ORIGINAL ARTICLE

Effect of β-blockers on 1-year survival and hospitalizations in patients with heart failure and atrial fibrillation: results from ESC-HF Pilot and ESC-HF Long-Term Registry

Krzysztof Ozierański[1], Agnieszka Kapłon-Cieślicka[1], Paweł Balsam[1], Agata Tymińska[1], Anna Wancerz[1], Michał Peller[1], Michał Marchel[1], Maria G. Crespo-Leiro[2], Aldo P. Maggioni[3,4], Jarosław Drożdż[5], Krzysztof J. Filipiak[1], Grzegorz Opolski[1]

1 1st Department of Cardiology, Public Central Teaching Hospital in Warsaw, Medical University of Warsaw, Warsaw, Poland
2 Unidad de Insuficiencia Cardiaca Avanzada y Trasplante Cardiaco, Hospital Universitario A Coruna, CIBERCV, La Coruña, Spain
3 ANMCO Research Centre, Florence, Italy
4 EURObservational Research Programme, European Society of Cardiology, Sophia-Antipolis, France
5 Department of Cardiology, Medical University of Lodz, Łódź, Poland

KEY WORDS

β-blockers, atrial fibrillation, heart failure, rate control, registry

ABSTRACT

INTRODUCTION The positive effect of β-blocker therapy in patients with heart failure (HF) and atrial fibrillation (AF) has been questioned.

OBJECTIVES We aimed to assess the effect of β-blockers and heart rate (HR) control on 1-year outcomes in patients with HF and AF.

PATIENTS AND METHODS Of the 2019 Polish patients enrolled in ESC-HF Pilot and ESC-HF Long-Term Registry, 797 patients with HF and AF were classified into 2 groups depending on β-blocker use. Additionally, patient survival was compared between 3 groups classified according to HR: lower than 80 bpm, between 80 and 109 bpm, and of 110 bpm or higher. The primary endpoint was all-cause death and the secondary endpoint was all-cause death or HF hospitalization.

RESULTS In patients treated with β-blockers, the primary and secondary endpoints were less frequent than in patients not using β-blockers (10.9% vs 25.6%, $P = 0.001$ and 30.6% vs 44.2%, $P = 0.02$, respectively). Absence of β-blocker treatment was a predictor of both endpoints in a univariate analysis but remained an independent predictor only of the primary endpoint in a multivariate analysis (hazard ratio for β-blocker use, 0.52; 95% CI, 0.31–0.89; $P = 0.02$). The primary and secondary endpoints were more frequent in patients with a HR of 110 bpm or higher, but the HR itself did not predict the study endpoints in the univariate analysis.

CONCLUSIONS β-blocker use might decrease mortality in patients with HF and AF, but it seems to have no impact on the risk of HF hospitalization. An HR of 110 bpm or higher may be related to worse survival in these patients.

Correspondence to:
Agnieszka Kaplon-Cieślicka, MD, PhD, 1st Department of Cardiology, Medical University of Warsaw, Public Central Teaching Hospital in Warsaw, ul. Banacha 1a, 02-097 Warszawa, Poland, +48 22 599 29 58, email: agnieszka.kaplon@gmail.com

Received: July 21, 2018.
Revision accepted: October 8, 2018.
Published online: October 10, 2018.
Conflict of interest: none declared.
Pol Arch Intern Med. 2018; 128 (11): 649-657
doi:10.20452/pamw.4346

INTRODUCTION According to the current guidelines, β-blockers are recommended in addition to angiotensin-converting enzyme inhibitors as the first-line therapy for patients with stable and symptomatic heart failure (HF) with reduced ejection fraction (HFrEF).[1] In that population, β-blockers have been proved to reduce the risk of HF hospitalization and mortality.[1] However, most HF patients included in clinical trials with β-blockers were in sinus rhythm, with only 11% to 35% of patients with atrial fibrillation (AF).[2-5] Moreover, a recent meta-analysis of 10 randomized controlled trials, including patients with HFrEF, has shown no improvement in

long-term prognosis on β-blocker therapy in patients with HF and AF.[6] Moreover, it has shown no benefit of β-blocker treatment in any of the AF subgroups (selected based on age, sex, left ventricular ejection fraction, New York Heart Association [NYHA] class, heart rate [HR], and baseline medical therapy).[6] In contrast, a large nationwide Swedish registry[7] and a post hoc analysis of the AF-CHF trial[8] (Atrial Fibrillation-Congestive Heart Failure) showed a significant reduction of all-cause mortality in patients with HF and AF treated with β-blockers (a relative risk reduction of 25% and 28%, respectively).

Another important consideration in HF patients with permanent AF is the optimal resting HR, which is still uncertain. It was observed that ventricular rates under 70 bpm may be associated with worse outcomes in patients with HF and AF.[9] The current European Society of Cardiology (ESC) guidelines on HF management suggest a threshold of 60 to 100 bpm, while the ESC guidelines on AF propose a less strict threshold of less than 110 bpm (and avoiding bradycardia), as a target for rate control therapy in this population.[1,10]

The aim of this study was to investigate the effect of β-blockers on 1-year outcomes in real-life patients with HF and concomitant AF. An additional analysis was designed to assess the relationship between HR control and 1-year outcomes in these patients.

PATIENTS AND METHODS

Study design This cohort study was based on data from 2 prospective observational ESC registries: ESC-HF Pilot and ESC-HF Long-Term. The current analysis included data collected in Polish cardiology centers. Detailed information on the design of both registries was published previously.[11-13] Both surveys were approved by a local institutional review board and all patients signed informed consent to participate in the registries.

Study population and group selection The ESC-HF Pilot and Long-Term registries enrolled 5118 and 12 440 patients with HF, respectively, across Europe. The current analysis comprised 2019 white Polish patients including those who were discharged in stable condition following HF hospitalization (n = 1415) and ambulatory HF patients (n = 604). Both HF registries collected the same type of clinical data.

The main analysis was designed to assess clinical characteristics and 1-year prognosis of HF patients with concomitant AF treated with β-blockers in comparison with patients with HF and AF who did not receive β-blockers. Patients were eligible for inclusion in the study if they had a diagnosis of AF based on a 12-lead electrocardiogram (ECG) or Holter monitoring performed during baseline visit or earlier. A case report form enabled the investigators to choose only one leading heart rhythm for each patient (sinus rhythm, AF, paced rhythm, or other) based on a 12-lead ECG. The study included patients with all types of AF (ie, paroxysmal, persistent, and permanent). The exclusion criteria were as follows: death during baseline hospitalization (in the case of hospitalized patients; n = 42), lack of data on β-blocker prescription (n = 3), and lack of ECG documentation on the leading heart rhythm or presence of rhythm other than AF (n = 1177).

Of the 2019 Polish patients with HF (including ambulatory patients and patients discharged after hospitalization for HF), 797 individuals (39.5%) with AF were selected and included in the present study. Patients were classified into 2 groups depending on β-blocker use and were followed for 1 year. The population included 445 patients (56%) with a left ventricular ejection fraction (LVEF) of 40% or lower and 300 patients (38%) with a LVEF higher than 40% (LVEF data were missing in 52 patients [6%]). Data on 1-year survival were available for 763 patients (96.2%), and on hospitalization for decompensated HF at 1-year follow-up, for 711 of the 797 patients (89.2%).

Clinical endpoints and design of analyses Patients treated with β-blockers were compared with those not receiving β-blockers in terms of baseline characteristics and 1-year outcomes. The primary endpoint was all-cause death at 1 year, while the secondary endpoint was a composite of all--cause death and hospitalization for worsening HF at 1 year. We also sought to determine whether β-blocker treatment was an independent predictor of both endpoints in the study cohort.

An additional analysis was performed to assess the relationship between baseline resting HR and 1-year outcomes in the study population. Patients were divided into 3 subgroups depending on baseline resting HR (791 of the 797 patients with known resting HR): 464 patients (58.7%) with an HR below 80 bpm; 297 patients (37.5%) with an HR between 80 and 109 bpm; 30 patients (3.8%) with an HR of 110 bpm or higher. We chose the cutoff value of 110 bpm according to the latest 2016 ESC guidelines,[10] and the cutoff value of 80 bpm as adopted in the previous 2010 ESC guidelines and the RACE II study.[14,15]

Statistical analysis For a between-group comparison, we used the Fisher exact test and the Mann–Whitney test for categorical and continuous variables, respectively. Categorical data were presented as the number and percentage of patients. Normally distributed continuous variables were presented as a mean value with SD. For ordinal variables and nonnormally distributed continuous variables, a median value with interquartile range (IQR) was used. To identify predictors of the primary and secondary endpoints, we performed the Cox proportional hazards regression model. Variables found to be significant in univariate analyses were included in multivariate models. The Kaplan–Meier curves were plotted for the 2 primary subgroups (with and without

TABLE 1 Baseline characteristics (demographic data, heart failure, and medical history) of patients with heart failure and atrial fibrillation depending on β-blocker use

Parameter	Total population (n = 797)	β-blocker treatment (n = 715)	No β-blocker treatment (n = 82)	*P* value
Demographic data				
Age, y, median (IQR)	69.2 (60.6–78.0); n = 797	68.9 (60.1–77.3); n = 715	75.0 (65.5–80.9); n = 82	0.002
Male sex, % (n/N)	66.4 (529/797)	67.6 (483/715)	56.1 (46/82)	0.048
BMI, kg/m^2, median (IQR)	28.1 (25.0–31.4); n = 771	28.0 (25.0–31.2); n = 694	28.4 (25.0–32.3); n = 77	0.7
Heart failure				
LVEF, %, median (IQR)	38 (27.5–50); n = 745	37 (27–50); n = 667	45 (35–54); n = 78	0.001
Ischemic etiology, % (n/N)	45.3 (361/797)	44.5 (318/715)	52.4 (43/82)	0.2
Dilated cardiomyopathy, % (n/N)	18.2 (145/797)	19.4 (139/715	7.3 (6/82)	0.01
Patients discharged after HF hospitalization, % (n/N)	70.1 (561/797)	69.0 (493/715	82.9 (68/82)	0.01
Medical history, % (n/N)				
Hypertension	65.7 (522/795)	65.4 (466/713	68.3 (56/82)	0.6
Coronary artery disease	47.3 (377/797)	45.6 (326/715)	62.2 (51/82)	0.01
Prior PCI or CABG	30.5 (243/797)	32.0 (229/715)	17.1 (14/82)	0.01
Peripheral artery disease	12.4 (99/796)	11.8 (84/714)	18.3 (15/82)	0.1
Diabetes	33.0 (263/797)	32.3 (231/715)	39.0 (32/82)	0.2
CKD	20.4 (162/796)	19.9 (142/714)	24.4 (20/82)	0.4
COPD	17.4 (139/797)	15.9 (114/715)	30.5 (25/82)	0.002
Stroke	13.8 (110/796)	13.9 (99/714)	13.4 (11/82)	1.00
Current smoking	51.5 (404/785)	52.6 (370/704)	42.0 (34/81)	0.08

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; IQR, interquartile range; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention

β-blocker treatment), as well as for the 3 subgroups divided according to HR. All tests were 2-tailed. A *P* value of less than 0.05 was considered significant. The SPSS software, version 22 (IBM SPSS Statistics 22, New York, United States) was used for analysis.

RESULTS **Baseline characteristics** The mean (SD) age of the overall population was 68.0 (12.0) years and the mean (SD) resting HR was 80.2 (18.6) bpm. At baseline, 715 patients (89.7%) received β-blockers, while 82 patients (10.3%) were not treated with a β-blocker. Detailed comparative characteristics of both groups are presented in TABLES 1 and 2.

One-year outcomes Patients treated with β-blockers were less likely to reach the primary and secondary endpoints than those not receiving β-blockers (10.9% vs 25.6%, *P* = 0.001 and 30.6% vs 44.2%, *P* = 0.02, respectively). The Kaplan–Meier curves for the primary and secondary endpoints for both subgroups are shown in FIGURES 1 and 2, respectively.

In the univariate analysis, β-blocker use in patients with HF and AF was a predictor of both the primary and secondary endpoints. In the multivariate analysis, β-blocker use remained an independent predictor of the primary endpoint (hazard ratio, 0.52; 95% CI, 0.31–0.89; *P* = 0.02) but not of the secondary endpoint (hazard ratio, 0.74; 95% CI, 0.49–1.11; *P* = 0.14) (TABLE 3).

Heart rate control Heart rate, assessed as a continuous variable, was not a predictor of either the primary or the secondary endpoint in the total population, even in the univariate analysis. However, the Kaplan–Meier curves (FIGURES 3 and 4) showed increased rates of the primary and secondary endpoints in patients with an HR of 110 bpm or higher. Both study endpoints were less frequent in patients with an HR of 80 to 109 bpm when compared with the remaining HR subgroups. However, significance was reached only for the secondary endpoint (27.5% vs 35.0%; *P* = 0.046) and not for the primary one (9.9% vs 14.2%; *P* = 0.09) (FIGURE 5).

DISCUSSION The results of this study may support current recommendations to prescribe β-blockers in patients with HF, irrespective of the simultaneous presence of AF. In our population, β-blocker use was an independent prognostic factor in the 1-year follow-up. The most favorable 1-year prognosis was observed in patients with a resting HR of 80 to 109 bpm.

Patients with AF constitute a specific subgroup within the HF population, and AF is a highly prevalent condition in patients with HF.[1,16] Its prevalence increases with the severity of HF, from 10% in NYHA functional class I to 50% in class IV.[16,17] The presence of AF in patients with HF is associated with increased severity of symptoms, high risk of thromboembolic events, and worse long-term prognosis.[18-20] AF patients are more likely

TABLE 2 Baseline characteristics (clinical status, laboratory findings, pharmacotherapy and implantable devices) and 1-year outcomes of patients with heart failure and atrial fibrillation depending on β-blocker use

Variable	Total (n = 797)	β-Blocker treatment (n = 715)	No β-blocker treatment (n = 82)	*P* value
Clinical status at baseline, median (IQR)				
NYHA class	2 (2–3); n = 777	2 (2–3); n = 696	2 (2–3); n = 81	0.8
SBP, mmHg	120 (110–130); n = 796	120 (110–130); n = 714	120 (110–130); n = 82	0.3
DBP, mmHg	70 (70–80); n = 795	70 (70–80); n = 713	70 (68–80); n = 82	0.2
Heart rate, bpm	75 (68–83); n = 791	75 (70–83); n = 709	70 (65–80); n = 82	0.06
Laboratory findings at baseline, median (IQR)				
Serum sodium, mmol/l	139.0 (136.0–141.0); n = 745	139.0 (136.2–141.0); n = 490	139.0 (136.0–141.0); n = 66	0.9
Serum potassium, mmol/l	4.4 (4.1–4.8); n = 749	4.4 (4.1–4.7); n = 498	4.5 (4.0–4.9); n = 67	0.4
Serum creatinine, mg/dl	1.10 (0.92–1.37); n = 746	1.10 (0.90–1.38); n = 456	1.06 (0.90–1.52); n = 60	0.8
Hemoglobin, g/dl	13.5 (12.1–14.7); n = 730	13.2 (11.9–14.6); n = 369	12.1 (11.0–13.5); n = 51	0.002
Pharmacotherapy and implantable devices, % (n/N)				
ACEIs	75.6 (602/796)	76.5 (547/715)	67.9 (55/81)	0.1
ARBs	10.9 (87/796)	10.5 (75/715)	14.8 (12/81)	0.3
MRAs	70.4 (560/796)	72.7 (520/715)	49.4 (40/81)	<0.001
Diuretics	86.7 (690/796)	87.4 (625/715)	80.2 (65/81)	0.08
Amiodarone	11.3 (90/796)	11.6 (83/715)	8.6 (7/81)	0.6
Other antiarrhythmic drugs	6.8 (54/796)	6.9 (49/715)	6.2 (5/81)	1.00
Statins	59.7 (475/796)	62.0 (443/715)	39.5 (32/81)	<0.001
Anticoagulants	74.0 (589/796)	75.4 (539/715)	61.7 (50/81)	0.01
Antiplatelets	41.1 (327/796)	42.2 (302/715)	30.9 (25/81)	0.06
Digoxin	36.9 (294/796)	36.2 (259/715)	43.2 (35/81)	0.2
ICD	16.3 (130/797)	17.3 (124/715)	7.3 (6/82)	0.02
CRT	4.9 (39/797)	5.3 (38/715)	1.2 (1/82)	0.1
One-year outcome				
Death	12.5 (95/763)	10.9 (74/681)	25.6 (21/82)	0.001
Death or rehospitalization	32.1 (228/711)	30.6 (194/634)	44.2 (34/77)	0.02

SI conversion factors: to convert hemoglobin to g/l, multiply by 0.6206; creatinine to μmol/l, by 0.00884.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; ICD, implantable cardioverter–defibrillator; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SBP, systolic blood pressure; others, see TABLE 1

to require a more intensive symptomatic treatment with the use of loop diuretics and mineralocorticoid receptor antagonists than patients in sinus rhythm.[18] Coexistence of HF and AF is associated with an increased risk of HF hospitalizations and mortality.[19,21]

In our analysis, patients who received and who did not receive β-blockers did not differ in severity of HF symptoms. Patients who did not receive β-blockers were older, more often were female, and more frequently had chronic obstructive pulmonary disease (COPD), which might have affected underprescription of these medications. Patients with coexisting COPD are at high risk of adverse reactions associated with β-blocker use. However, Andell et al,[22] based on data from a large Swedish registry (SWEDEHEART), found that COPD patients with a history of HF and after myocardial infarction treated with β-blockers had a significantly lower all-cause mortality. Moreover, a previous analysis from the ESC-HF Pilot registry showed that mortality in patients with HF and concomitant COPD did not differ compared with patients without COPD.[23] According to the current guidelines, β-blockers are not contraindicated in patients with HF and COPD, although more selective β_1-antagonists (such as bisoprolol, metoprolol succinate, or nebivolol) are preferred.[1]

In our study, patients who did not receive β-blockers had a higher mean LVEF value (45%), thus most patients had HF with preserved LVEF (HFpEF) or HF with mid-range LVEF (HFmrEF). This might explain why those patients did not receive β-blockers, as so far there has been no evidence of survival benefit of this therapy in HFpEF and HFmrEF.[1] Still, in these patients, β-blockers should be considered for rate control.[1] Recent data from the QUALIFY study (QUality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure surveY) showed that most patients with HFrEF in Poland receive adequate treatment (including β-blockers), but the proportion of patients reaching the target

FIGURE 1
Kaplan–Meier curves for the primary endpoint in patients with heart failure and concomitant atrial fibrillation treated and not treated with β-blockers

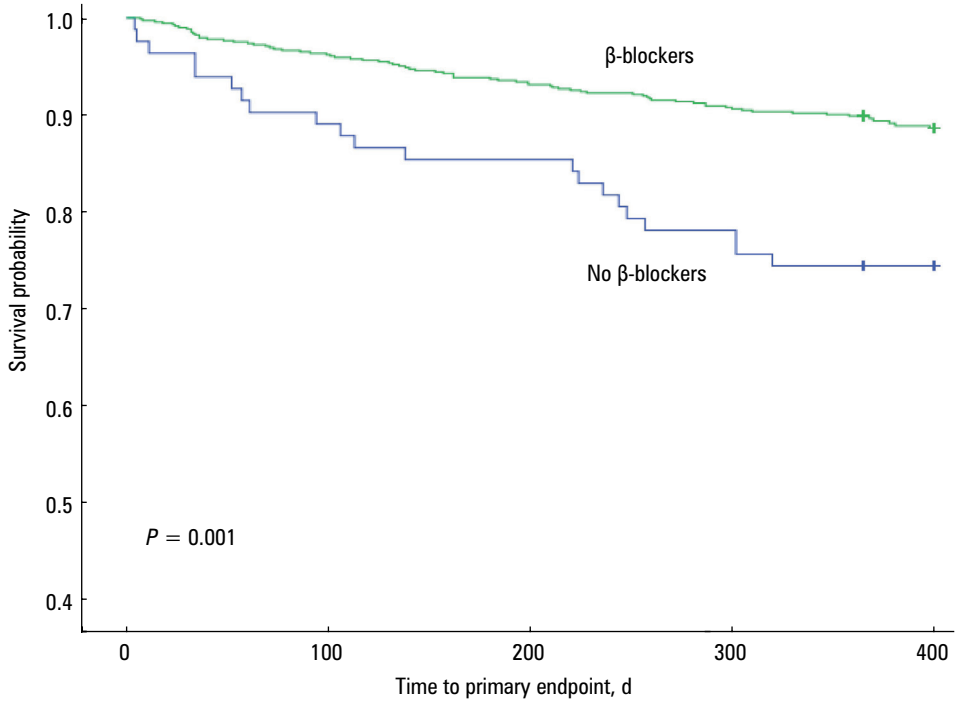
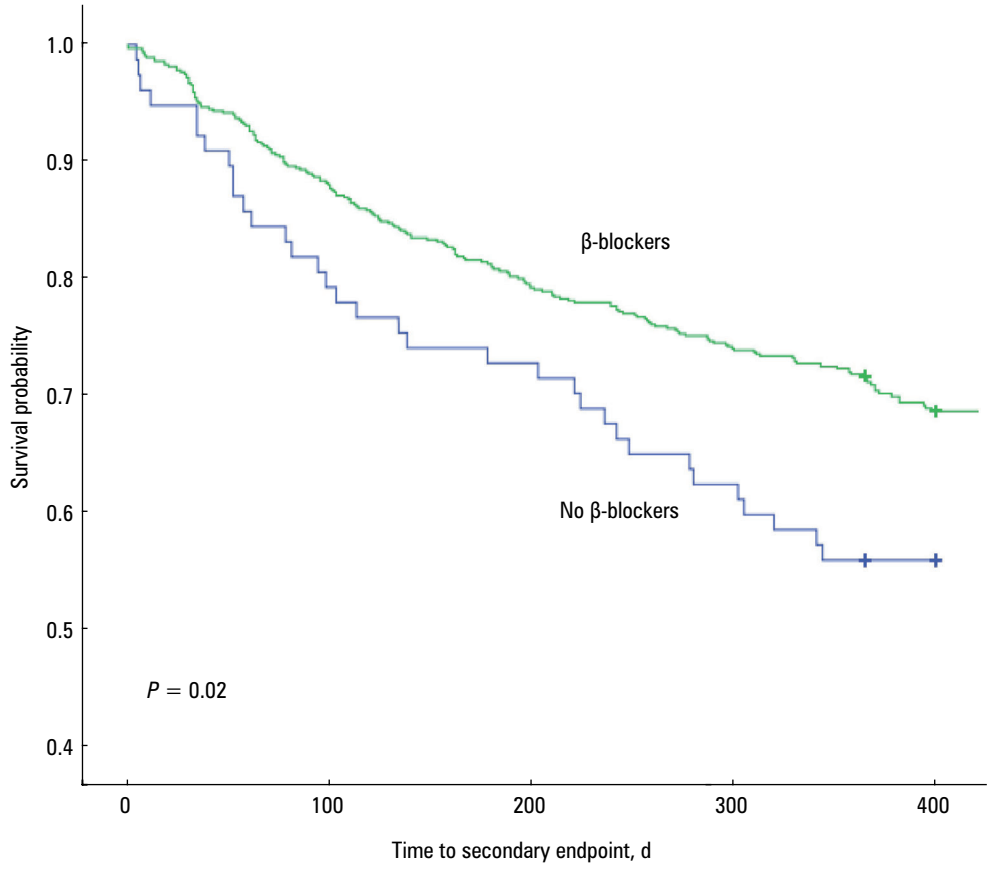


FIGURE 2
Kaplan–Meier curves for the secondary endpoint in patients with heart failure and concomitant atrial fibrillation treated and not treated with β-blockers



doses is suboptimal.[23] Nevertheless, it seems that β-blocker prescription in the study group might have been also, at least in part, motivated by a resting HR: patients who received β-blockers had higher baseline HR compared with those who were not prescribed β-blockers (75 bpm vs 70 bpm, $P = 0.06$).

Patients treated with β-blockers were also more likely to receive other evidence-based medications, including oral anticoagulation (OAC). Of note, as all AF patients in our study had a diagnosis of HF, all had at least 1 point in the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age >75 years, diabetes mellitus, history of stroke or thromboembolism, vascular disease, age 65 to 74 years, female sex) and therefore at least class IIa indication for OAC.[10] However, only 75.4% of participants on β-blockers and 61.7% of those not

TABLE 3 Predictors of the primary and secondary endpoints at 1-year in patients with heart failure and atrial fibrillation in a multivariate analysis

Variable	Primary endpoint		Secondary endpoint	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Demographic data				
Age, per 10 years	1.02 (1.10–1.63)	0.06	0.98 (0.95–1.34)	1.01
Heart failure				
LVEF, per 5%	–	–	1.32 (0.98–1.01)	0.1
Medical history				
CAD	1.17 (0.75–1.84)	0.5	1.09 (0.80–1.50)	0.6
Diabetes	–	–	1.52 (1.12–2.05)	0.007
COPD	2.29 (1.45–3.63)	<0.001	1.39 (0.98–1.95)	0.06
CKD	1.53 (0.95–2.47)	0.08	1.32 (0.95–1.92)	0.09
Laboratory findings				
Hemoglobin, per 1 g/dl	0.97 (0.86–1.09)	0.6	0.94 (0.87–1.02)	0.1
Serum sodium, per 1 mmol/l	0.95 (0.91–0.99)	0.03	0.98 (0.95–1.01)	0.3
Clinical status				
NYHA class, per 1 class	0.98 (0.69–1.38)	0.9	1.17 (0.93–1.50)	0.2
SBP, per 10 mmHg	0.82 (0.74–0.90)	0.01	0.99 (0.98–1.01)	0.2
Hospitalization status[a]	3.33 (1.32–8.41)	0.01	2.87 (1.72–4.78)	<0.001
Pharmacotherapy				
Diuretics	–	–	1.32 (0.77–2.29)	0.3
β-blockers	0.52 (0.31–0.89)	0.02	0.76 (0.51–1.15)	0.2

a On enrollment

The table includes only variables that were significant predictors of either the primary or secondary endpoint in univariate analyses. Variables found to be predictors of the study endpoints in univariate analyses were subsequently included in multivariate analyses.

Abbreviations: CAD, coronary artery disease; HR, hazard ratio; others see TABLES 1 and 2

on β-blockers ($P = 0.01$) received OAC. The underprescription of OAC, especially in the non–β-blocker subgroup, might be partly explained by older age and lower hemoglobin levels. However, it was shown that elderly patients with AF rarely have absolute contraindications to OAC and it is therefore underused.[24]

In our study, patients not treated with β-blockers were significantly more likely to reach the primary and secondary endpoints than patients receiving β-blockers. In the multivariate analysis, β-blocker use was proved to be an independent positive predictor of 1-year survival, but not of the composite endpoint of death and hospital readmissions. It should be stressed that, because of a small group of patients who were not treated with β-blockers, our analysis was performed regardless of LVEF, which might have biased the results. However, our findings are in line with data from 2 large registries with a similar methodology.[7,25] The first one was a propensity-matched cohort from a Danish nationwide registry, including 23 896 AF patients with concomitant HF (both HFrEF and HFpEF).[7] It revealed that patients treated with β-blockers had a 25% reduction in all-cause mortality in comparison with those who did not receive β-blockers.[7] Similarly, in the other study, β-blockers were associated with a significant 29% reduction in mortality.[25] The analysis was based on the Swedish Heart Failure Registry and comprised 7392 HFrEF patients with concomitant AF.[25] In a recent post hoc analysis of the AF-CHF trial, β-blockers were associated with a significant 28% reduction in all-cause mortality during a median follow-up of 37 months.[8] Similarly to our study, the AF-CHF trial showed a trend towards the association of β-blocker use with a reduced hospitalization rate, but the result was not significant.[8] It remains unclear why β-blockers have no favorable effect on the reduction of hospital readmissions in patients with HF and AF. One possible explanation might be that these patients are frequently more symptomatic than HF patients in sinus rhythm, which may reduce the beneficial effect of β-blockers.

The findings of the above analyses are in contrast to the results of a recent meta-analysis that included data from 10 randomized trials of β-blockers versus placebo in patients with HFrEF.[6] The meta-analysis indicated that, in contrast to HF patients with sinus rhythm, β-blockers do not improve prognosis in HF patients with AF (hazard ratio, 0.97; $P = 0.73$).[6] The authors recommended against β-blocker use in patients with HF and AF.[6] Similar results were observed in a smaller meta-analysis including 4 randomized placebo-controlled trials, which enrolled 1677 patients with HF and AF.[26] Rienstra et al[26] suggested that in these patients β-blockers did not reduce mortality (odds ratio [OR], 0.86; 95% CI, 0.66–1.13; $P = 0.28$) and hospitalizations (OR, 1.11; 95% CI, 0.85–1.47; $P = 0.44$), in contrast to patients in sinus rhythm. However, both meta-analyses generated some controversies. The first meta-analysis included patients with advanced disease, highly symptomatic (70% had NYHA class III or IV), with a high proportion of digoxin use and OAC underuse (only 58% of patients), which might have reduced the benefit of β-blocker therapy.[6] In the meta-analysis by Rienstra et al,[26] the actual prevalence of AF might have been low (patients were included in the study based only on one ECG). However, in the AF-CHF trial, the association of β-blocker use and outcomes was consistent regardless of AF type (persistent or paroxysmal) and its duration.[8] Despite these controversies, the 2016 ESC guidelines on HF maintained the recommendation of β-blocker use in patients with HF and AF.[1]

Higher HR in HF patients was proved to be associated with higher long-term mortality.[27,28] In our previous study, HR at hospital discharge was a predictor of 1-year death in HF patients, both those with AF and those in sinus rhythm.[18] However, based on the results of the MAGGIC meta-analysis conducted in HF patients, resting HR does not have the same prognostic implications in patients with AF as it does in those in sinus

FIGURE 3
Kaplan–Meier curves for the primary endpoint in patients with heart failure and concomitant atrial fibrillation depending on heart rate

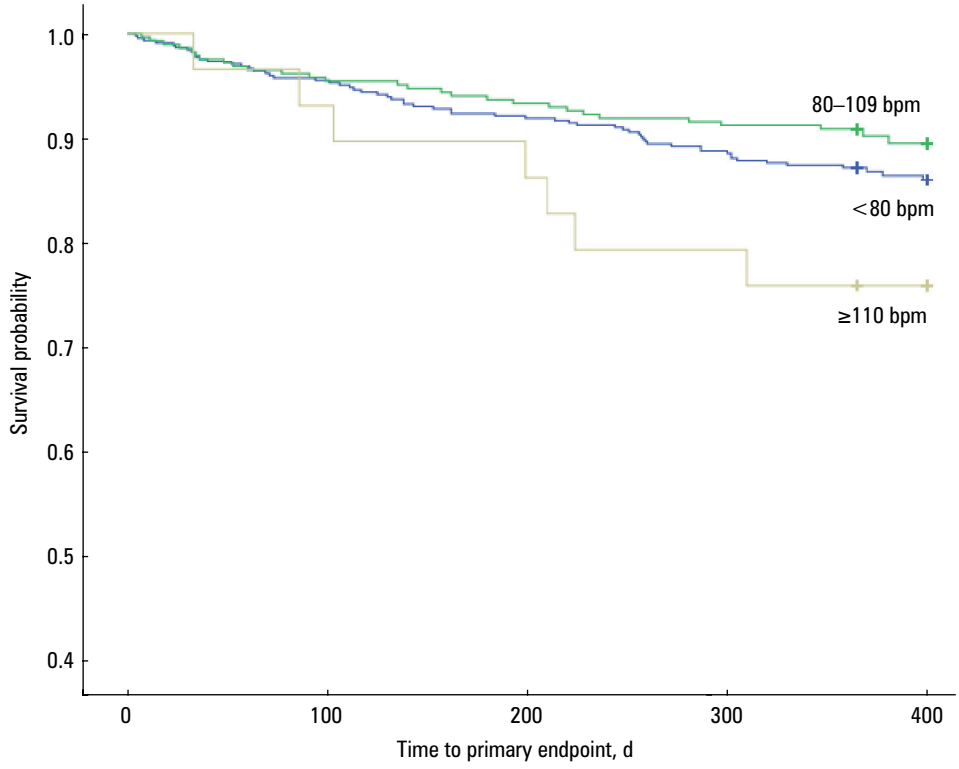
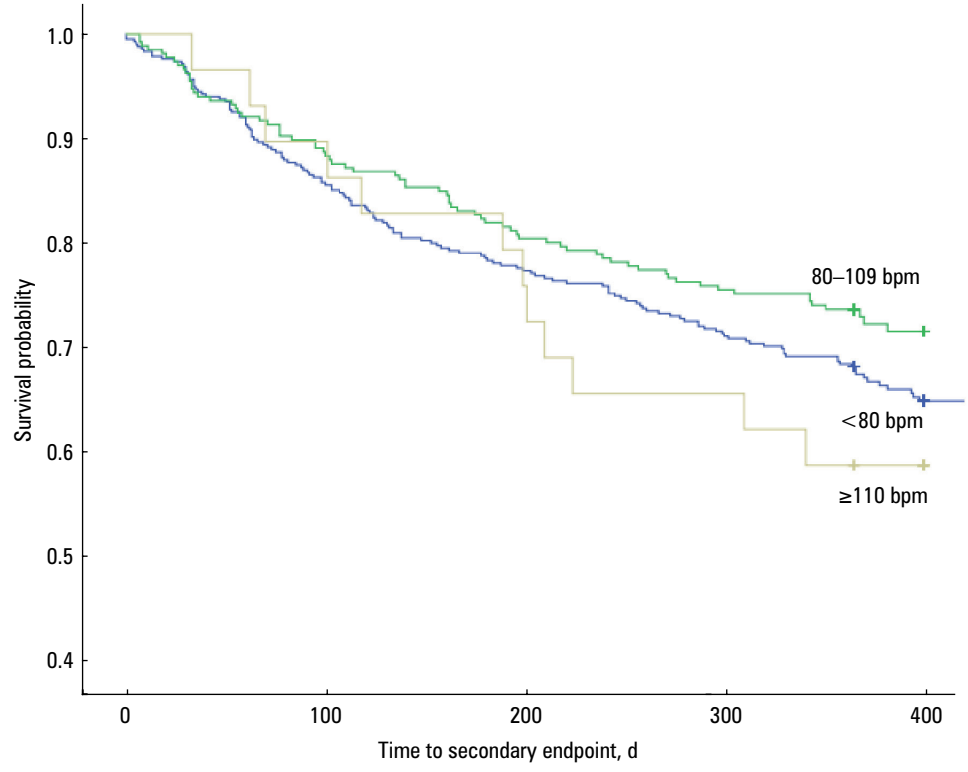


FIGURE 4
Kaplan–Meier curves for the secondary endpoint in patients with heart failure and concomitant atrial fibrillation depending on heart rate



rhythm.[29] In our study, patients with HF and AF with an HR of 110 bpm or higher had a higher risk of death in 1-year follow-up than patients with an HR in the range of 80 to 109 bpm. Moreover, the risk of death or hospitalization for HF worsening was observed less frequently in patients with an HR of 80 to 109 bpm when compared with patients with an HR of 110 bpm or higher or less than 80 bpm. However, it should be stressed that because of the small size of the total population, there were only few events in each subgroup.

According to the guidelines, β-blockers are the first-line drugs to control ventricular rate in patients with HF and AF.[1] However, the optimal resting HR remains uncertain, as previous studies (AFFIRM, RACE) showed no difference in clinical events in the strict rate-control groups versus lenient rate-control groups.[14,30] The current ESC

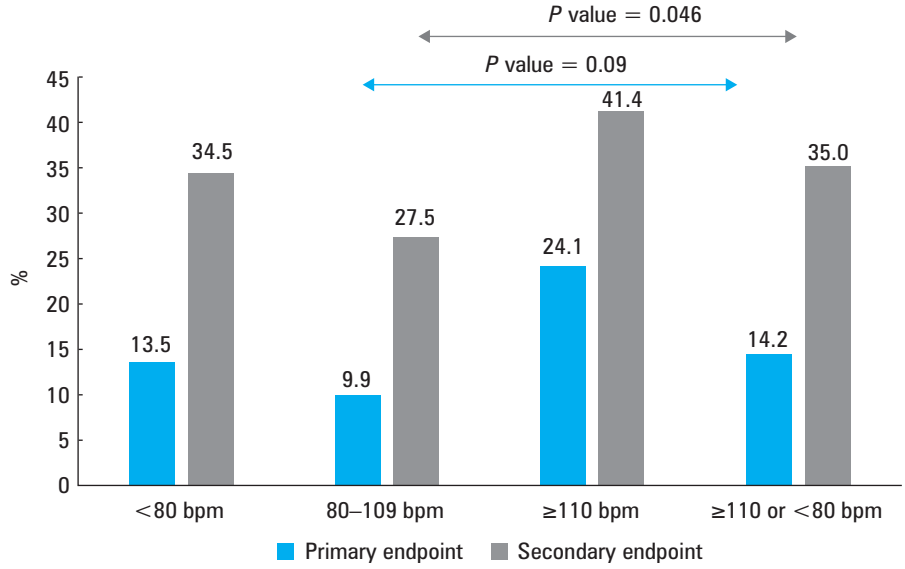


FIGURE 5 One-year outcomes in patients with heart failure and concomitant atrial fibrillation depending on resting heart rate at baseline

guidelines on HF suggest that the optimal HR for patients with HF and AF might be between 60 bpm and 100 bpm,[1] while the ESC guidelines on AF accept a resting ventricular rate of up to 110 bpm and recommend avoiding bradycardia.[10] In an analysis of data from the EORP-AF Pilot registry (EURObservational Research Programme--Atrial Fibrillation General Registry Pilot Phase), Lenarczyk et al[31] showed that a rhythm-control strategy is used more frequently in Poland than in other European countries. A recent analysis of the CIBIS II trial showed that in HFrEF patients with AF, in contrast to HFrEF patients in sinus rhythm, higher HR was not associated with worse outcomes.[3] Similarly, in the Swedish Heart Failure Registry, mortality was increased with higher HR in sinus rhythm, while in AF, mortality was increased only for an HR higher than 100 bpm.[25]

Limitations of the study The main limitation of our study is a relatively low number of patients, especially in the control group (ie, patients not receiving β-blockers) and in the subgroup of patients with an HR of 110 bpm or higher. Thus, the reporting of findings for the HR subgroups may be underpowered. Due to relatively small groups, we were not able to assess the effect of β-blockers with respect to LVEF or to conduct a propensity score matching analysis.

Another important limitation of our study is a joint analysis of ambulatory HF patients and HF patients discharged after HF hospitalization. We decided to combine these 2 subgroups to increase the number of study patients and thus the statistical power of the analysis. The proportion of patients discharged after HF hospitalization was significantly higher in the group not treated with β-blockers. Still, in the multivariate analysis, β-blocker treatment remained a significant predictor of the primary endpoint irrespective of the recent hospitalization.

Due to a relatively small number of patients, we decided to perform a combined analysis of patients with all types of AF (paroxysmal, persistent, and permanent) as a single study group. The most appropriate approach would probably be to evaluate patients with permanent AF and those with paroxysmal AF separately. However, this would increase the complexity of the study and further reduce the size of the study subgroups, thus precluding any reliable analysis.

An important advantage of registries is inclusion of real-life patients, but drawbacks include partial incompleteness of the data, as shown in TABLES 1 and 2. The findings of our study correspond with previously published data from large registries,[7,19,25,32] but randomized clinical trials are needed to clarify the effect of β-blockers on long-term outcomes in HF patients with concomitant AF.

Conclusions In patients with HF and AF treated with β-blockers, we observed lower mortality rates at 1 year in comparison with those not receiving β-blockers. In these patients, an HR of 80 bpm to 109 bpm may be associated with better outcomes, while patients with an HR of 110 bpm or higher have worse survival. However, β-blocker treatment seemed to have no impact on the risk of hospitalization for HF worsening in patients with HF and AF. These data indicate the need for further properly designed comparative studies to confirm the possible benefits of β-blocker treatment, as well as to establish a target resting HR value in this patient population.

ACKNOWLEDGMENTS The study was financed from statutory funds of the European Society of Cardiology (ESC).

CONTRIBUTION STATEMENT KO conceived the concept for the study and performed statistical analysis. KO and AK-C designed the analysis, interpreted the data, and wrote the manuscript. KO, AK-C, PB, AT, AW, MP, and MM contributed to data research. KJF and GO reviewed

the manuscript. MGC-L and APM designed and coordinated the registries. JD coordinated the registry nationwide. All authors edited and approved the final version of the manuscript.

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