CHEST

# Effects of β-Blockers on the Outcomes in Patients With Pulmonary Arterial Hypertension Stratified by the Presence of Comorbid Conditions

## A Multicenter Prospective Cohort Study: The Database of Pulmonary Hypertension in the Polish Population (BNP-PL)

*Marcin Waligóra, MD, PhD; Marcin Kurzyna, MD, PhD; Tatiana Mularek-Kubzdela, MD, PhD; Ilona Skoczylas, MD, PhD; Łukasz Chrzanowski, MD, PhD; Piotr Błaszczak, MD, PhD; Miłosz Jaguszewski, MD, PhD; Beata Kuśmierczyk, MD, PhD; Katarzyna Ptaszyńska, MD, PhD; Grzegorz Grześk, MD, PhD; Katarzyna Mizia-Stec, MD, PhD; Ewa Malinowska, MD, PhD; Małgorzata Peregud-Pogorzelska, MD, PhD; Ewa Lewicka, MD, PhD; Michał Tomaszewski, MD, PhD; Wojciech Jacheć, MD, PhD; Michał Florczyk, MD, PhD; Ewa Mroczek, MD, PhD; Zbigniew Gąsior, MD, PhD; Agnieszka Pawlak, MD, PhD; Katarzyna Betkier-Lipińska, MD, PhD; Piotr Pruszczyk, MD, PhD; Katarzyna Widejko, MD, PhD; Wiesława Zabłocka, MD, PhD; and Grzegorz Kopeć, MD, PhD*

**BACKGROUND:** Current guidelines do not recommend β-blockers in pulmonary arterial hypertension (PAH) unless indicated by comorbidities. However, the evidence regarding the role of β-blockers in PAH is contradictory.

**RESEARCH QUESTION:** What are the effects of β-blockers on clinical outcomes in patients newly diagnosed with PAH, and how do these outcomes differ based on the presence of cardiovascular comorbidities that are standard indications for β-blocker use?

**STUDY DESIGN AND METHODS:** We analyzed data from 806 patients newly diagnosed with PAH enrolled prospectively in the Database of Pulmonary Hypertension in the Polish Population (BNP-PL). The end points were all-cause mortality and a composite of hospitalization due to right-sided heart failure, syncope, or death. Indications for β-blocker use included hypertension, significant arrhythmia, and coronary artery disease. Propensity score matching was used to form a control group based on age, PAH mortality risk variables, and initially introduced PAH-specific therapy.

**RESULTS:** Of the 806 patients, 469 (58.2%) received β-blockers at the time of PAH diagnosis. In propensity score matching, β-blocker treatment showed a higher incidence of the composite end point (hazard ratio, 1.44; 95% CI, 1.04-1.99; $P = .03$) and had a neutral impact on mortality (hazard ratio, 1.22; 95% CI, 0.87-1.72; $P = .25$). When stratified according to the presence of comorbidities, β-blockers showed adverse effects on the composite end point in patients without comorbidities and a neutral effect in patients with at least one comorbidity.

**INTERPRETATION:** Our results indicate that β-blockers pose significant risks in patients with PAH, especially in patients without coexisting systemic hypertension, coronary artery disease, or arrhythmia.

**CLINICAL TRIAL REGISTRATION:** ClinicalTrials.gov; No.: NCT03959748; URL: www.clinicaltrials.gov.

CHEST 2025; 167(4):1171-1181

**KEY WORDS:** β-blockers; BNP-PL; cardiovascular comorbidities; PAH registry; pulmonary arterial hypertension

FOR EDITORIAL COMMENT, SEE PAGE 935

## Take-Home Points

**Study Question:** What is the impact of β-blocker therapy on clinical outcomes in patients newly diagnosed with pulmonary artery hypertension, and how does the presence of cardiovascular comorbidities influence these effects?

**Results:** In propensity score-matched analysis, β-blocker treatment showed a higher incidence of the composite end point and no change in mortality. In addition, β-blocker treatment increased the risk of the composite end point in patients without comorbidities, while having a neutral effect in patients with hypertension, coronary artery disease, significant arrhythmias, or the presence of ≥ 2 comorbidities.

**Interpretation:** Our results indicate that β-blockers pose a significant risk if used in patients with PAH without specific indications for their use.

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by increased pulmonary vascular resistance leading to right ventricular (RV) failure and ultimately death. The mechanism of vessel narrowing involves vasoconstriction and vessel wall remodeling.[1]

The current treatment strategy in PAH aims to regulate pulmonary vascular tone by combining different pulmonary vasodilators, which induce the nitric oxide/cyclic guanosine monophosphate and the prostacyclin/cyclic adenosine monophosphate pathways and inhibit the endothelin-1 pathway. The role of targeting the activin signaling pathway in treating PAH has recently been reported.[2,3]

β-Blockers are a group of drugs broadly used in various cardiovascular diseases. Guideline-supported clinical algorithms indicate their role in heart failure with reduced left ventricular ejection fraction,[4] systemic hypertension,[5] cardiac arrhythmias,[6,7] and coronary artery disease (CAD).[8] These diseases are widespread in the PAH population as shown by national and international registries.[9,10]

Considering the pharmacodynamics of β-blockers, their use may be limited in PAH because they reduce cardiac output[11,12] and systemic BP and inhibit the relaxation of pulmonary arteries.[13] However, clinical evidence regarding their role in this group of patients is contradictory.[11,12,14-19] Therefore, the European Society of Cardiology guidelines based on expert consensus (Level of Evidence C)[20] discourage use of β-blockers in patients with PAH unless indicated by comorbidities.

The aim of the current study was to validate or challenge this expert consensus statement. We thus assessed the effect of β-blockers on long-term clinical outcomes in a large prospective cohort of patients newly diagnosed with PAH, stratified according to the presence of cardiovascular comorbidities such as systemic

**ABBREVIATIONS:** BNP-PL = Database of Pulmonary Hypertension in the Polish Population; CAD = coronary artery disease; HR = hazard ratio; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary artery hypertension; RV = right ventricular; WHO = World Health Organization

**AFFILIATIONS:** From the Department of Cardiac and Vascular Diseases (M. W. and G. K.), St. John Paul II Hospital; Pulmonary Circulation Centre (M. W. and G. K.), Department of Cardiac and Vascular Diseases, and Center for Innovative Medical Education (M. W.) Faculty of Medicine, Jagiellonian University Medical College, Krakow; Department of Pulmonary Circulation (M. K. and M. F.), Thromboembolic Diseases and Cardiology, Centre of Postgraduate Medical Education, Fryderyk Chopin Hospital in European Health Centre, Otwock; Department of Cardiology (T. M.-K.), Poznan University of Medical Sciences, Poznan, Poland; 3rd Department of Cardiology (I. S.), Faculty of Medical Sciences in Zabrze, and First Department of Cardiology (K. M.-S.), School of Medicine in Katowice, Medical University of Silesia, Katowice; Cardiology Department (Ł. C.), Medical University of Lodz, Lodz; Department of Cardiology (P. B.), Cardinal Wyszynski Hospital, Lublin; 1st Department of Cardiology (M. J.), and the Department of Cardiology and Electrotherapy (E. L.), Medical University of Gdansk, Gdansk; Department of Congenital Heart Disease (B. K.), Institute of Cardiology, Warsaw; Department of Cardiology (K. P.), Medical University of Bialystok, Bialystok; Department of Cardiology and Clinical Pharmacology (G. G.), Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Toruń; Pulmonary Department (E. Malinowska), University of Warmia and Mazury, Olsztyn; Department of Cardiology (M. P.-P.), Pomeranian Medical University, Szczecin; Department of Cardiology (M. T.), Medical University of Lublin, Lublin; 2nd Department of Cardiology (W. J.), Faculty of Medical Sciences in Zabrze, Silesian Medical University in Katowice; Department of Cardiology (E. Mroczek), Institute of Heart Diseases, Wroclaw Medical University; Department of Cardiology (Z. G.), School of Health Sciences, Medical University of Silesia in Katowice, Katowice; Department of Invasive Cardiology (A. P.), Polish Academy of Sciences, Mossakowski Medical Research Centre, Central Clinical Hospital of the Ministry of Interior; Department of Cardiology and Internal Medicine (K. B.-L.), Military Institute of Medicine-National Research Institute; Department of Internal Medicine and Cardiology (P. P.), Center for Diagnosis and Treatment of Venous Thromboembolism, Medical University of Warsaw; Department of Cardiology (K. W.), Copper Health Center, Lubin; and the Department of Cardiology (W. Z.), Provincial Specialist Hospital, Szczecin, Poland.

Some results from this article were previously presented as a poster at the 2024 European Society of Cardiology Congress, August 30-September 2, 2024, London, United Kingdom.

**CORRESPONDENCE TO:** Grzegorz Kopeć, MD, PhD; email: grzegorzkrakow1@gmail.com



**DOI:** https://doi.org/10.1016/j.chest.2024.10.051

hypertension, CAD, and arrhythmias, which are the standard indications for β-blockers in the general population. We also analyzed the effect of different classes of β-blockers on patients' prognosis.

## Study Design and Methods

This study used data from the Database of Pulmonary Hypertension in the Polish Population (BNP-PL), a prospective, multicenter registry, the protocol of which has been described previously in detail.[21] For the current analysis, we assessed only prospectively enrolled incident cases, defined as patients who were diagnosed with PAH (group 1 according to the European Society of Cardiology and the European Respiratory Society classification with the exclusion of patients with idiopathic PAH who are responders at acute vasoreactivity testing) between March 1, 2018, and August 31, 2023. Data were contributed by 20 of 21 Polish participating centers; data from one center were excluded from the analysis due to inadequate follow-up data as of August 2023. The study is registered at ClinicalTrials.gov.[22]

Based on the guidelines of the European Society of Cardiology,[5-8] we selected a group of cardiovascular comorbidities that are considered indications for the use of β-blockers, namely: CAD, significant arrhythmias (defined by the presence of atrial flutter, atrial fibrillation, or history of sustained supraventricular tachycardia or any ventricular tachycardia), and systemic arterial hypertension. Patients with left-sided heart failure with reduced ejection fraction are also considered candidates for therapy with β-blockers; however, this group was excluded a priori because they represent group 2 in the World Health Organization (WHO) PAH classification. To mitigate the impact of potential confounding factors in the study, we used propensity score matching by evenly dividing patients according to whether they were treated and not treated with β-blockers.

The initial risk of each individual patient was calculated at the time of PAH diagnosis based on a 3-strata risk model recommended by the European Society of Cardiology. The following parameters were considered: WHO functional class, 6-minute walk distance, blood N-terminal pro-B-type natriuretic peptide levels (NT-proBNP), right atrial area as measured by echocardiography, presence of pericardial effusion, mean right atrial pressure, cardiac index, mixed venous oxygen blood saturation, and stroke volume index. Each parameter was categorized based on the corresponding mortality risk (low, intermediate, high) and assigned 1, 2, or 3 points. The sum of points was divided by the number of assessed parameters. The mean grade was rounded to the nearest integer, and the results were used to define the patient's risk group. The PAH targeted drugs administered within the first 3 months following the PAH diagnosis were defined as the initially introduced treatment.

### Follow-Up

Two primary end points were considered: all-cause mortality and a composite end point comprising hospitalization due to right-sided heart failure, syncope, or death. For all-cause mortality, patients were followed up until death, with observation time censored at the time of lung transplantation or on August 31, 2023, if neither event occurred. For the composite end point, patient follow-up was censored at the time of the first event, which could include hospitalization due to right-sided heart failure or syncope, or death. If none of these events occurred, the observation time was censored at lung transplantation or on August 31, 2023. Lung transplantation was treated as a censoring time, not as an event.

### Ethical Considerations

The study protocol adhered to the ethical guidelines of the Declaration of Helsinki and was reviewed and accepted by the local bioethical committee (OIL/KBL/27/2018).

### Statistical Analysis

Categorical variables are presented as counts (percentages). Continuous variables are presented as means ± SD or medians with quartiles (Q1, Q3) for skewed distributions. Details are provided in the Skewness section of e-Appendix 1.

Survival analysis was performed by using the Kaplan-Meier method with the $\chi^2$ test. Outcome analysis was adjusted for variations in baseline characteristics using propensity score analysis between the 2 groups (treated and not treated with β-blockers) to minimize the impact of initial treatment variations and baseline risk scores. Caliper matching was performed at a 1:1 ratio without replacements, using a caliper of 0.1, ensuring alignment on key covariables: age, type of initial therapy (monotherapy, dual therapy, or triple combination therapy), mean pulmonary artery pressure, pulmonary vascular resistance, and other mortality risk variables (NT-proBNP level, 6-minute walk distance, cardiac index, and right atrial area). The propensity score model

was verified by comparing covariate distributions between the 2 patient groups using standardized mean differences, with details provided in e-Appendix 1.

To compare the effect of β-blocker type (nonselective vs selective), a secondary propensity score matching was performed by using caliper matching at a ratio of 1:5 without replacements with a caliper ratio of 0.1, aiming an optimal alignment on key covariables (age, type of initial therapy [monotherapy, dual therapy, or triple combination therapy], and mortality risk variables) while retaining all patients treated with nonselective β-blockers.

Forest plots were drawn according to the results of Cox proportional hazards regression models, which were conducted separately within subgroups based on the presence or absence of comorbidities. The hazard ratio (HR) for the end point was estimated where β-blocker use was treated as a predictor variable. The number-needed-to-harm calculation is presented in e-Appendix 1.

Statistical analysis was conducted in accordance with established standards and guidelines[23] and were executed by using the Dell Statistica data analysis software system version 13.3 (TIBCO Software Inc) and MedCalc version 19.2.6 (MedCalc Software).

## Results

### Group Characteristics

The study enrolled 806 patients newly diagnosed with PAH, including patients with idiopathic PAH (n = 439 [54.5%]), PAH associated with connective tissue disease (n = 176 [21.8%]), congenital heart disease (n = 147 [18.2%]), portopulmonary PAH (n = 20 [2.5%]), and other types of PAH (n = 24 [3%]). The majority were in WHO functional class III (57.8%). A comprehensive overview of patient characteristics is presented in Table 1, while the extended data, including *P* values and skewness coefficients, are detailed in e-Table 1. The detailed flowchart illustrating the process of patient inclusion and exclusion is depicted in Figure 1.

### Comorbidities

Systemic hypertension was diagnosed in 489 (60.7%) patients, CAD in 118 (14.5%), and arrhythmia in 205 (25.4%). Significant arrhythmia included atrial fibrillation or atrial flutter (n = 201 [24.9%]), atrioventricular nodal re-entrant tachycardia (n = 1), or a history of nonsustained ventricular tachycardia (n = 1). Hypertension existed as a single comorbidity in 277 (56%) patients. Among patients with CAD, most (n = 102 [86.4%]) had at least one additional comorbidity, including hypertension (n = 96 [81.4%]) or significant arrhythmia (n = 51 [43.2%]). Similarly, among 205 patients with arrhythmia, most (n = 168 [82%]) had at least one additional comorbidity, including systemic arterial hypertension (n = 161 [78.5%]) or CAD (n = 51 [24.9%]). There were 331 (41.4%) patients with only 1 comorbidity, 173 (21.4%) patients with 2 comorbidities, and 45 (5.6%) patients with 3 comorbidities. A total of 257 patients, however, did not have any of the 3 specified comorbidities: hypertension, CAD, or arrhythmia. Details of cardiovascular comorbidities are presented in e-Table 2.

### β-Blocker Use

At the time of PAH diagnosis, β-blockers were used by 469 (58.2%) patients. Patients were receiving various types of β-blockers, including selective $\beta_1$-blockers (bisoprolol, n = 226; metoprolol succinate, n = 94; betaxolol, n = 4), a selective $\beta_1$-blocker acting as a $\beta_3$-agonist (nebivolol, n = 106), nonselective β-blockers (carvedilol, n = 25; propranolol, n = 3), and a nonselective β-blocker combined with a class III antiarrhythmic agent (sotalol, n = 10). In one patient, the data on the type of β-blocker were missing. Patients who received β-blockers had 3 (n = 35), 2 (n = 144), or 1 (n = 218) comorbidity. However, 72 (15.4%) patients did not have a clear indication for using β-blockers.

### Unmatched Cohorts

Patients who used β-blockers compared with patients who did not were older, had higher WHO functional class and NT-proBNP levels, shorter 6-minute walk distance, lower mean pulmonary artery pressure and pulmonary vascular resistance, larger right atrial area, a higher mean 3-strata risk score, and more frequent use of PAH treatment in the form of monotherapy. Deaths and hospitalizations due to right-sided heart failure or syncope predominated in the groups of patients using β-blockers.

### Matched Cohorts

A total of 466 patients were included in the propensity score-matched cohort. The set included matched pairs of 233 patients treated with β-blockers and 233 untreated patients, who were similar in terms of confounding factors (Table 1).

### Outcomes

In the propensity score-matched cohort, death occurred in 131 patients (mean time to death, 17.8 ± 14. months)

**TABLE 1** ] Characteristics of the Study Population

| Characteristic | Unmatched Cohort | | | | Matched Cohort | | |
|---|---|---|---|---|---|---|---|
| | Whole Cohort (n = 806) | Treated With β-Blocker (n = 469) | Not Treated With β-Blocker (n = 337) | SMD | Treated With β-Blocker (n = 233) | Not Treated With β-Blocker (n = 233) | SMD |
| Age at PAH diagnosis, y | 66 (52, 73 | 69 (63, 75) | 57 (42, 68) | 0.789 | 65 (55, 75) | 63 (53, 72) | −0.06 |
| Female sex | 542 (67.2%) | 325 (69.3) | 217 (64.4) | −0.104 | 144 (62.23) | 153 (65.67) | −0.07 |
| WHO-FC | | | | | | | |
| I/II | 153 (19) | 74 (15.8) | 79 (23.4) | 0.213 | 49 (21.03) | 46 (19.74) | |
| III/IV | 641 (79.5) | 390 (83.2) | 251 (74.5) | 0.213 | 184 (78.97) | 187 (80.26) | 0.03 |
| Diagnosis of IPAH | 439 (54.5) | 265 (56.5) | 174 (51.6) | 0.098 | 130 (55.79) | 128 (54.94) | −0.02 |
| NT-proBNP, pg/mL | 1,783 (845, 4,186.5) | 2,198.5 (1,006, 4,889.25) | 1,315.5 (635, 3,413.0) | 0.257 | 1,817 (755, 4,150.1) | 1,681.5 (658.75, 3642) | −0.02 |
| 6MWD, m | 273 ± 151.4 | 245 ± 140 | 311 ± 158 | −0.446 | 265.40 ± 139.75 | 272.63 ± 146.47 | 0.05 |
| Right heart catheterization | | | | | | | |
| mPAP, mm Hg | 44 (36, 57 | 41.5 (34, 52) | 48 (39, 60) | −0.421 | 45 (35, 56) | 47 (39, 56) | 0.06 |
| mRAP, mm Hg | 7 (5, 11.25) | 8.0 (5, 11) | 7 (4, 10) | 0.128 | 7 (5, 10) | 7 (4, 10.25) | −0.03 |
| Cardiac index, L/min/$m^2$ | 2.19 (1.83, 2.70) | 2.19 (1.76, 2.60) | 2.20 (1.88, 2.77) | −0.129 | 2.20 (1.86, 2.59) | 2.18 (1.84, 2.66) | −0.092 |
| $SVO_2$ in MVB, % | 63.6 (56.9, 69.6) | 63 (56, 68) | 64 (57, 69.6) | −0.148 | 62.25 (56.1, 68.5) | 62.8 (57, 68.85) | 0.05 |
| PVR, WU | 8.3 (5.39, 12.48) | 7.8 (4.94, 11.89) | 9.36 (6.11, 13.41) | −0.289 | 8.7 (6.2, 12.7) | 9.1 (6.3, 12.9) | 0.01 |
| SVI, mL/$m^2$ | 28.62 (23.22, 36.22) | 29.13 (23.77, 37.40) | 27.93 (23.36, 35.79) | 0.005 | 28.87 (21.84, 35.59) | 27.78 (20.80, 32.31) | −0.05 |
| PAWP, mm Hg | 9.2 ± 3.3 | 9.6 ± 3.3 | 8.6 ± 3.2 | 0.301 | 9.16 ± 3.33 | 8.81 ± 3.30 | −0.1 |
| Echocardiography | | | | | | | |
| RAA, $cm^2$ | 25.0 (19.0, 30.0) | 25.1 (19.0, 30.0) | 24.0 (19.0, 30.0) | 0.224 | 25.0 (19.0, 30.0) | 24.0 (19.0, 30.0) | −0.08 |
| TAPSE, mm | 17.2 ± 4.5 | 17.2 ± 4.3 | 17.1 ± 4,7 | 0.038 | 17.22 ± 4.39 | 16.90 ± 4.45 | 0.06 |
| Presence of pericardial effusion | 171 (21.2) | 101 (21.9) | 70 (21.1) | 0.019 | 49 (21.49) | 52 (22.71) | 0.03 |
| 3-strata risk assessment | | | | | | | |
| Low risk | 98 (12.2) | 41 (8.7) | 57 (16.9) | 0.203 | 29 (13.06) | 26 (11.82) | |
| Intermediate risk | 621 (77) | 375 (80) | 246 (73) | 0.203 | 163 (73.42) | 170 (77.27) | |
| High risk | 87 (10,8) | 53 (11.3) | 34 (10) | 0.203 | 30 (13.51) | 24 (10.91) | −0.03 |
| Mean score | 2 ± 0.41 | 2.04 ± 0.39 | 1.96 ± 0.44 | 0.195 | 2.01 ± 0.43 | 2.02 ± 0.41 | 0.02 |
| Specific therapy | | | | | | | |
| Initial monotherapy | 359 (44.5) | 229 (48.8) | 130 (38.6) | −0.266 | 94 (40.34) | 92 (39.48) | |
| Initial dual combination therapy | 314 (39) | 171 (36.5) | 143 (42.4) | −0.266 | 96 (41.20) | 100 (42.92) | |
| Initial triple combination therapy | 103 (12.8) | 48 (10.2) | 55 (16.3) | −0.266 | 38 (16.31) | 36 (15.45) | 0.017 |

Data are presented as medians (Q1, Q3), No. (%), or mean ± SD. 6MWD = 6-minute walk distance; IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure; mRAP = mean right atrial pressure; MVB = mixed venous blood; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PAWP = pulmonary wedge pressure; PVR = peripheral vascular resistance; RAA = right atrial area; SMD = standardized mean difference; SVI = stroke volume index; $SVO_2$ = venous oxygen saturation; TAPSE = tricuspid annular plane systolic excursion; WHO-FC = World Health Organization functional class.

[a]Yates correction was applied.

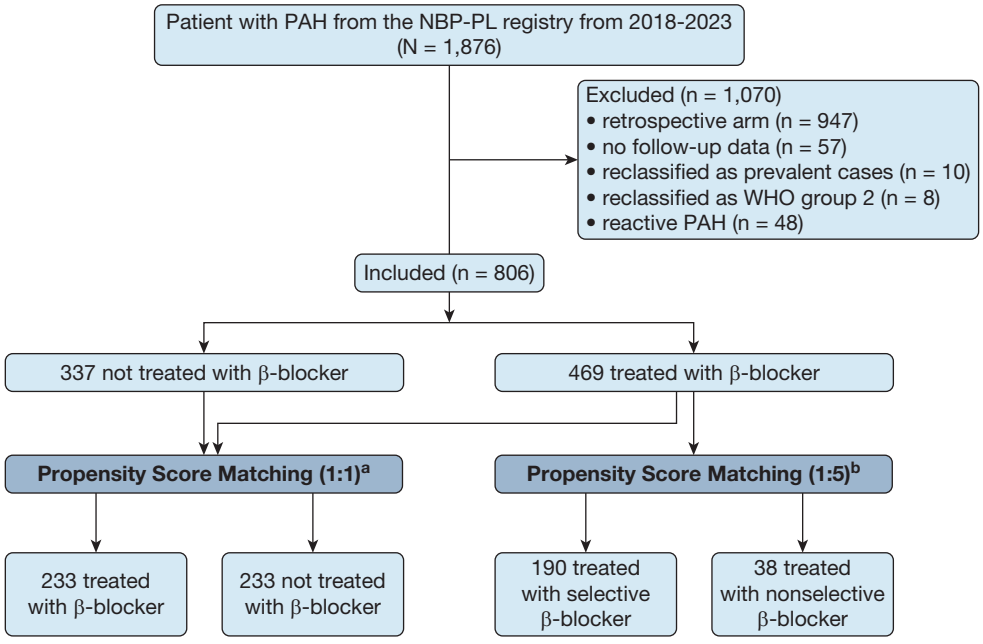


Figure 1 – *Flowchart illustrating the process of patient inclusion and exclusion, detailing the number of patients in each group prior to and following matching. BNP-PL = Database of Pulmonary Hypertension in the Polish Population; PAH = pulmonary arterial hypertension; WHO = World Health Organization. [a]Between patients treated and untreated with β-blockers. [b]Among patients treated with β-blockers according to selectivity.*

and the composite end point occurred in 148 patients (mean time to the first event, 16.8 ± 14.4 months). Treatment with a β-blocker was associated with a significant risk for the composite end point (Kaplan-Meier, $P = .027$) (univariate Cox proportional hazards model: HR, 1.44; 95% CI, 1.04-1.99; $P = .029$) (Fig 2A) but not mortality (Kaplan-Meier, $P = .25$) (univariate Cox proportional

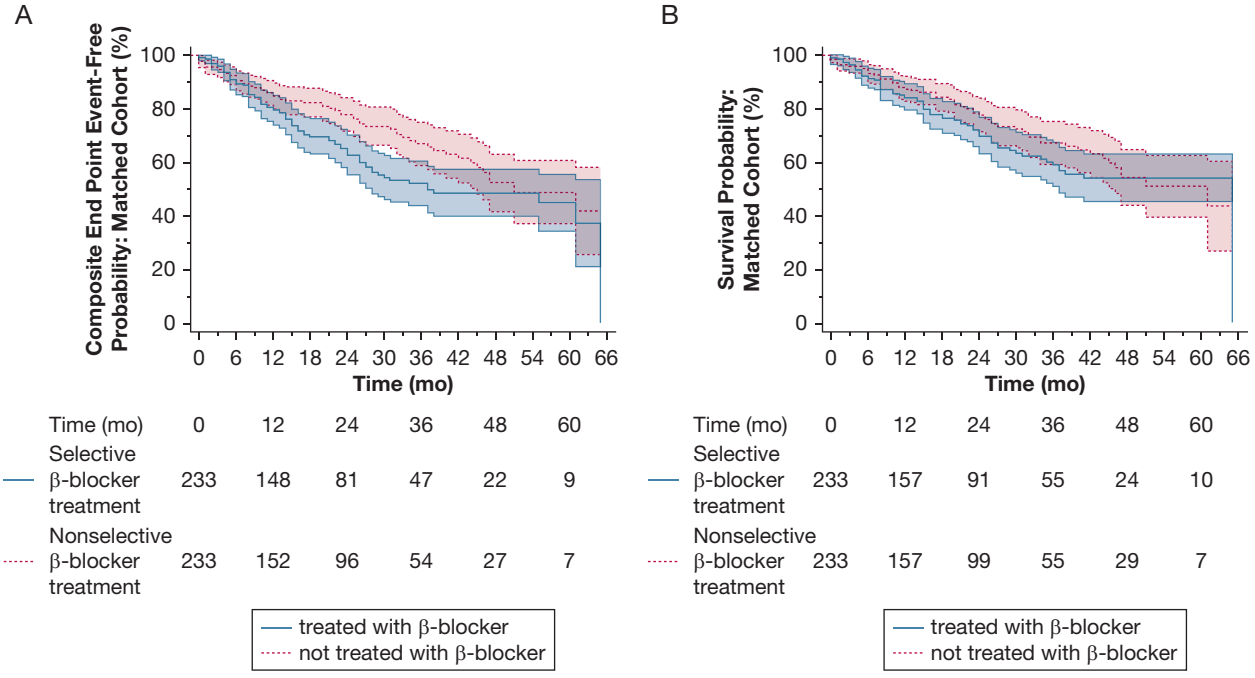


Figure 2 – *A, B, Kaplan-Meier curves. A, Time to the composite end point in the propensity score-matched cohort of patients* (P = .027). *B, Time to all-cause mortality in the propensity score-matched cohort of patients* (P = .25).

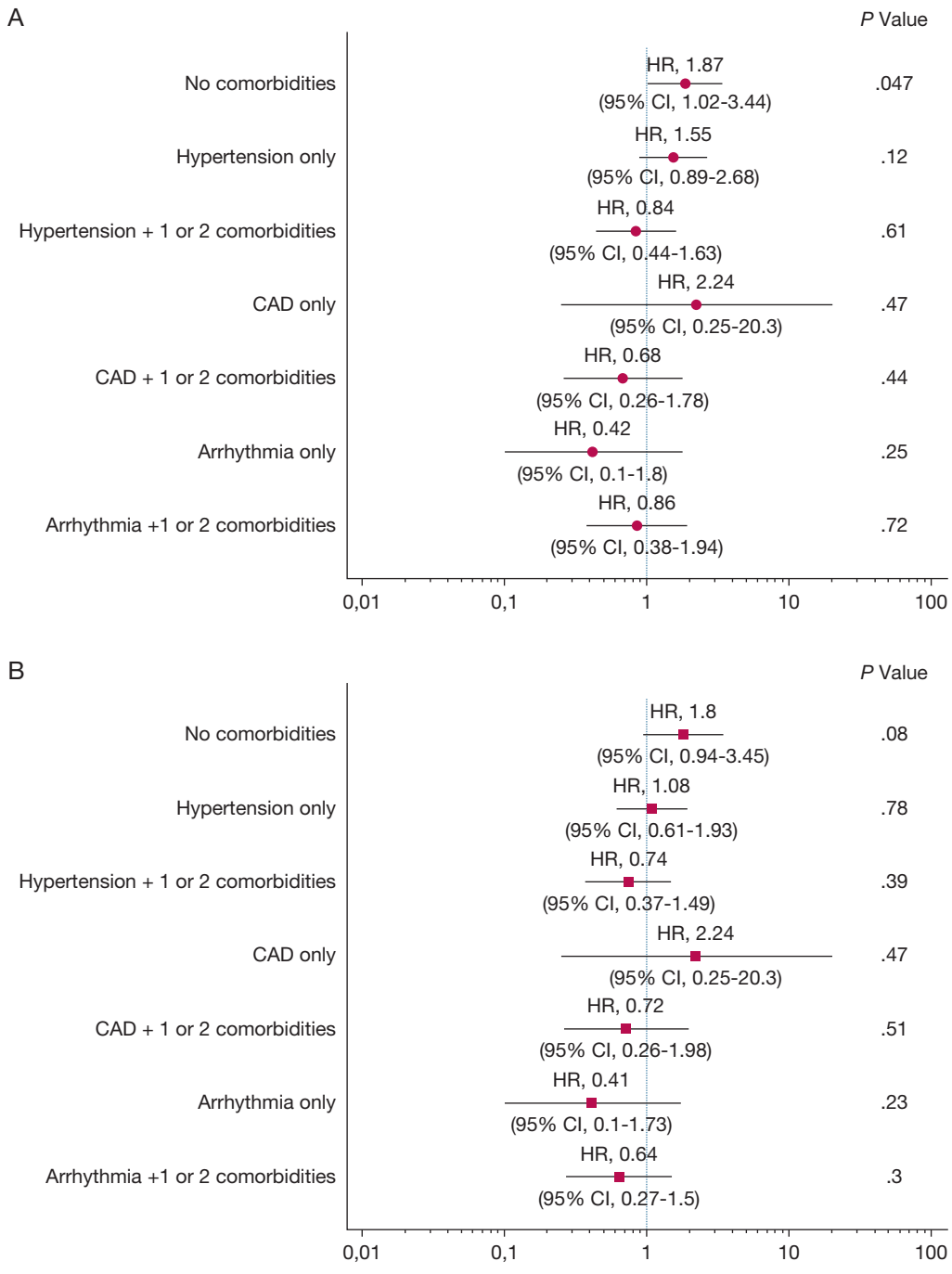


Figure 3 – *Impact of β-blocker therapy on the composite end point (A) and mortality (B) in the propensity score-matched cohort of patients with specific indications to the use of β-blockers. The circles represent the HR for the composite end point, the squares represent the HR for mortality, and the horizontal lines indicate the CI. CAD = cornary artery disease; HR = hazard ratio.*

hazards model: HR, 1.22; 95% CI, 0.87-1.72; $P = .25$) (Fig 2B). The numbers-needed-to-harm for mortality and for the composite end point were 25.91 (95% CI, 8.3-23.3; $P = .35$) and 11.7 (95% CI, 5.88-602.8; $P = .048$), respectively. The effects of β-blockers on outcome in the unmatched cohort are presented in e-Figure 1.

### *Outcomes Stratified According to the Presence of Comorbidities*

As presented in Figure 3 in the matched cohorts, β-blocker use increased the risk of a composite end point in patients without comorbidities and was neutral in patients who had hypertension, CAD, or arrhythmias as single conditions or combination of 2 or 3

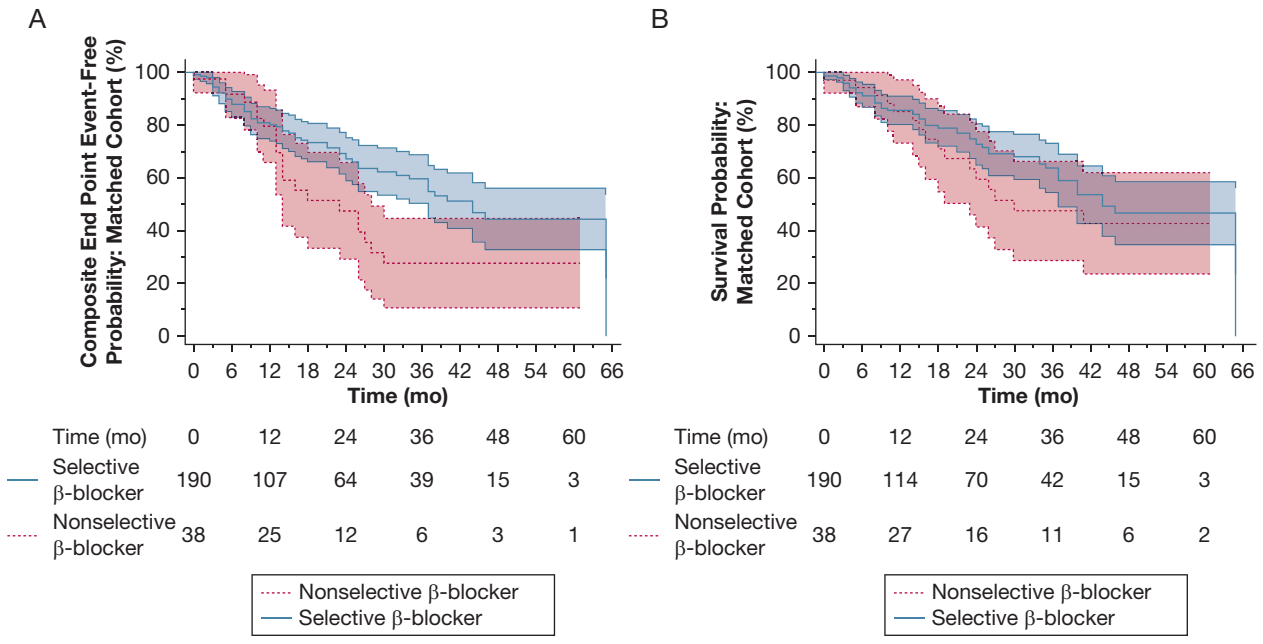


Figure 4 – *Kaplan-Meier curves showing the impact of the type of β-blocker (selective vs nonselective) treatment on mortality (P = .4) (A) and the composite end point (P = .03) (B) in the propensity score-matched cohort.*

comorbidities. In turn, β-blocker use did not affect mortality in the analyzed subgroups.

### *Outcomes Stratified According to β-Blocker Selectivity*

In the secondary propensity score matched cohort, treatment with nonselective agents (both $\beta_1$- and $\beta_2$-antagonists: propranolol, sotalol, carvedilol, n = 38) was associated with a higher risk of the composite end point (HR, 1.69; 95% CI, 1.03-2.79; $P = .038$) than treatment with selective $\beta_1$-agents (metoprolol, bisoprolol, betaxolol, and nebivolol; n = 190). This effect was neutral in terms of all-cause mortality (1.27; 95% CI, 0.72-2.22; $P = .41$). The characteristics of matched groups are presented in e-Table 1. Figure 4 presents the Kaplan-Meier curves for patients treated with a β-blocker according to selectivity.

## Discussion

The current study, to the best of our knowledge, is the largest prospective, multicenter cohort analysis to date providing comprehensive evidence regarding the effects of β-blockers on outcomes in patients newly diagnosed with PAH. Our findings show that β-blockers pose a significant risk of the composite end point of death and hospitalization in this population and that the presence of comorbidities such as hypertension, CAD, or significant arrhythmia overcome this risk. We also found that using nonselective agents compared with selective agents was associated with a higher risk of composite end points.

### *β-Blockers in PAH*

The argument opposing the use of β-blockers in PAH is based on the assumption of a fixed stroke volume that cannot be increased during exercise and on the substantial role of increased heart rate in enhancing cardiac output during periods of physiologic stress.[24] Therefore, β-blockers are thought to lead to hemodynamic compromise in PAH. Conversely, increased mortality in pulmonary hypertension is associated with sympathetic overactivity, and, theoretically, suppressing adrenergic activity could be expected to provide benefits.[25] A small, recently published study showed that esmolol improves RV diastolic function in exercise right heart catheterization in patients with PAH.[26] This was due to an increase in RV end-diastolic volume index and a decrease in RV end-diastolic pressure. Conversely, selective infusion of esmolol in that study resulted in a significant decrease in the RV ejection fraction.

Studies on the impact of β-blockers in various clinical cohorts of patients with PAH has generated unequivocal findings. In a cohort study involving 94 patients with PAH, 28% of whom received β-blockers, a 20-month follow-up revealed no significant alterations in pulmonary hemodynamics, RV size, or function.[17]

Despite a slightly higher percentage of adverse events (death or PAH-related hospitalization) in the β-blocker group (50%) compared with the no-β-blocker group (35%), the difference did not reach statistical significance ($P = .19$). In another retrospective analysis involving 564 patients with PAH who were referred to a single center between 1982 and 2013, 12.5% were treated with β-blockers.[27] Initially, β-blocker use was linked to increased all-cause mortality (unadjusted HR, 1.4). However, following propensity score matching and adjustments, the risk associated with β-blocker use was statistically nonsignificant (HR, 1.0). Similar findings came from a retrospective study from a single pulmonary hypertension center involving 508 patients with PAH, 26.2% of whom used β-blockers.[28] No significant differences were noted in the probability of survival or time to clinical worsening events; however, patients taking β-blockers covered a shorter 6-minute walk distance in the follow-up.

However, small-scale studies provide evidence of the potential harmful effects of β-blockers in the PAH population and a beneficial effect of their withdrawal. For instance, in a study of 10 patients with portopulmonary hypertension, discontinuation of β-blocker treatment resulted in an enhanced exercise capacity and improved pulmonary hemodynamics in 90% of cases.[11] This improvement was ascribed to an increase in cardiac output, primarily influenced by a 25% rise in heart rate ($P < .01$), while stroke volume remained unchanged. In a small double-anonymized, placebo-controlled, crossover study of 18 patients with idiopathic PAH, bisoprolol was generally well tolerated over 6 months, with lower heart rate and stable RV ejection fraction; however, a trend toward a decreased 6-minute walk distance was noted.[12] On the contrary, in another small study of 5 patients who were administered carvedilol, authors found a significant drop in systematic systolic BP and heart rate, followed by a trend toward an increase in the 6-minute walk distance and RV ejection fraction.[29] Notably, in that study, patients with worse RV function (RV ejection fraction < 45%) tolerated only low doses of carvedilol. In the PAH Treatment with Carvedilol for Heart Failure (PAHTCH) randomized controlled trial of 30 patients with PAH, carvedilol was well tolerated over 6 months of therapy and resulted in lowered heart rate and accelerated heart recovery from exercise.[30]

The failure to prove harmful or beneficial effects of β-blockers in previous studies could be due to the relatively small sample and selection and survival bias, resulting from their retrospective nature, or the enrollment of newly diagnosed and previously treated patients. Therefore, in the current study, we included only incident patients with PAH enrolled in our registry just following the diagnosis and prior to starting specific PAH therapies.

β-Blockers as a group of drugs include a variety of molecules with different modes of action. Nonselective agents, such as propranolol or carvedilol, have an affinity for both $\beta_1$ and $\beta_2$ receptors. $\beta_1$ receptors are found primarily in the heart muscle, and their stimulation leads to positive inotropic and chronotropic responses. In left-sided heart failure, the blockade of $\beta_1$ receptors reduces heart rate and myocardial contractility, which together reduce myocardial oxygen consumption, clinically resulting in symptoms and hemodynamic improvement.[31] Data from clinical trials indicate that not all β-blockers have an equal effect, with $\beta_1$-selective blockers (metoprolol and bisoprolol) and carvedilol favored in terms of survival.[31-33] $\beta_2$ receptors, primarily situated in the pulmonary vasculature, when blocked, can potentially lead to a heightened pulmonary vascular resistance and increased RV afterload.

In our study, patients treated with nonselective β-blockers (propranolol and carvedilol) displayed notably inferior outcomes compared with individuals treated with agents selectively targeting $\beta_1$ receptors. However, the role of different β-blocker classes in PAH remains disputable. As opposed to our findings, a prior pilot study on 6 patients showed that treatment with carvedilol was safe and resulted in slight improvement in RV function on cardiac MRI and, paradoxically, an increase in NT-proBNP levels.[19] Third-generation β-blockers such as nebivolol, a selective $\beta_1$-antagonist and $\beta_{2,3}$-agonist, have been reported in experimental studies to enhance endothelial function, ameliorate pulmonary vascular remodeling, and promote improved right heart function.[18]

### *β-Blockers in Patients With PAH With Comorbidities*

Although β-blockers are widely used to improve symptoms and prognosis in patients with hypertension, coronary heart disease, and arrhythmias, their role in the treatment of these diseases in patients with PAH has not been analyzed. Our study shows that although β-blockers had a negative impact on outcomes in the PAH population, the presence of comorbidities may overcome this effect. β-blockers are potent antiarrhythmic agents that are effective in the stopping of as well as the chronic management of

supraventricular arrhythmias and atrial fibrillation.[6,7] They are useful in CAD in patients following a myocardial infarction, especially complicated by decreased left ventricular ejection fraction, and in the chronic treatment of symptomatic coronary syndrome.[8] Finally, β-blockers are potent antihypertensive agents.[5] Therefore, we hypothesize that the harmful effect of β-blockers on clinical outcomes in patients with PAH is attenuated by the beneficial effect of these agents on the outcomes related to CAD or arrhythmias.

### *Strength and Limitations*

The current study had a number of strengths. As one of the largest prospective investigations in the field, it included a substantial cohort of 806 patients newly diagnosed with PAH, drawing from real-life clinical data from the Polish population. The exclusion of patients with prevalent PAH helped to mitigate survivor bias. The study provides a comprehensive characterization of patients at the time of diagnosis, encompassing demographic characteristics, cardiopulmonary comorbidities, and hemodynamic parameters, which added depth to the analysis. Clear and strong end points were defined, and the study adopted a multifaceted approach. Notably, we distinguished between types of β-blockers, shedding light on the distinct impact of nonselective vs selective agents on the outcomes.

However, certain limitations must be acknowledged. The study was observational and nonrandomized, with β-blockers introduced at the discretion of the leading physician. In addition, the exploration of various generations of β-blockers is somewhat limited, and the study does not account for changes in β-blocker doses, types, or their withdrawal. Although our assessment did not explicitly consider the potential impact of changes in risk profiles resulting from targeted therapy, it is crucial to note that baseline risk factors are among the most important influences for long-term survival. In addition, our analysis considered the type of initial PAH-specific therapy. There is also a risk of survival bias, as patients who were treated with β-blockers and died prior to PAH diagnosis could not have been included in the analysis.

## Interpretation

The current study does not support the routine administration of β-blockers in patients with PAH. Instead, a cautious approach is warranted, and their use should only be considered in patients with comorbidities that clearly justify their prescription (eg, hypertension, CAD, significant arrhythmia). Notably, nonselective β-blockers are linked to worse survival compared with $\beta_1$-selective agents.


## Funding/Support

This study was supported by the Polish Cardiac Society.


## Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: M. W. has served on a scientific advisory board for Merck & Co (fees paid to self); served as a speaker for Janssen Global Services, AOP Orphan Pharmaceuticals, and Merck & Co (fees paid to self); and received travel fees from AOP Orphan Pharmaceuticals. E. L. has participated in advisory board meetings for Johnson & Johnson and MSD; and has received payment for lectures from Bayer, Johnson & Johnson, and MSD. G. K. reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement; a relationship with Merck & Co Inc that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement; a relationship with Pfizer Poland that includes: speaking and lecture fees; and a relationship with AOP Orphan Pharmaceuticals GmbH that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. None declared (M. K., T. M.-K., I. S., Ł. C., P. B., M. J., B. K., K. P., G. G., K. M.-S., E. Malinowska, M. P.-P., M. T., W. J., M. F., E. Mroczek, Z. G., A. P., K. B.-L., P. P., K. W., W. Z.).

## Acknowledgments

**Author contributions:** M. W. and G.K. were responsible for contributions to concept and design, statistical analysis, and manuscript writing; and M. W., M. K., T. M.-K., I. S., Ł. C., P. B., M. J., B. K., K. P., G. G., K. M.-S., E. Malinowska, M. P.-P., E. L., M. T., W. J., M. F., E. Mroczek, Z. G., A. P., K. B.-L., P. P., K. W., W. Z., and G. K. contributed to acquisition or processing of the data. All authors reviewed, edited, and approved the final manuscript.

**Role of sponsors:** The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

**Additional information:** The e-Appendix, e-Figures, and e-Tables are available online under "Supplementary Data."

## References

1. Kopeć G. Sotatercept as a next-generation therapy for pulmonary arterial hypertension: insights from the STELLAR trial. *Cardiovasc Res*. 2023;119(16):E155-E157.
2. Hoeper MM, Badesch DB, Ghofrani HA, et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. *N Engl J Med*. 2023;388(16):1478-1490.
3. Souza R, Badesch DB, Ghofrani HA, et al. Effects of sotatercept on haemodynamics and right heart function: analysis of the STELLAR trial. *Eur Respir J*. 2023;62(3):2301107.
4. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726.
5. Williams B, Mancia G, Spiering W, et al. ESC/ESH guidelines for the management of arterial hypertension. *Eur Heart J*. 2018;39(33):3021-3104.
6. Hindricks G, Potpara T, Kirchhof P, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5):373-498.
7. Brugada J, Katritsis DG, Arbelo E, et al. 2019 ESC guidelines for the management of patients with supraventricular tachycardia. The Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41(5):655-720.
8. Neumann FJ, Sechtem U, Banning AP, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41(3):407-477.
9. Kopeć G, Kurzyna M, Mroczek E, et al. Characterization of patients with pulmonary arterial hypertension: data from the Polish Registry of Pulmonary Hypertension (BNP-PL). *J Clin Med*. 2020;9(1):173.
10. Hoeper MM, Pausch C, Grünig E, et al. Temporal trends in pulmonary arterial hypertension: results from the COMPERA registry. *Eur Respir J*. 2022;59(6):2102024.
11. Provencher S, Herve P, Jais X, et al. Deleterious effects of beta-blockers on exercise capacity and hemodynamics in patients with portopulmonary hypertension. *Gastroenterology*. 2006;130(1):120-126.
12. Van Campen JSJA, De Boer K, Van De Veerdonk MC, et al. Bisoprolol in idiopathic pulmonary arterial hypertension: an explorative study. *Eur Respir J*. 2016;48(3):787-796.
13. Leblais V, Delannoy E, Fresquet F, et al. Beta-adrenergic relaxation in pulmonary arteries: preservation of the endothelial nitric oxide-dependent beta2 component in pulmonary hypertension. *Cardiovasc Res*. 2008;77(1):202-210.
14. Provencher S, Chemla D, Hervé P, Sitbon O, Humbert M, Simonneau G. Heart rate responses during the 6-minute walk test in pulmonary arterial hypertension. *Eur Respir J*. 2006;27(1):114-120.
15. Perros F, De Man FS, Bogaard HJ, et al. Use of β-blockers in pulmonary hypertension. *Circ Heart Fail*. 2017;10(4):e003703.
16. Moretti C, Marra WG, D'Ascenzo F, et al. Beta blocker for patients with pulmonary arterial hypertension: a single center experience. *Int J Cardiol*. 2015;184:528-532.
17. So PPS, Davies RA, Chandy G, et al. Usefulness of beta-blocker therapy and outcomes in patients with pulmonary arterial hypertension. *Am J Cardiol*. 2012;109(10):1504-1509.
18. Perros F, Ranchoux B, Izikki M, et al. Nebivolol for improving endothelial dysfunction, pulmonary vascular remodeling, and right heart function in pulmonary hypertension. *J Am Coll Cardiol*. 2015;65(7):668-680.
19. Grinnan D, Bogaard HJ, Grizzard J, et al. Treatment of group I pulmonary arterial hypertension with carvedilol is safe. *Am J Respir Crit Care Med*. 2014;189(12):1562-1564.
20. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG). *Eur Heart J*. 2022;43(38):3618-3731.
21. Kopeć G, Kurzyna M, Mroczek E, et al. Database of Pulmonary Hypertension in the Polish Population (BNP-PL): design of the registry. *Kardiol Pol*. 2019;77(10):972-974.
22. Database of Pulmonary. Hypertension in the Polish Population (BNP-PL). ClinicalTrials.gov identifier: NCT03959748. Updated May 22, 2019. Accessed December 16, 2024. https://clinicaltrials.gov/ct2/show/NCT03959748
23. Kattan MW, Vickers AJ. Statistical analysis and reporting guidelines for CHEST. *Chest*. 2020;158(1S):S3-S11.
24. Groepenhoff H, Westerhof N, Jacobs W, Boonstra A, Postmus PE, Vonk-Noordegraaf A. Exercise stroke volume and heart rate response differ in right and left heart failure. *Eur J Heart Fail*. 2010;12(7):716-720.
25. Ciarka A, Doan V, Velez-Roa S, Naeije R, Van De Borne P. Prognostic significance of sympathetic nervous system activation in pulmonary arterial hypertension. *Am J Respir Crit Care Med*. 2010;181(11):1269-1275.
26. Samaranayake CB, Kempny A, Naeije R, et al. Beta-blockade improves right ventricular diastolic function in exercising pulmonary arterial hypertension. *Eur Respir J*. 2023;61(5):2300144.
27. Thenappan T, Roy SS, Duval S, Glassner-Kolmin C, Gomberg-Maitland M. β-blocker therapy is not associated with adverse outcomes in patients with pulmonary arterial hypertension: a propensity score analysis. *Circ Heart Fail*. 2014;7(6):903-910.
28. Bandyopadhyay D, Bajaj NS, Zein J, Minai OA, Dweik RA. Outcomes of β-blocker use in pulmonary arterial hypertension: a propensity-matched analysis. *Eur Respir J*. 2015;46(3):750-760.
29. Thenappan T, Weir EK, Prins KW, Pritzker MR, Archer SL. Carvedilol for treatment of right ventricular dysfunction in pulmonary arterial hypertension. *J Am Heart Assoc*. 2021;10(14):e021518.
30. Farha S, Saygin D, Park MM, et al. Pulmonary arterial hypertension treatment with carvedilol for heart failure: a randomized controlled trial. *JCI Insight*. 2017;2(16):e95240.
31. Waagstein F, Hjalmarson A, Swedberg K, et al; Metoprolol in Dilated Cardiomyopathy (MDC) trial study group. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet*. 1993;342(8885):1441-1446.
32. Poole-Wilson PA, Swedberg K, Cleland JGF, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet*. 2003;362(9377):7-13.
33. Hjalmarson Å, Goldstein S, Fagerberg B, et al. 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). *JAMA*. 2000;283(10):1295-1302.