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Outcomes of β-blocker use in pulmonary arterial hypertension: a propensity-matched analysis

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ABSTRACT The utility and safety of β-blockers in pulmonary hypertension is controversial. Anecdotal reports suggest that β-blockers may be harmful in these patients. The aim of our study was to evaluate outcomes of β-blocker use in pulmonary hypertension.

We reviewed patients from our pulmonary hypertension registry between 2000 and 2011. Patients who continued to use β-blockers were compared to those who never used β-blockers for all-cause mortality, time to clinical worsening events, defined as death, lung transplantation and hospitalisation due to pulmonary hypertension. We also evaluated the effect of β-blockers on 6-min walking distance and New York Heart Association (NYHA) functional class.

133 patients used β-blockers and 375 patients never used β-blockers. Mean±SD age was 57±16 years and the median follow-up period was 78 months. Propensity-matched analysis showed that the adjusted odds ratio (95% CI) for mortality with β-blocker use was 1.13 (0.69–1.82) and for clinical worsening events was 0.96 (0.55–1.68). No significant difference was noted in probability of survival and time to clinical worsening events. Patients on β-blockers walked a shorter distance on follow-up 6 min walk test; follow-up NYHA class was similar between groups.

Pulmonary hypertension patients receiving β-blockers had a similar survival and time to clinical worsening events compared to patients not receiving them. Functional outcomes were similar, although β-blocker use was associated with a tendency towards shorter walking distance.

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Introduction

Pulmonary arterial hypertension (PAH) is an incurable disease with poor prognosis. In the National Heart, Lung, and Blood Institute registry, estimated median survival for untreated idiopathic pulmonary arterial hypertension (IPAH) was 2.8 years [1]. The PAH is characterised by elevated mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance, which can lead to right ventricular (RV) hypertrophy/dilation, RV failure and death. Pulmonary vasodilators have been used to unload the right ventricle, resulting in improved outcomes, but overall survival remains poor [2].

Patients with PAH may be placed on β-blocker therapy for various reasons, including treatment for hypertension, cardiac dysrhythmias or prophylaxis of gastrointestinal bleeding. However, little is known about the frequency of this use and the exact role of β blockade in these patients remains controversial for several reasons. It plays a complex multifaceted role in pulmonary haemodynamics. Sustained β blockade has been found to increase mPAP by 20% at maximal exercise in normal healthy adults [3]. The negative chronotropic and inotropic effects of β-blockers can be detrimental in PAH patients during exercise, due to their limited ability to increase stroke volume, and anecdotal reports suggest that β-blockers may be harmful in these patients [4].

In contrast, recent evidence indicates that there is an excessive sympathetic activation in PAH patients [5, 6] which may portend a worse prognosis [6–8]. Attention has also focused on the diverse role of β-blockers on RV function in PAH patients. β blockade using carvedilol has been shown to reverse RV remodelling and maladaptive RV hypertrophy and improve RV function in experimental rats, similar to its effect on the left ventricle [9, 10]. In addition, bisoprolol has been found to delay RV failure and preserve RV function in experimental pulmonary hypertension [11]. Patients with PAH are also known to have a high prevalence of left ventricular diastolic dysfunction [12], where β blockade may produce a salutary effect. Thus, there is a rationale for a potential benefit of β-blocker therapy in these patients. We aimed to evaluate the prevalence of β-blocker use and its impact on long-term outcomes in PAH patients. We hypothesised that use of β-blockers would not be associated with worsening survival, clinical worsening events or functional outcomes.

Materials and methods

The Cleveland Clinic (Cleveland, OH, USA) institutional review board approved the study under approval number 10–331. We reviewed PAH patients from our pulmonary hypertension registry between 2000 and 2011 to select patients with established PAH. The presence of pulmonary hypertension was defined according to World Health Organization (WHO) criteria as mPAP >25 and pulmonary capillary wedge pressure ⩽15 mmHg [13]. Only the patients with a confirmed diagnosis of IPAH and connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) were included in this study. Those subjects aged <18 years at the time of diagnosis, presence of group 2, group 3 or group 4 pulmonary hypertension or any patients with possible overlap classes of pulmonary hypertension were excluded from the study.

Medical records were reviewed for patient profiles, comorbid illnesses, New York Heart Association (NYHA) functional class, 6 min walking test (6MWT) results, Doppler echocardiography reports, pulmonary haemodynamics at diagnosis and medications used for PAH. We specifically noted use of β-blockers and its duration as well as reasons for initiation and discontinuation. Follow-up data regarding NYHA functional class, 6MWT, lung transplantation and all-cause mortality were also collected. Data on hospitalisations due to PAH worsening were obtained and adjudicated by a physician blinded to the use of β-blockers in individual patients.

The study population included three different groups: those who had never used β-blockers (no BB), those who had continued to use β-blockers until they reached the end-points of the study (BB) and those who were started on β-blocker therapy but discontinued after a period (partial BB) (fig. 1). The BB and no BB groups were primarily utilised to analyse outcomes of interest. Those two groups were compared for all-cause mortality and clinical worsening events, defined as death, lung transplantation or hospitalisation due to PAH worsening. Patients in the two groups were also compared for time to clinical worsening (TtCW) defined as time from initiation of β-blocker therapy to first clinical worsening event. The impact of β-blocker use on functional capacity was evaluated for patients in the no BB and BB groups, by analysing the NYHA functional class and 6-min walking distance (6MWD). NYHA class was obtained at diagnosis and at 1, 3 and 5 years of follow-up and 6MWD data were acquired from the last test result available, which was commonly the most recent clinic visit. In order to eliminate selection bias, we also performed a separate all-cause mortality and TtCW analysis comparing all three groups.

Categorical variables are presented as frequency and percentage and the continuous variables as mean±SD or median (range), according to distribution of the dataset. The two groups were compared using Fisher's exact test, Wilcoxon rank sum test or Chi-squared test for univariate analysis. Kaplan–Meier estimates

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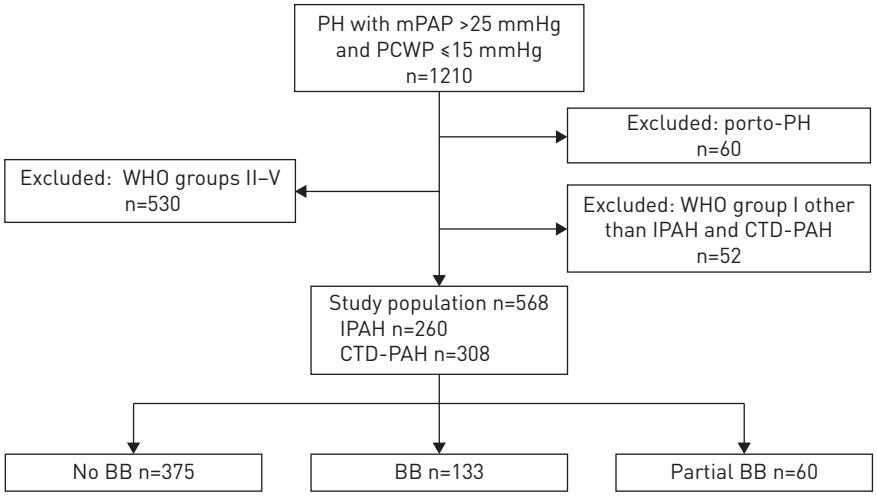


FIGURE 1 Flow diagram of study cohort. PH: pulmonary hypertension; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; WHO: World Health Organization; IPAH: idiopathic pulmonary arterial hypertension; CTD-PAH: connective tissue disease-associated pulmonary arterial hypertension; BB: β-blocker.

were used to present time-to-event analysis for the propensity-matched population, as well as univariate analysis. The threshold p-value for statistical significance was <0.05. The follow-up period started from the date of diagnosis to the date of either transplant or death, and for surviving patients without transplant, the cut-off date (end-point) was January 1, 2013.

In order to reduce the effect of selection bias and potential confounding in this study, we also performed a rigorous adjustment for differences in baseline characteristics by propensity score analysis between the two groups (BB and no BB) to assess the outcomes of interest. The effect of β-blocker treatment on mortality and functional outcomes (6MWD and NYHA functional class) were analysed by directly adjusting for the (linear) propensity score in a logistic regression model to obtain either propensity-adjusted odds ratio (aOR) or propensity-adjusted mean (95% CI), as appropriate. The individual (linear) propensity score was incorporated into the model as a covariate, to calculate aOR and mean (95% CI). The standardised differences between the covariates were reduced <10% for all the covariates, which were different at baselines and could affect outcomes (online fig. S1). The propensity score matching passed the Rubin rule. Outcome analysis of the matched samples after propensity score adjustments were obtained using optimal pairwise propensity score matching, weighted by the (inverse) linear propensity score. The missing values (<5% of data points) were imputated by the medians for continuous variables and at random for nominal variables. Ultimately, we had excellent propensity-matched cohorts to compare for. We performed propensity score matching using the R statistical package, version 2.15.3 (the R Project for Statistical Computing; www.r-project.org).

Results

Overall population characteristics

We identified 1210 patients receiving treatment for pulmonary hypertension on our database (fig. 1). We excluded 60 patients with porto-pulmonary hypertension and 582 patients with either WHO groups II–V pulmonary hypertension or WHO group I PAH other than IPAH and CTD-PAH, or any pulmonary hypertension with overlap classes. Our final study population included 568 (260 IPAH and 308 CTD-PAH) patients. In this cohort 375 (66%) subjects had never used β-blockers; 133 (23%) patients had received β-blockers continuously and 60 (11%) individuals were initiated with β-blockers but had discontinued.

Table 1 includes the baseline demographics of the study population (n=568). The mean±SD age of the patients was 56±16 years. The majority of patients were female (68%), Caucasian (73%), and 60% never smoked. Overall median (range) follow-up period was 78 (1–388) months. In this analysis 54% had CTD-PAH and 46% had IPAH. Among the CTD-PAH patients, scleroderma constituted 46% and 42% of patients in the BB and no BB groups, respectively. Associated comorbidities included renal failure (23%), coronary artery disease (12%) and hypertension (20%). Atrial fibrillation constituted the majority (74%) of all cardiac dysrhythmias. Left ventricular ejection fraction was comparable between the cohorts, but brain natriuretic peptide level was higher in the BB group (p<0.016).

Table 2 describes the pulmonary haemodynamic profiles of the groups from their baseline Doppler echocardiogram and right heart catheterisation (n=568). Cardiac index and output differed at diagnosis

TABLE 1 Baseline characteristics of the study population

Characteristics	BB	No BB	Partial BB	p-value
Subjects n	133	375	60	
Age years	59±14	57±16	55±16	0.22
BMI kg·m^{-2}	29±8	28±8	26±6	0.12
Race				0.84
Caucasian	97 (73)	280 (75)	40 (67)	
African-American	27 (20)	70 (18)	12 (20)	
Hispanic	4 (3)	15 (4)	7 (1)	
Asian	5 (4)	10 (3)	3 (0.5)	
Sex				0.24
Male	46 (35)	109 (29)	23 (38)	
Female	87 (65)	265 (71)	37 (62)	
Smoking history				0.27
Never smoked	74 (56)	229 (61)	37 (62)	
Ex-/current smoker	59 (44)	149 (39)	23 (38)	
Aetiology of PAH				0.005
Idiopathic	47 (35)	186 (50)	27 (45)	
Connective tissue disease	86 (65)	189 (50)	33 (55)	
Co-existing cardiac illness				
Coronary artery disease	13 (9)	47 (12)	7 (12)	0.38
Valvular heart disease	13 (10)	36 (10)	9 (15)	0.95
Cardiac arrhythmias	27 (20)	80 (21)	13 (22)	0.79
Dyslipidaemia	54 (41)	158 (42)	20 (33)	0.76
Pericardial effusion	21 (27)	54 (21)	10 (17)	0.24
Comorbidities				
Diabetes mellitus	27 (22)	73 (20)	14 (23)	0.63
Renal failure	31 (23)	88 (23)	16 (26)	0.64
Hypertension	27 (20)	72 (19)	13 (22)	0.78
Sleep apnoea	12 (9)	45 (12)	7 (13)	0.94
LVEF %	56±7	56±8	58±8	0.56
Heart rate beats·min^{-1}	71±17	84±15	74±19	0.01
Pro-BNP pg·mL^{-1}	780±218	349±852	511±403	<0.016
Baseline NYHA functional class#				0.52
I		2 (0.5)	0	
II	48 (38)	125 (34)	10 (19)	
III	58 (46)	180 (48)	26 (43)	
IV	20 (16)	62 (17)	16 (25)	
Baseline 6MWD m	286±111	303±102	221±59	0.15
Follow-up months median (range)	81 (1.5–247)	75 (1–388)	31 (1.5–145)	0.41
Transplant	9 (7)	25 (7)	4 (7)	0.97
Mortality	69 (52)	184 (49)	32 (53)	0.57

Data are presented as mean±SD or n (%), unless otherwise stated. BB: patients who had continued to use β-blockers until they reached the end-points of the study; no BB: patients who had never used β-blockers; partial BB: patients who were started on β-blocker therapy but discontinued after a period; BMI: body mass index; PAH: pulmonary arterial hypertension; LVEF: left ventricular ejection fraction; BNP: brain natriuretic peptide; NYHA: New York Heart Association; 6MWD: 6-min walking distance. #: n=126 (BB), n=369 (no BB) and n=52 (partial BB).

between the two cohorts. Patients in the no BB group were more likely to be on parenteral prostanoid therapy and sildenafil than those in the BB group. All other PAH medications, including oxygen therapy, were prescribed equally between the two cohorts.

β-blocker use in pulmonary hypertension patients

Among the patients who used β-blockers (n=193; BB n=133 and partial BB n=60), the most commonly prescribed was metoprolol (fig. 2a). The most common reason for initiation of treatment was cardiac arrhythmias (fig. 2b). Overall median duration of β-blocker use was 41 (1.5–203) months after diagnosis of PAH. 60 (31%) patients had their β-blocker therapy discontinued (the partial BB group) because of side-effects after a median period of 31 (1.5–145) months, compared to 133 (69%) subjects who continued to use them. The most common reasons for withdrawal of β-blockers were hypotension and worsening shortness of breath (fig. 2c). In the partial BB group, 25 patients were already taking β-blockers for

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TABLE 2 Pulmonary hypertension profiles of the patients at diagnosis

	BB	No BB	Partial BB	p-value
Subjects n	133	375	60	
RA dilatation	75 (97)	250 (97)	60 (100)	0.82
RV dilatation	61 (79)	206 (80)	46 (77)	0.90
TR jet velocity cm·s^{-1}	407±71	405±73	435±61	0.74
Positive bubble study	8 (10)	27 (11)	4 (7)	0.97
RVSP mmHg	73±23	74±24	77±27	0.68
sPAP mmHg	74±19	75±21	81±23	0.41
dPAP mmHg	30±9	32±11	35±12	0.08
mPAP mmHg	45±11	47±14	51±16	0.08
PCWP mmHg	9±3	10±6	10±3	0.16
Pulmonary vascular resistance Wood units	9±5	10±6	11±7	0.16
Cardiac index (Fick) L·min^{-1}·m^{-2}	2.6±0.9	2.4±2	2.5±1.8	0.04
Cardiac output (Fick) L·min^{-1}	4.9±2	4.5±2	4.5±2	0.04
Pulmonary arterial oxygen saturation %	63±12	64±13	62±11	0.41
PAH medications				
Epoprostenol	33 (25)	127 (34)	21 (35)	0.05
Sildenafil	66 (50)	144 (38)	28 (46)	0.02
Bosentan	32 (24)	112 (30)	20 (33)	0.20
Treprostinil	11 (8)	41 (11)	8 (13)	0.37
Ambrisentan	15 (11)	18 (5)	9 (15)	0.10
Tadalafil	12 (9)	19 (5)	6 (10)	0.10
Iloprost	4 (3)	11 (3)	3 (5)	0.96
Oxygen therapy	29 (22)	84 (23)	17 (28)	0.86

Data are presented as n (%) or mean±SD, unless otherwise stated. n=568. BB: patients who had continued to use β-blockers until they reached the end-points of the study; no BB: patients who had never used β-blockers; partial BB: patients who were started on β-blocker therapy but discontinued after a period; RA: right atrium; RV: right ventricle; TR: tricuspid regurgitation; RVSP: right ventricular systolic pressure; sPAP: systolic pulmonary artery pressure; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PAH: pulmonary arterial hypertension.

⩾6 months, prior to the diagnosis of PAH. The β-blocker was discontinued in six (24%) cases after a median 8 (3–20) months following detection of PAH, in that particular subset of patients.

Analysis of survival and clinical worsening in the overall cohort

The impact of β-blockade on survival and clinical worsening was analysed in univariate analysis and using propensity matching. Over the duration of follow-up, 98 (74%) patients in the BB group experienced

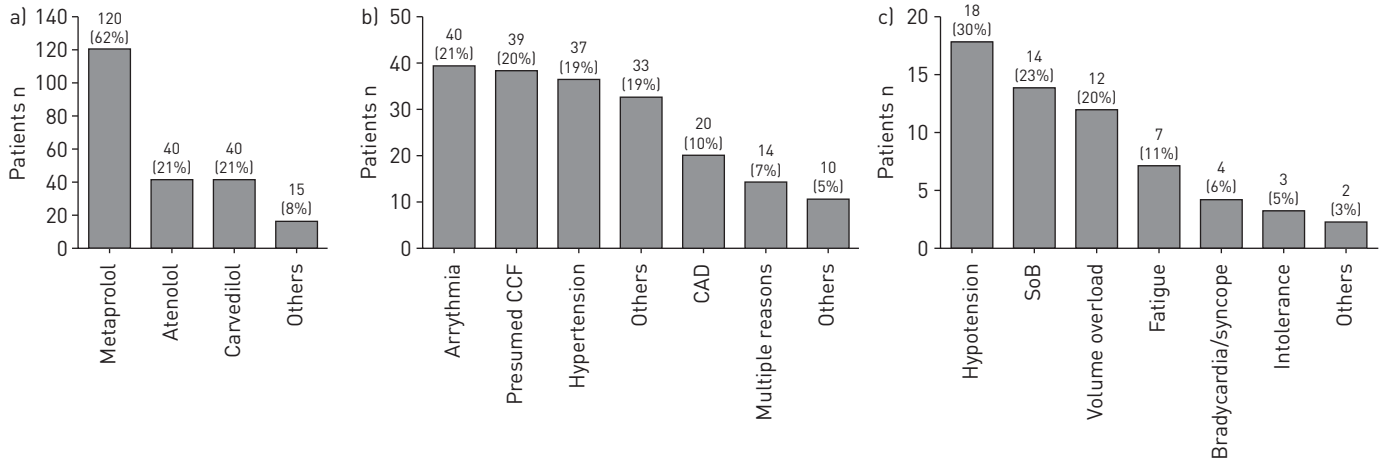


FIGURE 2 a) β-blockers used in pulmonary hypertension patients. "Others" include bisoprolol, propranolol, nebivelol and sotalol. n=193. Some patients received more than one β-blocker. b) Reasons for β-blocker initiation. "Others" include palpitations, autonomic dysfunction, peri-operative and thyroid disorders. n=193. c) Reasons for β-blocker discontinuation. "Others" include bronchospasm and unknown. n=60. CCF: congestive cardiac failure; CAD: coronary artery disease; SoB: shortness of breath.

clinical worsening events compared to 256 (68%) in the no BB group (p=0.27). Similarly, overall mortality was not significantly different between the two cohorts (52% *versus* 49%, respectively; p=0.57). Kaplan–Meier survival analysis did not show a significant difference between the two groups with respect to overall survival (p=0.46) and TtCW (p=0.34) (fig. 3).

In order to eliminate selection bias, we performed further Kaplan–Meier estimations comparing the three groups of our study population: no BB, BB and partial BB. Overall survival and TtCW events were comparable between the three groups (fig. 4).

Propensity matching was performed to obtain aOR for mortality. All the co-variates (online fig. S1) were included in the final model to analyse outcomes of β-blocker treatment. The aOR for mortality was 1.13 (95% CI 0.69–1.82) and for clinical worsening events was 0.96 (0.55–1.68) with β-blocker therapy (table 3). The propensity-adjusted analysis for probability of survival, as well as TtCW, stratified by β-blocker therapy, was not significantly different (fig. 3). The aOR for mortality with β-blocker use was 0.98 (95% CI 0.57–1.69) at 5 years and 0.44 (95% CI 0.25–0.77) at 10 years for the overall study population. Similarly, aOR for clinical worsening events with β-blocker use was 0.73 (95% CI 0.42–1.27) at 5 years and 0.54 (95% CI 0.30–0.99) at 10 years.

Impact of β-blocker therapy on functional outcomes

The NYHA class distribution at diagnosis was similar between the two groups (p=0.52). Over a 5-year follow-up period, the NYHA class did not change significantly with β-blocker therapy (table 3). We combined the study patients into two subcategories: NYHA classes I and II, and NYHA classes III and IV, for time-to-event analysis. Use of β-blockers did not lead to a significant impact in the probability of overall survival and TtCW based on the severity of NYHA class at diagnosis (fig. 5).

At baseline, the 6MWD was comparable between the patients in the BB and no BB groups (286±111 m *versus* 303±102 m, p=0.15). By propensity-matched analysis, follow-up 6MWD was not significantly different between the groups. Nonetheless, PAH patients on β-blocker therapy walked a mean 23 m less during follow-up 6MWD (table 3).

We also analysed the impact of different β-blockers on survival and likelihood of clinical worsening events (online fig. S2). The three major β-blockers used in our study population were metoprolol, atenolol and carvedilol. There were no significant differences in probability of survival or clinical worsening events with the use of any individual β-blocker compared to no β-blocker.

Analysis of CTD-PAH and IPAH subgroups for survival and clinical worsening

We assessed propensity score-adjusted survival and TtCW of our subcategories of patients: IPAH and CTD-PAH. Propensity score-adjusted overall survival and TtCW were comparable between the BB and no BB groups in IPAH and CTD-PAH (fig. 3). However, Kaplan–Meier estimation in IPAH patients suggested that those taking β-blockers had a trend towards more clinical worsening events, although it did not reach the threshold for significance. We performed further survival and likelihood of clinical worsening events analysis in the IPAH subset, excluding those patients with comorbidities such as diabetes, renal failure, hypertension and atrial fibrillation (online fig. S3). The outcomes did not change significantly.

Discussion

The present study is the largest single-centre cohort study to date to address directly the issues related to β-blocker use in pulmonary hypertension. Our analysis showed that IPAH and CTD-PAH patients on β-blocker therapy had similar survival, clinical worsening and TtCW rates compared to patients not taking β-blockers. We also found that β-blockers were used frequently in patients with PAH for their comorbid conditions and a significant proportion of them developed side-effects. We found no significant difference in measures of functional outcomes between the two groups.

Limited data are available in the literature addressing clinical outcomes of β-blocker use in PAH patients. Provencher *et al.* [14] first described the deleterious effects of β-blockers in the setting of porto-pulmonary hypertension. We excluded those patients from the current study because most of them are likely to be on β-blockers and we expected that a much higher proportion of those patients would develop clinical worsening, confounding the overall results.

More recently, a small prospective nonrandomised study described no harmful effects of β-blocker use in all categories of PAH patients [15]. The study found that the use of β-blockers did not increase odds of death, clinical worsening or hospitalisations for worsening of pulmonary hypertension by univariate or multivariate analysis. Although the outcomes of the two studies are strikingly similar, there are fundamental differences between our analysis and the previously published study. The previous analysis included an admixture of all patients belonging to group I PAH as described in the Dana Point

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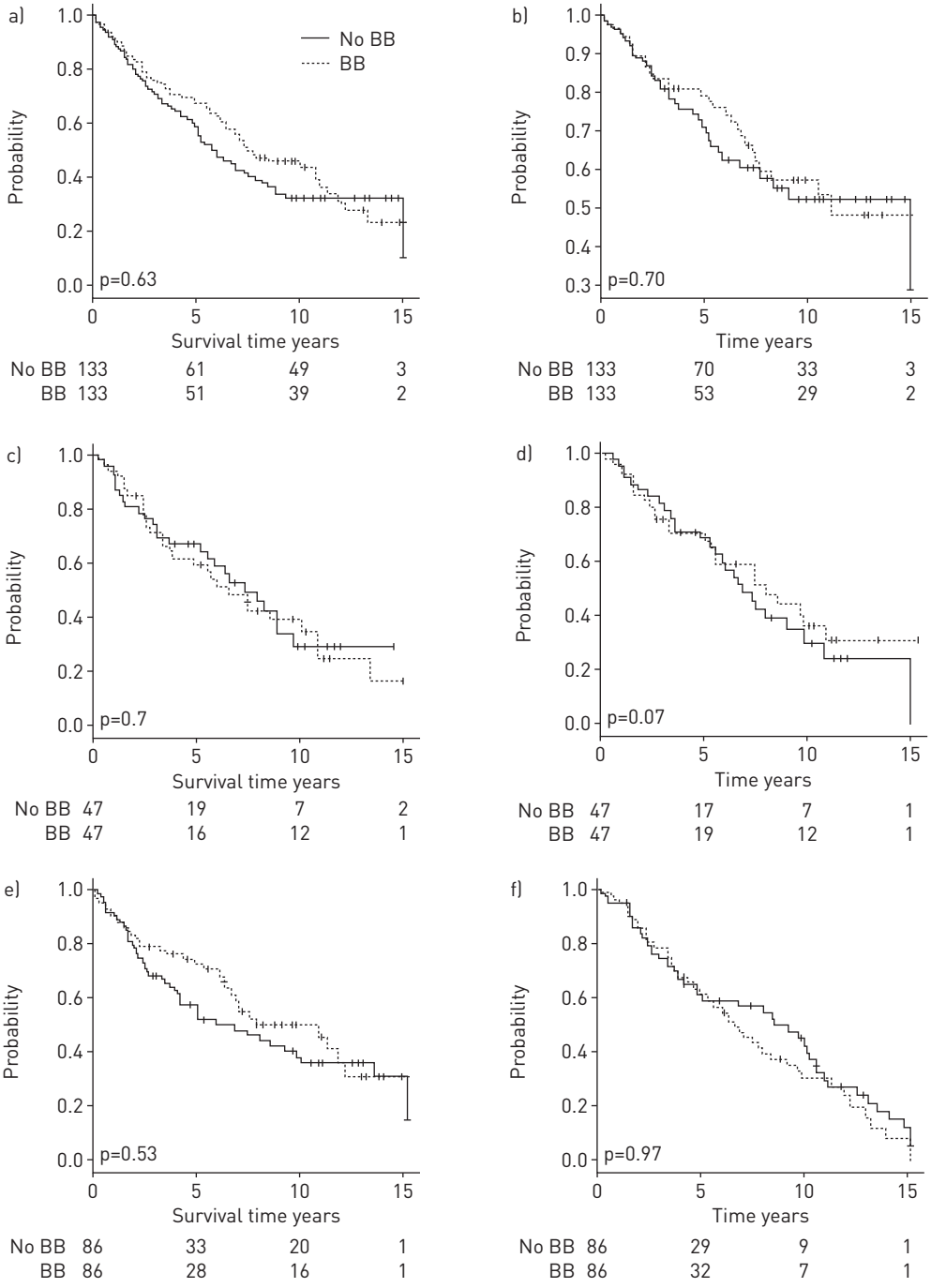
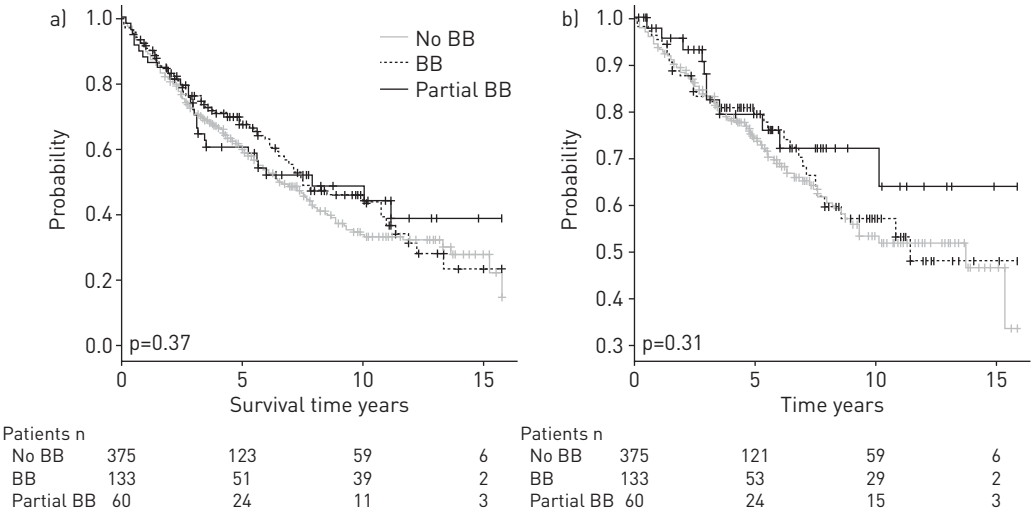


FIGURE 3 Propensity score-adjusted Kaplan–Meier analysis. a) Estimated survival of entire study cohort stratified by β-blocker therapy (relative risk 0.92, 95% CI 0.66–1.28; p=0.63); b) probability of clinical worsening over time in study patients stratified by β-blocker therapy (relative risk 0.93, 95% CI 0.66–1.32; p=0.70); c) probability of survival stratified by β-blocker therapy in the idiopathic pulmonary arterial hypertension (IPAH) subgroup (relative risk 0.57, 95% CI 0.31–1.05; p=0.7); d) estimated clinical worsening events stratified by β-blocker therapy in IPAH patients (relative risk 0.69, 95% CI 0.46–1.02; p=0.07); e) estimated survival with β-blocker therapy in the connective tissue disease pulmonary arterial hypertension (CTD-PAH) subgroup (relative risk 1.14, 95% CI 0.76–1.70; p=0.53); f) probability of clinical worsening events with β-blocker therapy in the CTD-PAH cohort (relative risk 1.01, 95% CI 0.72–1.41; p=0.97). Numbers beneath each chart denote the populations at risk. The aOR for mortality with β-blocker use is 0.98 (95% CI 0.57–1.69) at 5 years and 0.44 (95% CI 0.25–0.77) at 10 years for the overall study population. Similarly, aOR for clinical worsening events with β-blocker use is 0.73 (95% CI 0.42–1.27) at 5 years and 0.54 (95% CI 0.30–0.99) at 10 years. BB: patients who used β-blockers and continued to do so until they reached the end-points of the study; no BB: patients who had never used β-blockers.



Patients n				
No BB	375	123	59	6
BB	133	51	39	2
Partial BB	60	24	11	3

Patients n				
No BB	375	121	59	6
BB	133	53	29	2
Partial BB	60	24	15	3

FIGURE 4 Outcome analyses of the three groups of the study population: patients in the BB group continued to use a β-blocker; the no BB group had never used β-blockers and the partial BB group had started β-blocker therapy but it was discontinued because of side-effects. Numbers beneath each chart denote the populations at risk. a) Kaplan–Meier plot of probability of survival stratified by β-blocker therapy (relative risk 0.92, 95% CI 0.78–1.10; p=0.37); b) Kaplan–Meier plot of estimated time to clinical worsening events stratified by β-blocker therapy (relative risk 0.92, 95% CI 0.81–1.07; p=0.31).

classification of pulmonary hypertension. Unlike the previous study, we have a much larger cohort: the previous study had a total of 94 patients, while 508 patients particpiated in the present study. In addition, we selected a subset of group I PAH patients, who were followed-up for a much longer period (median follow-up 78 *versus* 20 months, respectively). Furthermore, different methodologies were used in the two studies: we performed a 1:1 propensity-matched analysis for our cohort, whereas the previous study included univariate and multivariate analysis.

While there were some differences between the two groups at baseline and following PAH-related therapy, we corrected those covariates by propensity matching. Our results did not change significantly following a propensity-matched analysis to calculate survival and TtCW events to account for significant differences between the groups. Our finding of survival with β-blocker is also corroborated in a study involving a much smaller patient cohort with a shorter follow-up period [16]. However, the present study also includes an extensive analysis of clinical worsening events and functional outcomes.

Attention has recently been focused on neurohormonal alterations in PAH patients and abnormalities of the sympathetic nervous system, similar to those described in left ventricular dysfunction [5, 6, 17]. Our clinical findings correlate with the accumulating evidence of sympathetic overactivation in patients with

TABLE 3 Effects of β-blocker therapy in pulmonary arterial hypertension patients: propensity-adjusted outcome analysis

	Unadjusted	Optimal matching
Mortality OR (95% CI)	1.11 (0.75–1.66)	1.13 (0.69–1.82)
Clinical worsening events OR (95% CI)	1.01 (0.64–1.60)	0.96 (0.55–1.68)
Transplant OR (95% CI)	1.02 (0.46–2.23)	1.17 (0.39–3.47)
Hospitalisation OR (95% CI)	0.89 (0.60–1.32)	1.06 (0.66–1.32)
NYHA class change from baseline		
Year 1	-0.12 (-0.35–0.10)	0.03 (-0.24–0.30)
Year 3	0.11 (-0.53–0.31)	0.07 (-0.53–0.40)
Year 5	0.24 (-0.01–0.49)	0.17 (-0.15–0.48)
6MWD m		
Baseline	-15 (-42–12)	-3 (-36–30)
Follow-up	-15 (-50–20)	-23 (-69–22)

Data are presented as mean difference (95% CI), unless otherwise stated. NYHA: New York Heart Association; 6MWD: 6-min walking distance.

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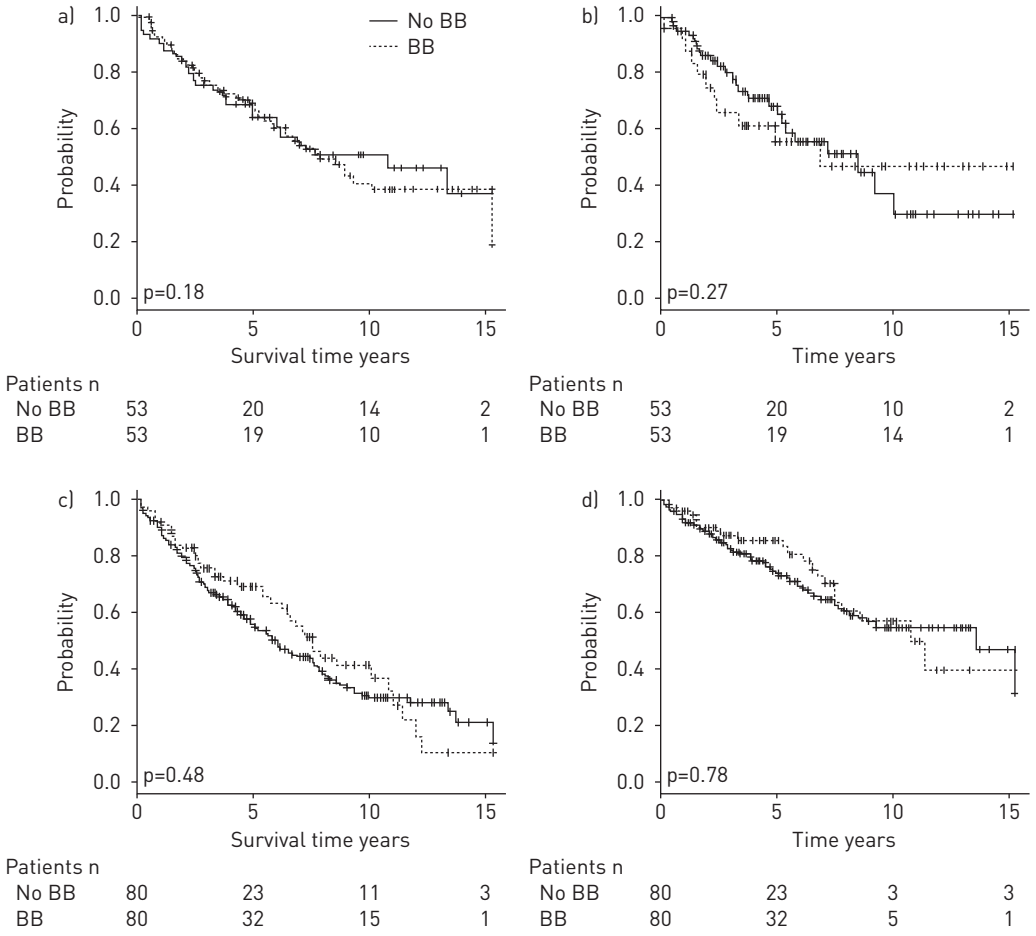


FIGURE 5 Propensity-matched outcome analyses based on New York Heart Association (NYHA) class at presentation. The study population was divided into two groups: NYHA classes I and II and NYHA classes III and IV at diagnosis. Numbers beneath each chart denote the populations at risk. a) Kaplan–Meier plot of estimated survival with β-blocker therapy for those patients in NYHA classes I and II at presentation (relative risk 0.71, 95% CI 0.43–1.17; p=0.18); b) Kaplan–Meier plot of likelihood of clinical worsening events over time with β-blocker therapy for those patients in NYHA classes I and II at presentation (relative risk 0.78, 95% CI 0.51–1.21; p=0.27); c) Kaplan–Meier plot of estimated survival with β-blocker therapy for those patients in NYHA classes III and IV at presentation (relative risk 1.19, 95% CI 0.74–1.91; p=0.48); d) Kaplan–Meier plot of likelihood of clinical worsening events over time with β-blocker therapy for those patients in NYHA classes III and IV at presentation (relative risk 1.05, 95% CI 0.72–1.54; p=0.78). BB: patients who used β-blockers and continued to do so until they reached the end-points of the study; no BB: patients who had never used β-blockers.

PAH. The increase in sympathetic activation in PAH patients [18] could be the cause or the consequences of RV failure. In either case, sympathetic stimulation leads to reduced chronotropic response to exercise, delayed heart rate recovery and ventilatory inefficiency, impairing exercise capacity [19, 20]. The beneficial effect of chronic β blockade on sympathetic activity is likely to be counterbalanced by this negative chronotropic effect during exercise. In our cohort, patients in the BB group showed a trend of lower 6MWD at baseline, despite similar haemodynamic characteristics to the no-BB group, and walked a shorter distance on follow-up 6MWT.

In this context, we reported that patients with IPAH had a reduced TtCW if they had reduced heart rate recovery (HRR) after 6MWT [6]. Interestingly, the reduced HRR was associated with a reduced chronotropic response during 6MWT and the majority (67%) of the patients taking β-blockers had a reduced HRR.

Opponents of β-blocker use in PAH patients have postulated that increased heart rate is required to maintain and increase cardiac output, already compromised by a reduced and fixed stroke volume [21]. In this context, a significant number of our patients had their β-blocker therapy stopped because of fatigue (11%), worsening shortness of breath (23%) and volume overload (20%). Bradycardia, hypotension and syncope together accounted for β-blocker withdrawal in 36% of the patients. Patients on β-blockers also tended to walk a shorter distance in the 6MWT.

It is interesting to note that the patients on β-blockers did not have worse outcomes, irrespective of NYHA functional class at baseline. Bouallal *et al.* [22] demonstrated the beneficial effects of β-blockers in RV dysfunction, with improvement of RV ejection fraction and NYHA class. However, the patients in that study had RV dysfunction secondary to congenital heart diseases. Beneficial effects of β-blockers in reversing RV remodelling and function have been demonstrated experimentally [8]. de Man *et al.* [11] showed that bisoprolol delays the progression of RV failure and preserves RV function in experimental pulmonary hypertension. Martyniuk *et al.* [23] demonstrated improvement in RV size and function with nebivelol treatment in a small population of IPAH patients. Our findings suggest no significant difference in the severity functional NYHA class on follow-up with or without BB use. This correlates with the data published by So *et al.* [15], although our β-blocker cohort had a shorter 6MWD at baseline.

Our study also showed a trend towards more clinical worsening events in IPAH patients, as opposed to survival. This trend is quite interesting but not easy to explain. Further analysis reveals that the trend towards longer TtCW in IPAH patients taking β-blockers ($p=0.07$) is not due to a difference in survival ($p=0.7$), and not likely to be due to lung transplant, since there were only a few with similar percentages in both groups (7% in each group, $p=0.97$) (table 1). Thus, it is most likely that this trend is due to differences in hospitalisations. However, it would be difficult to speculate why this would occur.

The lengthy duration of our study was useful for maintaining adequate patient numbers. The therapy and care of some patients may have changed over time, which may have introduced some confounders. Nevertheless, we believe that all the potential measurable cofounders for outcome were matched by propensity score. In our study, the partial BB group was excluded from propensity analysis for the comparison of two matched population. The intention-to-treat approach to β-blocker therapy is of debatable clinical significance in this regard. How β-blocker use for a brief duration may impact on clinical outcomes over a long-term follow-up is unclear, but certainly should not be considered effect- or disease-modifying. We acknowledge that the exclusion of this group could lead to a potential selection bias; however, our survival and TtCW analysis comparing the three different groups did not show any significant differences.

The current study has few limitations. It is a retrospective analysis, which accounts for some of the weaknesses inherent to the study design, such as selection bias. Few data were missing and missing values were imputed; however, the total imputed data accounted for <5%, which is within the acceptable range. Some of the baseline variables were different among the two groups and we attempted to correct for those confounders by propensity-matched analysis. Moreover, the current study does not address the safety and efficacy of initiation of β-blocker use in PH patients.

In conclusion, our analysis showed that long-term use of β-blockers in pulmonary hypertension patients is not associated with any deleterious effects in terms of overall survival or clinical worsening events. However, a significant number of patients did experience side-effects necessitating the withdrawal of therapy. Patients taking β-blockers did not show any significant worsening of NYHA functional class, but their 6MWD was lower than the patients in the no-BB group. Based on our data and the current literature, there is equipoise about the use of β-blockers in PAH patients, and a prospective controlled study would help to clearly define the beneficial or harmful role of β-blockers in these patients.

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