Association between beta-blocker use and mortality/morbidity in patients with heart failure with reduced, midrange, and preserved ejection fraction and advanced chronic kidney disease

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ORIGINAL ARTICLE

Association Between β-Blocker Use and Mortality/Morbidity in Patients With Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction and Advanced Chronic Kidney Disease

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BACKGROUND: It is unknown if β-blockers reduce mortality/morbidity in patients with heart failure (HF) and advanced chronic kidney disease (CKD), a population underrepresented in HF trials.

METHODS: Observational cohort of HF patients with advanced CKD (estimated glomerular filtration rate <30 mL/min per 1.73 m^2) from the Swedish Heart Failure Registry between 2001 and 2016. We first explored associations between β-blocker use, 5-year death, and the composite of cardiovascular death/HF hospitalization among 3775 patients with HF with reduced ejection fraction (HFrEF) and advanced CKD. We compared observed hazards with those from a control cohort of 15 346 patients with HFrEF and moderate CKD (estimated glomerular filtration rate <60–30 mL/min per 1.73 m^2), for whom β-blocker trials demonstrate benefit. Second, we explored outcomes associated to β-blocker among advanced CKD participants with preserved (HFpEF; N=2009) and midrange ejection fraction (HFmrEF; N=1514).

RESULTS: During a median follow-up of 1.3 years, 2012 patients had a subsequent HF hospitalization, and 2849 died in the HFrEF cohort, of which 2016 died due to cardiovascular causes. Among patients with HFrEF, β-blocker use was associated with lower risk of death (adjusted hazard ratio 0.85 [95% CI, 0.75–0.96]) and cardiovascular mortality/HF hospitalization (0.87 [0.77–0.98]) compared with nonuse. The magnitude of the associations was similar to that observed for HFrEF patients with moderate CKD. Conversely, no significant association was observed for β-blocker users in advanced CKD with HFpEF (death: 0.88 [0.77–1.02], cardiovascular mortality/HF hospitalization: 1.05 [0.90–1.23]) or HFmrEF (death: 0.95 [0.79–1.14], cardiovascular mortality/HF hospitalization: 1.09 [0.90–1.31]).

CONCLUSIONS: In HFrEF patients with advanced CKD, the use of β-blockers was associated with lower morbidity and mortality. Although inconclusive due to limited power, these benefits were not observed in similar patients with HFpEF or HFmrEF.

Key Words: chronic kidney disease ■ ejection fraction ■ heart failure ■ hospitalization ■ morbidity ■ mortality ■ registries

Chronic kidney disease (CKD) is highly prevalent in patients with heart failure (HF) and their coexistence is increasing due to an aging population and shared risk factors and mechanisms.[1–3] Patients with HF and CKD experience significant morbidity and mortality,[4,5] which is highest in those with advanced CKD (estimated glomerular filtration rate [eGFR] <30 mL/min per 1.73 m^2).[2,6–8] Although persons with advanced CKD typically represent 10% to 15% of the HF population, they have been systematically excluded or underrepresented in HF

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WHAT IS NEW?

- Patients with advanced chronic kidney disease (estimated glomerular filtration rate <30 mL/min per 1.73 m^2) have been severely underrepresented in landmark heart failure (HF) trials but represent 10% to 15% of the HF population. The effectiveness of medications in this population is not well known.
- In this study from the Swedish Heart Failure Registry, β-blocker therapy was associated with improved survival in patients with HF with reduced ejection fraction and advanced chronic kidney disease, as well as a lower risk for the composite outcome of cardiovascular death and HF hospitalization.
- Although inconclusive due to limited power, these benefits were not observed in patients with HF with midrange ejection fraction or HF with preserved ejection fraction and advanced chronic kidney disease.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Our findings highlight that β-blocker use should be considered in all patients with HF with reduced ejection fraction regardless of kidney function.

Nonstandard Abbreviations and Acronyms

CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
HF	heart failure
HFmrEF	heart failure with midrange ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
LVEF	left ventricular ejection fraction
RASi	renin-angiotensin system inhibitor

clinical trials,[9–12] leading to uncertainty about the effect of therapies and optimal management for them.[13]

β-Blockers are a cornerstone in the treatment of patients with HF with reduced ejection fraction (HFrEF) since they substantially reduce mortality and morbidity.[13–21] A recent meta-analysis of randomized trials showed consistent benefits of β-blockers in patients with HFrEF and moderate CKD (eGFR 30–60 mL/min per 1.73 m^2), but there were too few HF patients with advanced CKD (<3% of all patients included in the trials) to draw firm conclusions.[22] Furthermore, the few observational studies conducted to date show inconsistent results, being limited by a small number of patients with advanced CKD[23–25] and lacking information on ejection fraction.[26,27]

We here sought to evaluate outcomes associated with the use of β-blockers in a large, contemporary, and nationwide routine-cared cohort of patients with HFrEF and advanced CKD. As a secondary objective, we investigated whether potential benefits of β-blockers may also extend to patients with advanced CKD and HF with midrange (HFmrEF) or preserved ejection fraction (HFpEF), for whom no β-blocker trial evidence exist.

METHODS

Study Protocol and Setting

The data that support the findings of this study are available from the corresponding author, provided that data sharing is permitted by European Union General Data Protection Regulation regulations and appropriate ethics committees. The Swedish Heart Failure Registry has been described previously.[28] The inclusion criterion is clinician-judged HF. Approximately 80 variables are recorded at hospital discharge or after an outpatient clinic visit and entered into a web-based database managed by the Uppsala Clinical Research Center. Ejection fraction is categorized as <30%, 30% to 39%, 40% to 49%, and ≥50%. Deaths and causes of death are obtained from the Swedish Population Registry monthly. The National Patient Registry was used to obtain information on additional baseline comorbidities and the outcomes hospitalization due to HF, hospitalization due to syncope and cancer. Variable definitions are reported in Table I in the Data Supplement. Linkage with Statistics Sweden provided socioeconomic characteristics. Individual patient consent is not required, but patients are informed of entry into national registries and have the opportunity to opt-out. This study was approved by a multisite ethics committee and complies with the Declaration of Helsinki.

Study Population

Patients registered between May 11, 2000 and December 31, 2016, with an eGFR <30 mL/min per 1.73 m^2 at time of registration and no missing data for β-blocker use or ejection fraction were considered for this study. Patients receiving β-blockers other than those recommended by HF guidelines (ie, bisoprolol, carvedilol, or metoprolol) and those that died during the index hospitalization/outpatient visit were excluded. The index date was defined as the date of hospital discharge or date of outpatient clinic visit. If the same patient was registered more than once, we considered the first registration with eGFR <30 mL/min per 1.73 m^2. eGFR was calculated using the CKD Epidemiology Collaboration equation.[29] Patients undergoing chronic dialysis at index date where considered to have advanced CKD. Individuals were followed from index date until occurrence of an event or end of follow-up (December 31, 2016), whichever occurred first. A flow chart describing patient flow is reported in Figure I in the Data Supplement.

Outcomes

Our primary outcome was mortality due to any cause up to 5 years. Secondary outcomes included a combined end point of 5-year cardiovascular mortality and HF hospitalization (definitions in Table I in the Data Supplement), and each component

separately. As safety outcome we considered hospitalization for syncope, as β-blocker use is associated with increased risk of bradycardia and hypotension.[10] As a negative control outcome, we used hospitalization for cancer.

Covariates

Study covariates were recorded at HF registration/discharge and were used in multivariable adjustments and included age, sex, civil status, location (inpatient or outpatient), follow-up referral specialty, New York Heart Association class, left ventricular ejection fraction (LVEF; <30 versus 30%–39% in HFrEF analyses; EF not used for adjustment in the HFpEF or HFmrEF analyses), systolic, diastolic and mean arterial pressure, heart rate, eGFR, HF duration, comorbidities (hypertension, diabetes mellitus, smoking, ischemic heart disease, peripheral artery disease, stroke/transient ischemic attack, atrial fibrillation, anemia, valvular disease, lung disease, and dilated cardiomyopathy), concomitant medications (renin-angiotensin system inhibitors [RASi], mineralocorticoid receptor antagonists, digoxin, diuretic, nitrate, platelet inhibitor, oral anticoagulant, and statins) and history of interventions (revascularization, valve intervention, pacemaker, cardiac resynchronization therapy, and implantable cardioverter-defibrillator). We further extracted information on NT-proB-type natriuretic peptide and body mass index but did not adjust for these variables due to a high proportion of missing values.

Statistical Analysis

Continuous variables are presented as mean with SD or median with interquartile range, depending on the distribution, and categorical variables as number and percentages.

The primary analysis compared outcomes associated with β-blocker use in patients with HFrEF (ejection fraction ≤39%). Incidence rates per 100 person-years with 95% confidence interval (CI) were calculated for each outcome. We computed survival curves standardized to the distribution of the baseline variables in the study population to provide absolute survival probabilities and risk differences.[30,31] Survival probabilities were log-log transformed before pooling and combined using Rubin's rules.[32] The combined estimates were back transformed onto the original scale after pooling. Multivariable Cox proportional hazards regression was used to estimate hazard ratios (HRs) for the association between β-blocker use and outcomes. The proportional hazards assumption was verified by assessment of the Schoenfeld residuals. We performed subgroup analyses in a priori defined strata of sex, location, New York Heart Association class (I/II versus III/IV), ejection fraction (<30% versus 30%–39%), eGFR (<15 versus 15–30 mL/min per 1.73 m^2), atrial fibrillation, diabetes mellitus, hypertension, ischemic heart disease and chronic obstructive pulmonary disease, and nonprespecified subgroups of RASi and mineralocorticoid receptor antagonist use. In addition, we compared outcomes according to the β-blocker dose received.

Observed estimates were contrasted with those from a positive control cohort of patients with HFrEF and moderate CKD (eGFR between 30 and 60 mL/min per 1.73 m^2), for whom a risk benefit has been observed in landmark trials.[10–12,33,34] The positive control cohort was defined in the same way as our primary cohort. As a sensitivity analysis, we repeated our analyses using a maximum follow-up of 1 year. Furthermore, to evaluate the extent of residual confounding, we used hospitalization for cancer as a negative control outcome, which is not expected to be associated with β-blocker use.

Finally, we evaluated outcomes associated with β-blocker use in persons with advanced CKD and HFmrEF (ejection fraction 40%–49%) or HFpEF (ejection fraction ≥50%) separately, in a manner identical to our primary analysis.

Missing confounder values were imputed using a multiple imputation by chained equations algorithm (generating 50 imputed datasets), including the confounder information, β-blocker use, the censoring indicator of the composite outcome and the Nelson-Aalen estimate of the cumulative hazard. Missing data for each variable are reported in Table II in the Data Supplement for all cohorts separately. Statistical analyses were performed using R version 3.6.2.

RESULTS

Among a total of 76 506 patients in the Swedish Heart Failure Registry, 7298 had advanced CKD (Figure I in the Data Supplement). Based on the LVEF evaluation, 3775 were classified as HFrEF, 2009 as HFpEF, and 1514 as HFmrEF. Characteristics for the overall HF cohort are shown in Table III in the Data Supplement; β-blockers were used in 6317 (87%) individuals.

Primary Analysis: β-Blockers in HFrEF With Advanced CKD

Baseline characteristics for the HFrEF cohort, stratified by β-blocker use are reported in the Table. Of the 3775 patients with HFrEF, 3371 (89%) were treated with β-blockers and 404 were not (11%). The majority of patients received metoprolol (53%), followed by bisoprolol (41%) and carvedilol (6%). As many as 26% received target doses, 36% received 50% to 99% of the target dose, and the remaining 38% received <50% of target dose (Table IV and Figure II in the Data Supplement). Median (interquartile range) age was 80 (74–85) years among β-blocker users, compared with 82 (75–87) years among nonusers, and in both groups, the proportion of women was 36%. Among β-blocker users, 51% had an ejection fraction <30%, compared with 54% among nonusers. Atrial fibrillation was a common comorbidity, occurring in 62% of β-blocker users and 58% of nonusers (Table).

The median follow-up time was 1.3 years, for a total of 6138 person-years of follow-up. A total of 2849 (75.5%) individuals died, of whom 2016 (70.8% of total deaths) due to cardiovascular causes. The 5-year incidence rate of all-cause mortality was 44.8 per 100 (95% CI, 43.1–46.6) person-years among β-blocker users versus 64.0 (57.2–71.3) for nonusers (Figure 1). The 5-year survival was 12.9% for nonusers and 16.2% for β-blocker users (Figure 2, Table V in the Data Supplement). Compared with no use, β-blocker users had a 3.2% (95% CI, 0.9%–5.6%) lower mortality risk, with an adjusted HR of 0.85

Table. Baseline Characteristics of Individuals With HFrEF and Advanced CKD (eGFR <30 mL/min per 1.73 m²), Overall and Stratified by β-Blocker Use

	β-Blocker Users (N=3371)	β-Blocker Nonusers (N=404)
Age, y, median [IQR]	80 [74–85]	82 [75–87]
Women, n (%)	1213 (36)	145 (36)
Location, outpatient (%)	1109 (33)	84 (21)
Follow-up location, specialty (%)	1830 (58)	168 (47)
NYHA class (%)		
I	70 (3)	7 (3)
II	670 (28)	54 (22)
III	1355 (57)	128 (53)
IV	279 (12)	54 (22)
EF, n (%)		
<30	1721 (51)	218 (54)
30–39	1650 (49)	186 (46)
Clinical measures		
BMI, kg/m², mean (SD)	27 (5)	26 (5)
SBP, mm Hg, mean (SD)	122 (22)	122 (23)
DBP, mm Hg, mean (SD)	70 (12)	70 (13)
MAP, mm Hg, mean (SD)	87 (14)	87 (15)
Heart rate (bpm), median [IQR]	75 (16)	76 (17)
eGFR, mL/min per 1.73 m², median [IQR]	25 [20–28]	24 [19–28]
eGFR <15 mL/min per 1.73 m² (%)	347 (10)	57 (14)
eGFR between 15 and 30 mL/min per 1.73 m² (%)	3024 (90)	347 (86)
NT-proBNP, pg/L, median [IQR]	9176 [3914–19894]	9950 [4241–24107]
Smoking, n (%)		
Never	1100 (44)	122 (45)
Former	1176 (47)	123 (45)
Current	209 (8)	29 (11)
Medical history, n (%)		
Atrial fibrillation	2084 (62)	235 (58)
Anemia	2031 (61)	254 (63)
COPD	553 (16)	73 (18)
Dilated cardiomyopathy	379 (12)	50 (13)
Diabetes mellitus	1339 (40)	147 (36)
Hypertension	2573 (76)	274 (68)
Ischemic heart disease	2542 (75)	272 (67)
Peripheral artery disease	632 (19)	89 (22)
Stroke and TIA	636 (19)	94 (23)
Valvular disease	1204 (36)	167 (41)
Cancer in the previous 3 years	418 (12)	66 (16)
Procedures		
Coronary revascularization	1410 (42)	138 (34)
Devices (CRT or ICD)	412 (12)	25 (6)
Pacemaker (CRT-D, CRT-P, or pacemaker)	668 (20)	71 (18)
Medication use, n (%)		
RAS inhibitors	2320 (69)	215 (53)
MRA	827 (25)	109 (27)
Digoxin	313 (9)	36 (9)
Diuretics	3178 (95)	374 (94)
Statins	1661 (49)	141 (35)
Anticoagulants	1358 (40)	130 (32)
Antiplatelets	1798 (54)	192 (48)
Nitrates	928 (28)	93 (23)
Socioeconomic characteristics, n (%)		
Marital status		
Married	1600 (48)	191 (47)
Single	742 (22)	84 (21)
Widowed	1022 (30)	129 (32)
Education level		
Compulsory school	1751 (54)	209 (53)
Secondary school	1132 (35)	135 (34)
University	387 (12)	51 (13)
Income > median	1511 (45)	173 (43)

BMI indicates body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillation; CRT-P, cardiac resynchronization therapy with pacemaker; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HFrEF, HF with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RAS, renin-angiotensin system; SBP, systolic blood pressure; and TIA, transient ischemic attack.

(95% CI, 0.75–0.96). A total of 2779 (73.6%) patients experienced the composite outcome of cardiovascular mortality or HF hospitalization, with again a lower incidence among β-blocker users (incidence rate 69.8 [95% CI, 67.2–72.5]) than among for nonusers (incidence rate 92.3 [95% CI, 82.3–103.1]). The 5-year composite-free survival was 10.3% among nonusers and 12.9% for β-blocker users (Figure 2, Table VI in the Data Supplement). Compared with no use, β-blocker users had a 2.6% (95% CI, 0.3%–4.8%) lower cardiovascular mortality/HF hospitalization risk (HR 0.87 [95% CI, 0.77–0.98]), primarily attributed to a reduction in cardiovascular death (HR 0.81 [0.71–0.93]), whereas the adjusted HR for HF hospitalization was 0.94 (95% CI, 0.81–1.10) (Figure III in the Data Supplement). Results were similar when using a shorter maximum 1-year follow-up (Table VII in the Data Supplement). No differences were observed for the safety outcome, risk of syncope hospitalization, with a HR of 0.99 (95% CI, 0.47–2.07) for β-blocker users compared with no use. We also observed no association between β-blocker use and the negative control outcome of cancer hospitalization, with a HR of 1.08 (0.63–1.84; Table VIII in the Data Supplement).

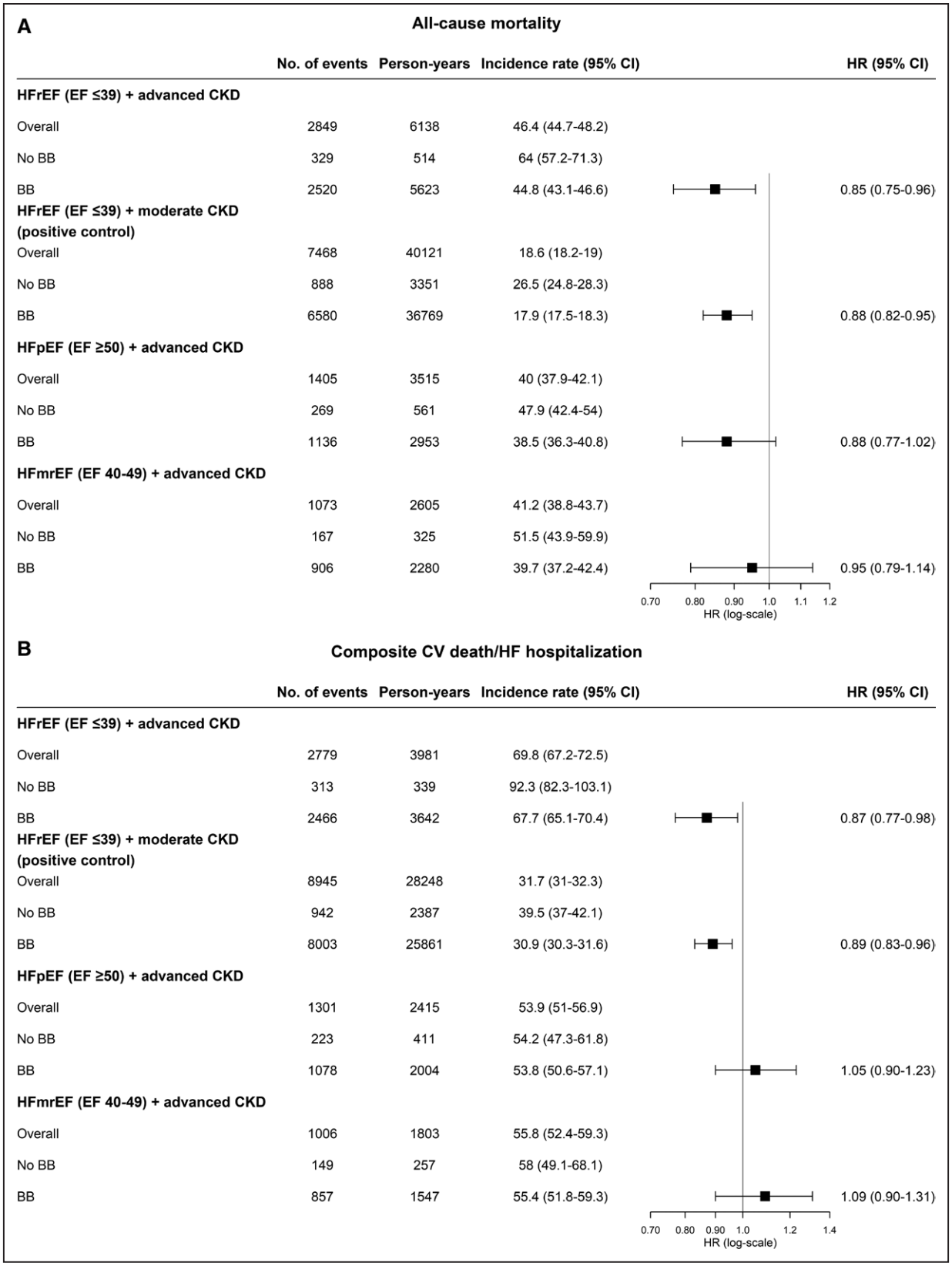

Figure 1. Number of events, incidence rates, and adjusted hazard ratios for the association between β-blocker use and 5-year all-cause mortality, and composite outcome of cardiovascular (CV) mortality/heart failure (HF) hospitalization in patients with HF with reduced ejection fraction (HFrEF), positive control cohort, HF with preserved ejection fraction (HFpEF) and HF with midrange ejection fraction (HFmrEF).

Analyses were adjusted for age, sex, New York Heart Association (NYHA) class, ejection fraction, mean arterial pressure, heart rate, (*Continued*)

Figure 1 Continued. estimated glomerular filtration rate (eGFR), smoking, atrial fibrillation, anemia, chronic obstructive pulmonary disease, dilated cardiomyopathy, diabetes mellitus, hypertension, ischemic heart disease, peripheral artery disease, stroke/transient ischemic attack, valvular disease, cancer, dementia, coronary revascularization, devices (cardiac resynchronization therapy [CRT] or implantable cardioverter-defibrillator [ICD]), renin-angiotensin system (RAS) inhibitor, mineralocorticoid receptor antagonist (MRA), digoxin, diuretics, statins, anticoagulants, antiplatelets, nitrates, marital status, education level, income, location (inpatient/outpatient), follow-up location (specialist yes/no), index year, and duration of heart failure. Incidence rates are depicted per 100 person-years. HFrEF was defined as ejection fraction ≤39%, HFmrEF between 40% and 49%, and HFpEF ≥50%. CKD indicates chronic kidney disease; and EF, ejection fraction.

Stratified analyses (Figure 3) showed significant interaction terms, with the association between β-blocker use and mortality being stronger for inpatient than for outpatient cases, and also stronger in the absence of ischemic heart disease and those not receiving RASi. The association between β-blocker use and the composite outcome was more favorable in patients with an eGFR <15 mL/min per 1.73 m^2 than in those with an eGFR between 15 and <30 mL/min per 1.73 m^2, among those without atrial fibrillation and those not receiving RASi. Compared with nonuse, the observed point estimates for benefit of β-blocker use were similar regardless of the dose prescribed, although the confidence intervals exclude 1 only for doses that are 50% or more of target (Tables IX and X in the Data Supplement).

Positive Control Cohort: β-Blockers in HFrEF With Moderate CKD

From a total of 15 346 identified individuals with HFrEF and moderate CKD, 13 890 (90.5%) were treated with β-blockers. Median eGFR was 48 mL/min per 1.73 m^2 (interquartile range, 40–54), 60.2% had CKD G3a and 39.8% CKD G3b (Table XI in the Data Supplement). The pattern of β-blocker drug class use was similar to that observed for patients with advanced CKD (Table IV in the Data Supplement). During follow-up, they experienced a much lower event rate for all-cause mortality (incidence rate 18.6 [95% CI, 18.2–19.0]) and the composite outcome (incidence rate 31.7 [95% CI, 31.0–32.3]) than patients with advanced CKD (Figure 1). The 5-year survival was 38.4% for nonusers and 42.0% for β-blocker users (Figure 2, Table VI in the Data Supplement). Compared with no use, patients receiving β-blockers had a 3.6% (95% CI, 1.5%–5.8%) lower risk of death (HR 0.88 [95% CI, 0.82–0.95]). The risk of cardiovascular death/HF hospitalization was also lower among β-blocker users (HR 0.89 [95% CI, 0.83–0.96]), attributed both to a lower cardiovascular death risk (HR 0.86 [95% CI, 0.79–0.94]) and a lower HF hospitalization risk (HR 0.88 [0.81–0.96]; Figure III in the Data Supplement).

Secondary Analyses: β-Blockers in HFpEF and HFmrEF With Advanced CKD

We identified 2009 individuals with HFpEF and 1514 individuals with HFmrEF and advanced CKD. In patients with HFpEF, 1649 (82.1%) used β-blockers, and 1297 (85.7%) patients with HFmrEF used β-blockers. Their characteristics are shown in Tables XII and XIII in the Data Supplement, and the number of outcomes during follow-up in Figure 1 and Figure III in the Data Supplement. The pattern of specific β-blocker class and recommended target dose within each class were similar to our primary analysis (Table IV in the Data Supplement). In patients with HFpEF, the use of β-blockers did not significantly associate with the risk of death (0.88 [0.77–1.02]) or cardiovascular death/HF hospitalization (1.05 [0.90–1.23]; Figure 1). The association was neither observed in β-blocker users with HFmrEF (HR 0.95 [95% CI, 0.79–1.14] for death and 1.09 [0.90–1.31] for cardiovascular death/HF hospitalization; Figure III in the Data Supplement).

DISCUSSION

This large prospective registry analysis of patients with HF and advanced CKD has the following findings: (1) overall β-blocker use was high despite lack of trial evidence; (2) use of β-blocker in HFrEF and advanced CKD was associated with lower risk of all-cause mortality and the composite outcome of cardiovascular mortality/HF hospitalization. The observed risk magnitude was similar to that of patients with HFrEF and moderate CKD; and (3) use of β-blockers in HFmrEF or HFpEF and advanced CKD showed inconsistent and nonsignificant associations with study outcomes.

Between 10% and 15% of patients with HF have advanced CKD.[2,7] This population is at the highest risk of complications and (cardiovascular) death,[5,6,8,9,35] attributed to the coexistence of both traditional (such as hypertension, dyslipidemia, and diabetes mellitus) and nontraditional cardiovascular risk factors (inflammation, mineral and bone disorders, oxidative stress, and clinical frailty) that emerge with the failing kidney.[36,37] In our study, we indeed observed that the incidence rates of death or composite cardiovascular death/HF outcomes were doubled in those with advanced CKD compared with the moderate CKD positive control cohort. Since the event rates are much higher, the absolute risk reduction of β-blocker use may actually be largest in individuals with the lowest kidney function, similarly to what has been observed for RASi in HFrEF and advanced CKD[38] or older age.[39]

β-Blockers are class I guideline-recommended therapies for patients with HFrEF,[13,14] without specifications by severity of CKD. A recent meta-analysis which pooled results of 16 740 patients from ten placebo-controlled

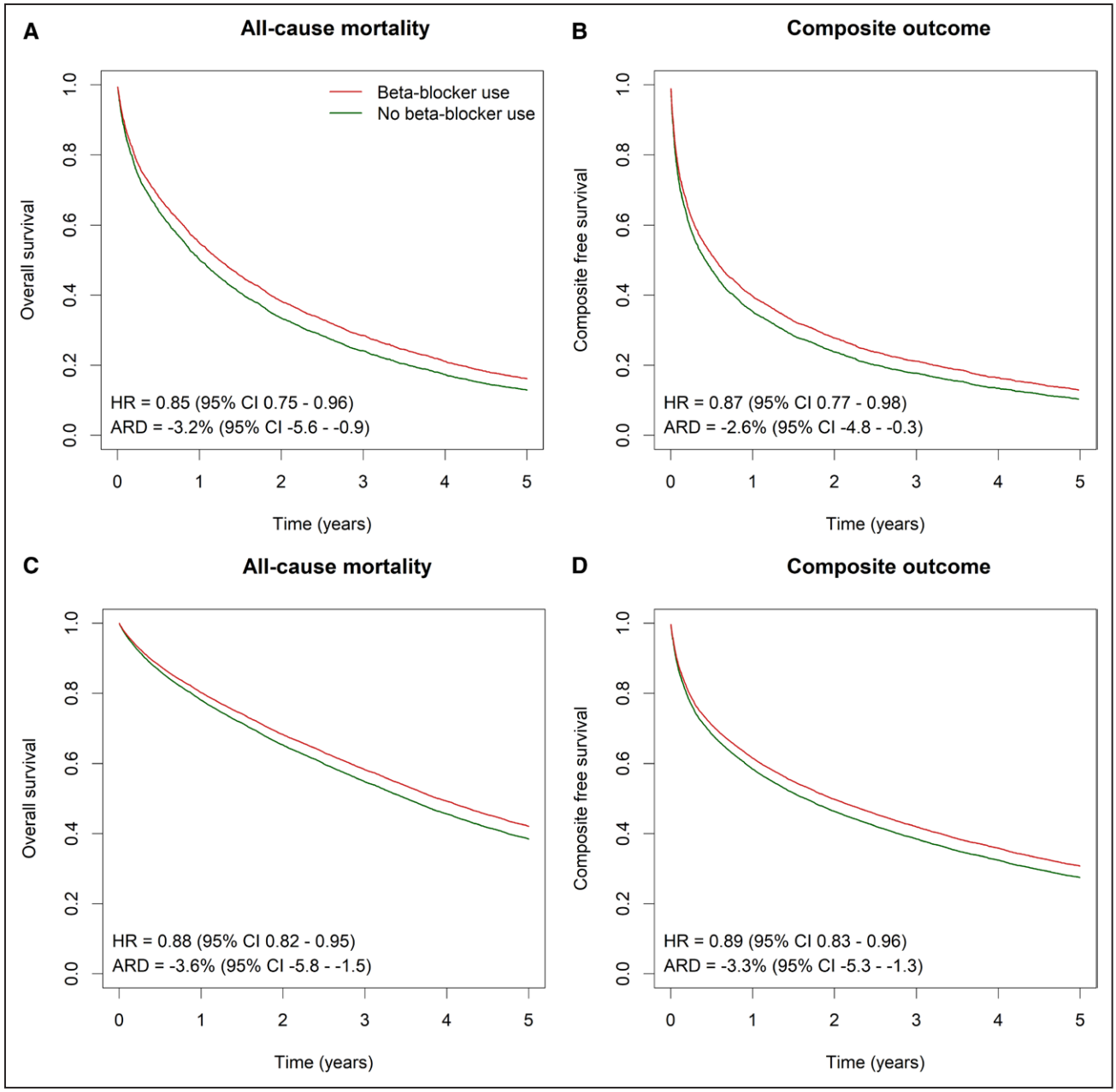

Figure 2. Standardized survival curves for the association between β-blocker use and all-cause mortality and the composite outcome cardiovascular mortality or heart failure hospitalization.
A and **B**, Patients with HF with reduced ejection fraction (HFrEF) and advanced chronic kidney disease (CKD). **C** and **D**, Patients with HFrEF and moderate CKD (positive control analysis). ARD indicates absolute risk difference at 5 y; and HR, hazard ratio.

trials, reported consistency in the death risk reduction of β-blockers for persons with moderate CKD (eGFR 30–60 mL/min per 1.73 m^2), reporting a HR of 0.73 (95% CI, 0.62–0.86) for patients with an eGFR of 45 to 59 mL/min per 1.73 m^2 and of 0.71 (95% CI, 0.58–0.87) for patients with eGFR 30 to 44 mL/min per 1.73 m^2.[22] The results from our positive control cohort align with these findings and found a slightly lower HR of 0.88 (0.82–0.95) for mortality. However, we note that patients in our routine-care cohort were considerably older (78 versus 68 years, respectively) and used different medications (mineralocorticoid receptor antagonist use 38% in our cohort versus 10% in the trials, respectively) than the patients included in those trials.

β-Blocker Use in HFrEF and Advanced CKD

There is a lack of evidence-based therapies for HFrEF patients with advanced CKD as they have been severely underrepresented in landmark randomized trials.[9–13,16–22] In the recent meta-analysis of 10 pooled randomized trials in HFrEF, only 448 out of 16740 patients (2.7%)

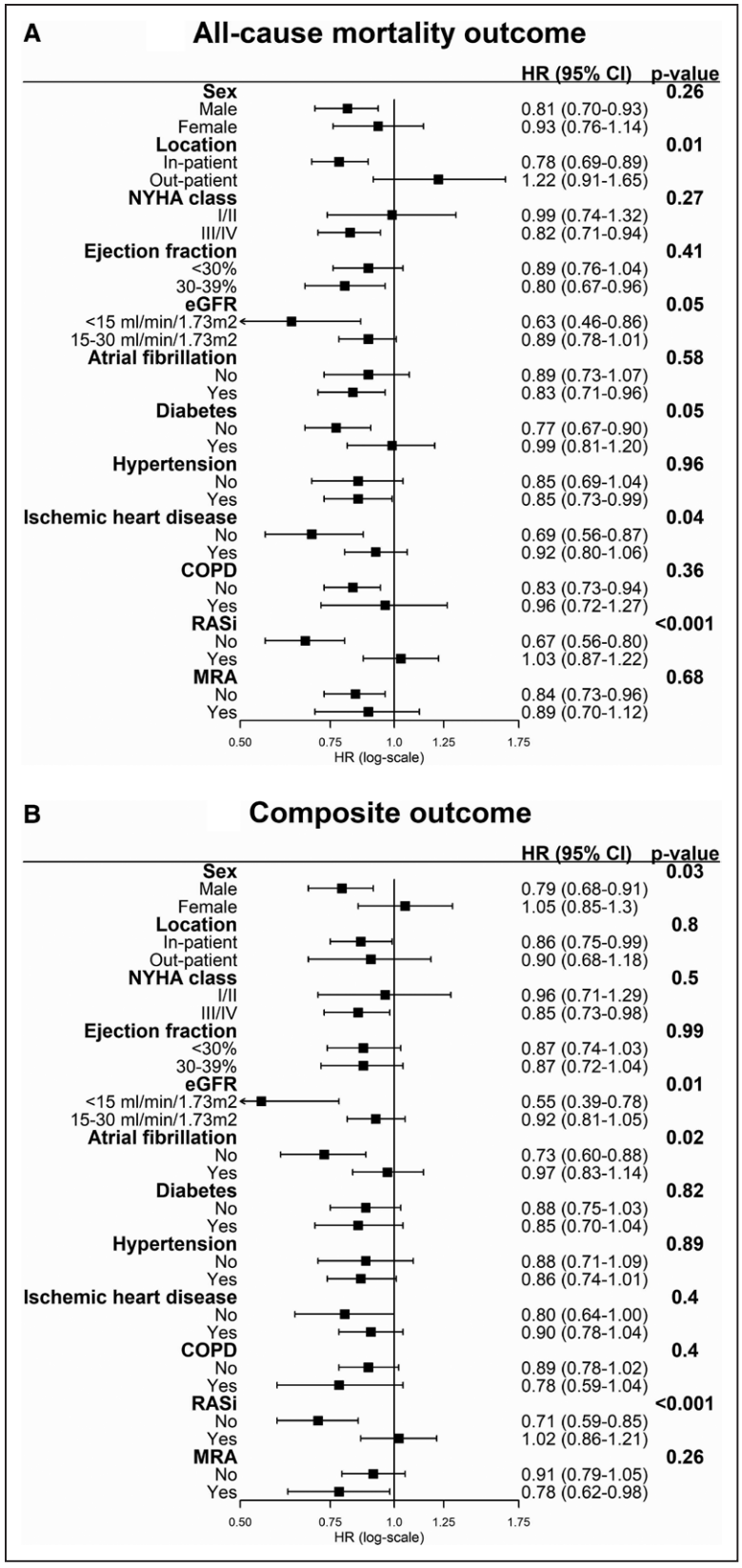

Figure 3. Association between β-blocker use, 5-year all-cause mortality and the composite of cardiovascular mortality and heart failure (HF) hospitalization in subgroups of patients with HF with reduced ejection fraction (HFrEF) and advanced chronic kidney disease (CKD). COPD indicates chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; and RASi, renin-angiotensin system inhibitor.

were identified to have advanced CKD at inclusion.[22] Due to this low number the authors were unable to comment on the efficacy of β-blockers in this population. Despite a lack of trial evidence, the majority (89%) of advanced CKD patients in our register used β-blockers. However, we note that a large proportion did not receive the recommended target dose, perhaps due to fear for side effects in this vulnerable population. Our main analysis in

HFrEF patients with advanced CKD suggests a possible therapeutic benefit similar to that observed for persons with moderate CKD. In support of our findings, a recent Canadian observational study (although small, with a sample size of only 200) reported a HR of 0.55 (95% CI, 0.41–0.73) in the risk of death in elderly patients with HF and advanced CKD initiating β-blockers versus no use.[26] However, this study lacked information on ejection fraction. Importantly, subgroup analyses in our study showed that the benefit on all-cause mortality and cardiovascular mortality/HF hospitalization also extended to those with the lowest level of kidney function (eGFR <15 mL/min per 1.73 m^2) and indicated no increased risk for syncope, although CIs were wide. In addition, the negative control outcome indicated no increased risk for cancer, thereby strengthening our inferences that observed differences are not primarily explained by a worse health status. Our subgroup analyses indicated no benefit of β-blocker use with regard to cardiovascular mortality/HF hospitalization in persons with HFrEF and atrial fibrillation, consistent with a recent meta-analysis.[40] However, we observed no effect modification for all-cause mortality. Although a number of recent studies have shown absent mortality benefit for β-blockers among patients with concomitant HF and atrial fibrillation, these analyses did not focus on patients with advanced CKD.[22,40–42] A meta-analysis specifically investigating patients with renal impairment found that β-blockers versus placebo were associated with HRs of 0.58 (0.21–1.63; N=72) for those with HFrEF, atrial fibrillation, and an eGFR <30 mL/min per 1.73 m^2 and 0.83 (0.58–1.19; N=458) for those with an eGFR between 30 and 44 mL/min per 1.73 m^2.[22] It may be that patients with advanced CKD and HF benefit from β-blockers via mechanisms that are different from those with less severe renal impairment. Alternatively, residual confounding or chance may explain the benefit in individuals with HFrEF and atrial fibrillation. The larger benefit of β-blocker use in certain subgroups such as those not receiving RASi needs replication in future studies.

β-Blocker Use in HFpEF or HFmrEF and Advanced CKD

Information on ejection fraction further allowed us to evaluate the potential effectiveness of β-blockers separately according to LVEF strata. We found that the observed benefit associated with β-blocker use in those with HFrEF and severe renal dysfunction was not extended to those with HFmrEF (ejection fraction 40%–49%) and HFpEF (ejection fraction ≥50%). A recent individual patient-level meta-analysis of randomized trials found that β-blockers conferred similar (cardiovascular) mortality benefit in persons with LVEF between 40% and 49% compared with LVEF <40% (adjusted HR 0.59 [95% CI, 0.34–1.03] for mortality and 0.48 [0.24–0.97] for cardiovascular mortality), although no benefit for cardiovascular hospitalization was observed (adjusted HR 0.95 [95% CI, 0.68–1.32]). Similar findings of a benefit in this mildly reduced EF range have been observed for angiotensin receptor blockers,[43] mineralocorticoid receptor antagonists,[44] and sacubitril/valsartan,[45] which is also consistent with the HFmrEF resembling HFrEF in most regards, rather than being an intermediate between HFrEF and HFpEF.[43,46] In addition, this meta-analysis found no evidence of benefit from β-blockers in the small subgroup of 244 patients with LVEF >50% in sinus rhythm. The absence of an effect of β-blockers in persons with HFmrEF and advanced CKD in our analyses was unexpected and inconsistent with the HFrEF data in our analysis and may be caused by effect modification according to renal function, or due to limited sample size and low event rate. Future studies should therefore confirm our findings.

Strengths and Limitations

Our analysis including 3775 patients with HFrEF and advanced CKD is the largest evaluation to date of β-blocker effectiveness in this population. Strengths of our study include the large sample size together with detailed information available in the Swedish Heart Failure Registry, which allowed extensive adjustment for a wide range of confounders. We were also able to study multiple outcomes across the ejection fraction spectrum, and results were robust in several sensitivity analyses, including the positive control cohort and negative control outcome. However, our study also has limitations. Residual confounding by indication may be present despite adjustment for 36 variables. In addition, the cohort size was considerably smaller for those with HFmrEF and HFpEF compared with HFrEF, which may have limited power. We further defined β-blocker use at baseline and potential cross-over may have diluted the association, although outcomes with 1 year of follow-up, for which we would expect less cross-over, showed similar results to the primary analysis with 5 years of follow-up. We did not use propensity score methods to control for confounding since there were few patients unexposed to β-blockers at baseline.[47] However, empirical studies have shown that multivariable-adjusted and propensity score-adjusted studies in general do not differ much in the estimated effect size.[48,49] Our results should be considered as hypothesis generating and need confirmation in randomized trials.

In conclusion, in patients with HFrEF and advanced CKD, β-blocker use was associated with improved survival. Our analyses support current guideline recommendations on β-blocker therapy in HFrEF patients regardless of kidney function.

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