Newman J, Oudiz RJ, Provencher S, Torbicki A, Voelkel NF, Hassoun PM. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. *J Am Coll Cardiol*. 2013;62(25 Suppl):D22–D33.
6. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. 1991;115:343–349.
7. van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A, Marques KM, Westerhof N, Vonk-Noordegraaf A. Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol*. 2011; 58:2511–2519.
8. Bristow MR, Minobe W, Rasmussen R, Larrabee P, Skerl L, Klein JW, Anderson FL, Murray J, Mestroni L, Karwande SV. Beta-adrenergic neuroeffector abnormalities in the failing human heart are produced by local rather than systemic mechanisms. *J Clin Invest*. 1992;89:803–815.
9. Bristow MR. beta-adrenergic receptor blockade in chronic heart failure. *Circulation*. 2000;101:558–569.
10. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vítovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Jánosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA*. 2000;283:1295–1302.
11. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999; 353:9–13.
12. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651–1658.
13. Peacock A, Ross K. Pulmonary hypertension: a contraindication to the use of {beta}-adrenoceptor blocking agents. *Thorax*. 2010;65:454–455.
14. Bogaard HJ, Natarajan R, Mizuno S, Abbate A, Chang PJ, Chau VQ, Hoke NN, Kraskauskas D, Kasper M, Salloum FN, Voelkel NF. Adrenergic receptor blockade reverses right heart remodeling and dysfunction in pulmonary hypertensive rats. *Am J Respir Crit Care Med*. 2010;182:652–660.
15. de Man FS, Handoko ML, van Ballegoij JJ, Schalij I, Bogaards SJ, Postmus PE, van der Velden J, Westerhof N, Paulus WJ, Vonk-Noordegraaf A. Bisoprolol delays progression toward right heart failure in experimental pulmonary hypertension. *Circ Heart Fail*. 2012;5:97–105.
16. Ishikawa M, Sato N, Asai K, Takano T, Mizuno K. Effects of a pure alpha/beta-adrenergic receptor blocker on monocrotaline-induced pulmonary arterial hypertension with right ventricular hypertrophy in rats. *Circ J*. 2009;73:2337–2341.
17. Provencher S, Herve P, Jais X, Lebrec D, Humbert M, Simonneau G, Sitbon O. Deleterious effects of beta-blockers on exercise capacity and hemodynamics in patients with portopulmonary hypertension. *Gastroenterology*. 2006;130:120–126.
18. So PP, Davies RA, Chandy G, Stewart D, Beanlands RS, Haddad H, Pugliese C, Mielniczuk LM. Usefulness of beta-blocker therapy and outcomes in patients with pulmonary arterial hypertension. *Am J Cardiol*. 2012;109:1504–1509.
19. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982–2006. *Eur Respir J*. 2007;30:1103–1110.
20. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, Langleben D, Manes A, Satoh T, Torres F, Wilkins MR, Badesch DB. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol*. 2013;62(25 Suppl):D42–D50.
21. Shah SJ, Thenappan T, Rich S, Sur J, Archer SL, Gomberg-Maitland M. Value of exercise treadmill testing in the risk stratification of patients with pulmonary hypertension. *Circ Heart Fail*. 2009;2:278–286.

22. Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Hervé P, Simonneau G. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation*. 2005;111:3105–3111.
23. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J; American College of Cardiology Foundation Task Force on Expert Consensus Documents; American Heart Association; American College of Chest Physicians; American Thoracic Society, Inc; Pulmonary Hypertension Association. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol*. 2009;53:1573–1619.
24. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. *Am J Epidemiol*. 2010;172:1092–1097.
25. Austin PC, Small DS. The use of bootstrapping when using propensity-score matching without replacement: a simulation study. *Stat Med*. 2014;33:4306–4319.
26. Bril A, Slivjak M, DiMartino MJ, Feuerstein GZ, Linee P, Poyser RH, Ruffolo RR Jr, Smith EF III. Cardioprotective effects of carvedilol, a novel beta adrenoceptor antagonist with vasodilating properties, in anaesthetised minipigs: comparison with propranolol. *Cardiovasc Res*. 1992;26:518–525.
27. Wendt T, van der Does R, Schräder R, Landgraf H, Kober G. Acute hemodynamic effects of the vasodilating and beta-blocking agent carvedilol in comparison to propranolol. *J Cardiovasc Pharmacol*. 1987;10 Suppl 11:S147–S150.
28. de Man FS, Handoko ML, Guignabert C, Bogaard HJ, Vonk-Noordegraaf A. Neurohormonal axis in patients with pulmonary arterial hypertension: friend or foe? *Am J Respir Crit Care Med*. 2013;187:14–19.

CLINICAL PERSPECTIVE

Pharmacological blockade of the β-adrenergic receptor with β-blockers is one of the main treatment strategies in left ventricular systolic dysfunction. However, the safety and efficacy of β-blocker therapy in isolated right ventricular failure associated with pulmonary arterial hypertension (PAH) is unclear. There is a theoretical concern for worsening right ventricular failure with β-blockers in patients with PAH because they are highly dependent on the heart rate to maintain their cardiac output. Human studies, thus far, have reported conflicting results with respect to the safety and efficacy of β-blockers in PAH. We evaluated the association between β-blocker therapy and long-term outcomes in 564 patients with PAH in our Pulmonary Hypertension Connections. Propensity score matching was used to match pairs of PAH patients with and without β-blocker use. We found that β-blockers were frequently used in patients with severe PAH for other existing illness in the Pulmonary Hypertension Connections registry. Compared with PAH patients without β-blocker use, those with a β-blocker use were older, had higher prevalence of comorbidities, and were more often on diuretics, digoxin, and angiotensin-converting enzyme inhibitors. The severity of PAH and right ventricular failure was similar between those with and without β-blocker use. There was no statistically significant difference in long-term mortality between propensity score–matched pairs of PAH patients with and without β-blocker use. Prospective clinical trials that assess the safety and efficacy of β-adrenergic receptor antagonists in PAH are needed in the future.

Circulation
Heart Failure

β-Blocker Therapy Is Not Associated With Adverse Outcomes in Patients With Pulmonary Arterial Hypertension: A Propensity Score Analysis

Thenappan Thenappan, Samit S. Roy, Sue Duval, Cherylanne Glassner-Kolmin and Mardi Gomberg-Maitland

Circ Heart Fail. 2014;7:903-910; originally published online October 2, 2014;
doi: 10.1161/CIRCHEARTFAILURE.114.001429
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3289. Online ISSN: 1941-3297