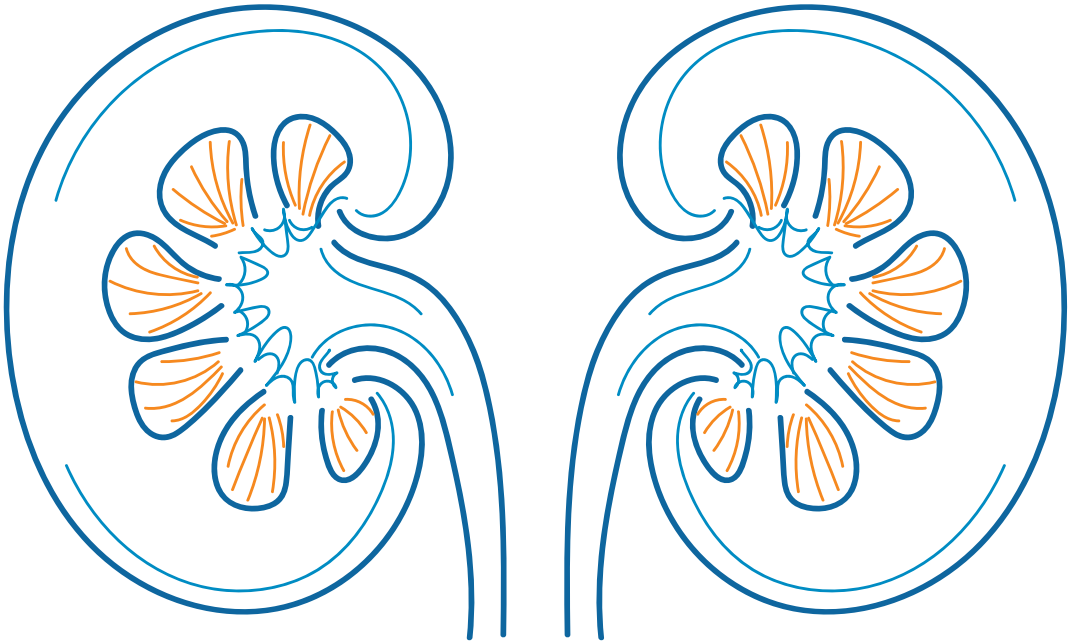
Optimal cardiovascular treatment strategies in kidney disease: casual inference from observational data

Fu, E.L.



CHAPTER 7

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

Edouard L. Fu, Alicia Uijl, Friedo W. Dekker, Lars H. Lund, Gianluigi Savarese, Juan-Jesus Carrero

Circ Heart Fail 2020; 13: e007180

Abstract

Background: It is unknown if beta-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 (eGFR [estimated glomerular filtration rate] <30 mL/min/1.73m^2) from the Swedish Heart Failure Registry between 2001-2016. We first explored associations between beta-blocker use, 5-year death, and the composite of cardiovascular (CV) death/HF hospitalization among 3,775 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 (eGFR<60-30 mL/min/1.73m^2), for whom beta-blocker trials demonstrate benefit. Secondly, we explored outcomes associated to beta-blocker among advanced CKD participants with preserved (HFpEF; N=2,009) and midrange ejection fraction (HFmrEF; N=1,514).

Results: During median 1.3 years, 2,012 patients had a subsequent HF hospitalization, and 2,849 died in the HFrEF cohort, of which 2,016 due to cardiovascular causes. Among patients with HFrEF, beta-blocker use was associated with lower risk of death (adjusted hazard ratio 0.85; 95% confidence interval 0.75-0.96) and CV mortality/HF hospitalization (0.87; 0.77-0.98) compared to non-use. The magnitude of the associations was similar to that observed for HFrEF patients with moderate CKD. Conversely, no significant association was observed for beta-blocker users in advanced CKD with HFpEF (death: 0.88; 0.77-1.02, CV mortality/HF: 1.05; 0.90-1.23) or HFmrEF (death: 0.95; 0.79-1.14, CV mortality/HF: 1.09; 0.90-1.31).

Conclusion: In HFrEF patients with advanced CKD, use of beta-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.

Introduction

Chronic kidney disease (CKD) is highly prevalent in patients with heart failure (HF) and their coexistence is increasing due to an ageing 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/1.73m^2) (2, 6-8). Although persons with advanced CKD typically represent 10-15% of the HF population, they have been systematically excluded or underrepresented in HF clinical trials (9-12), leading to uncertainty about the effect of therapies and optimal management for them (13).

Beta-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 beta-blockers in patients with HFrEF and moderate CKD (eGFR 30-60 ml/min/1.73m^2), but there were too few HF patients with advanced CKD (less than 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/or lacking information on ejection fraction (26, 27).

We here sought to evaluate outcomes associated with the use of beta-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 beta-blockers may also extend to patients with advanced CKD and heart failure with midrange (HFmrEF) or preserved ejection fraction (HFpEF), for whom no beta-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 heart failure. Approximately 80 variables are recorded at hospital discharge or after an out-patient clinic visit and entered into a web-based database managed by the Uppsala Clinical Research Center. Ejection fraction is categorized as <30%, 30-39%, 40-49% 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 **Supplemental Table S1**. 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 11 May 2000 and 31 December 2016 with an eGFR <30 ml/min/1.73m^2 at time of registration and no missing data for beta-blocker use or ejection fraction were considered for this study. Patients receiving beta-blockers other than those recommended by HF guidelines (i.e. 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/1.73m^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 (31 December 2016), whichever occurred first. A flow chart describing patient flow is reported in **Supplemental Figure S1**.

Outcomes

Our primary outcome was mortality due to any cause up to 5 years. Secondary outcomes included a combined endpoint of 5-year cardiovascular mortality and HF hospitalization (definitions in **Supplementary Table S1**), and each component separately. As safety outcome we considered hospitalization for syncope, as beta-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 (NYHA) class, left ventricular ejection fraction (LVEF) [<30 vs. 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, heart failure duration, comorbidities

(hypertension, diabetes mellitus, smoking, ischemic heart disease, peripheral artery disease, stroke/transient ischemic attack, atrial fibrillation, anemia, valvular disease, lung disease, dilated cardiomyopathy), concomitant medications (renin-angiotensin-system inhibitors [RASi], mineralocorticoid receptor antagonists [MRA], digoxin, diuretic, nitrate, platelet inhibitor, oral anticoagulant, statins) and history of interventions (revascularization, valve intervention, pacemaker, cardiac resynchronization therapy, 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 (IQR), depending on the distribution, and categorical variables as number and percentages.

The primary analysis compared outcomes associated with beta-blocker use in patients with HFrEF (ejection fraction ≤39%). Incidence rates per 100 person-years with 95% confidence intervals (95% confidence intervals [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 beta-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, NYHA class (I/II vs. III/IV), ejection fraction (<30% vs. 30-39%), eGFR (<15 ml/min/1.73m^2 vs. 15-30 ml/min/1.73m^2), atrial fibrillation, diabetes, hypertension, ischemic heart disease and COPD, and non-prespecified subgroups of RASi and MRA use. In addition, we compared outcomes according to the beta-blocker dose received.

Observed estimates were contrasted with those from a positive control cohort of patients with HFrEF and moderate CKD (eGFR between 30-60 ml/min/1.73m^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 beta-blocker use.

Finally, we evaluated outcomes associated with beta-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, beta-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 **Supplemental Table S2** for all cohorts separately. Statistical analyses were performed using R version 3.6.2.

Table 1. Baseline characteristics of individuals with HFrEF and advanced CKD (eGFR<30 ml/min/1.73m^2), overall and stratified by beta-blocker use.

	Beta-blocker users (N = 3371)	**Beta-blocker non-users (N = 404)**
Age, years, median (IQR)	80 [74, 85]	82 [75, 87]
Women (%)	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 (%)		
<30	1721 (51)	218 (54)
30-39	1650 (49)	186 (46)
Clinical measures		
BMI (kg/m^2), mean (SD)	27 (5)	26 (5)
SBP (mmHg), mean (SD)	122 (22)	122 (23)
DBP (mmHg), mean (SD)	70 (12)	70 (13)
MAP (mmHg), mean (SD)	87 (14)	87 (15)
Heart rate (bpm), median [IQR]	75 (16)	76 (17)
eGFR (mL/min/1.73m^2), median [IQR]	25 [20, 28]	24 [19, 28]
eGFR <15 ml/min/1.73m^2 (%)	347 (10)	57 (14)
eGFR between 15-30 ml/min/1.73m^2 (%)	3024 (90)	347 (86)

	Beta-blocker users (N = 3371)	Beta-blocker non-users (N = 404)
NT-proBNP, pg/L, median [IQR]	9176 [3914, 19894]	9950 [4241, 24107]
Smoking (%)		
Never	1100 (44)	122 (45)
Former	1176 (47)	123 (45)
Current	209 (8)	29 (11)
Medical history (%)		
Atrial fibrillation	2084 (62)	235 (58)
Anaemia	2031 (61)	254 (63)
COPD	553 (16)	73 (18)
Dilated cardiomyopathy	379 (12)	50 (13)
Diabetes	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/or 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 (%)		
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)

	Beta-blocker users (N = 3371)	Beta-blocker non-users (N = 404)
Socioeconomic characteristics (%)		
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)

NYHA = New York Heart Association; EF = ejection fraction; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; eGFR = estimated Glomerular Filtration Rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; CRT-D = cardiac resynchronization therapy with defibrillation; CRT-P = cardiac resynchronization therapy with pacemaker.

Results

Among a total of 76,506 patients in the Swedish Heart Failure Registry, 7,298 had advanced CKD (**Supplemental Figure S1**). Based on LVEF evaluation, 3,775 were classified as HFrEF, 2,009 as HFpEF and 1,514 as HFmrEF. Characteristics for the overall HF cohort are shown in **Supplemental Table S3**; beta-blockers were used in 6,317 (87%) individuals.

Primary analysis: Beta blockers in HFrEF with advanced CKD

Baseline characteristics for the HFrEF cohort, stratified by beta-blocker use are reported in **Table 1**. Of the 3,775 patients with HFrEF, 3,371 (89%) were treated with beta 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 50-99% of the target dose, and the remaining 38% received <50% of target dose (**Supplemental Table S4**, **Supplemental Figure S2**). Median (IQR) age was 80 (74-85) years among beta-blocker users, compared with 82 (75-87) years among non-users, and in both groups the proportion of women was 36%. Among beta-blocker users, 51% had an ejection fraction <30%, compared with 54% among non-users. Atrial fibrillation was a common comorbidity, occurring in 62% of beta-blocker users, and 58% of non-users (**Table 1**).

The median follow-up time was 1.3 years, for a total of 6,138 person-years of follow-up. A total of 2,849 (75.5%) individuals died, of whom 2,016 (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 beta-blocker users vs. 64.0 (57.2-71.3) for non-users (**Figure 1**). The 5-year survival was 12.9% for non-users and 16.2% for beta-blocker users (**Figure 2**, **Supplemental Table S5**). Compared to no-use, beta-blocker users had a 3.2% (95% CI 0.9%-5.6%) lower mortality risk, with an adjusted HR of 0.85 (95% CI 0.75-0.96). A total of 2,779 (73.6%) patients experienced the composite outcome of CV mortality or HF hospitalization, with again a lower incidence among beta-blocker users (incidence rate 69.8; 95% CI 67.2-72.5) than among for non-users (incidence rate 92.3; 95% CI 82.3-103.1).

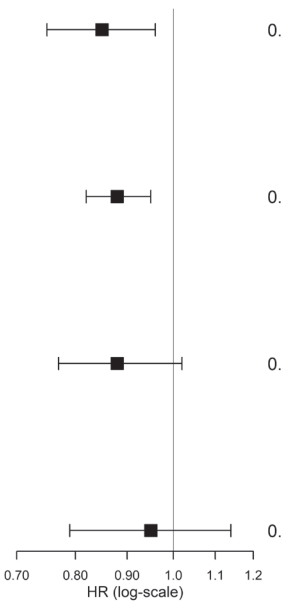
The 5-year composite-free survival was 10.3% among non-users and 12.9% for beta-blocker users (**Figure 2**, **Supplemental Table S6**). Compared to no-use, beta-blocker users had a 2.6% (95% CI 0.3%-4.8%) lower CV mortality/HF hospitalization risk (HR 0.87; 95% CI 0.77-0.98), primarily attributed to a reduction in cardiovascular death (HR 0.81; 0.71-0.93), whereas the adjusted HR for heart failure hospitalization was 0.94 (95% CI 0.81-1.10) (**Supplemental Figure S3**). Results were similar when using a shorter maximum 1-year follow-up (**Supplemental Table S7**). 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 beta-blocker users compared with no use. We also observed no association between beta-blocker use and the "negative control outcome" of cancer hospitalization, with a HR of 1.08 (0.63-1.84) (**Supplemental Table S8**).

Stratified analyses (**Figure 3**) showed significant interaction terms, with the association between beta-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 beta-blocker use and the composite outcome was more favorable in patients with an eGFR <15 ml/min/1.73m^2 than in those with an eGFR between 15-<30 ml/min/1.73m^2, among those without atrial fibrillation and those not receiving RASi. Compared to non-use, the observed point estimates for benefit of beta-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 (**Supplemental Tables S9-10**).

Figure 1. Number of events, incidence rates and adjusted hazard ratios for the association between beta-blocker use and 5-year all-cause mortality, and composite outcome of CV mortality/HF hospitalization in patients with HFrEF, positive control cohort, HFpEF and HFmrEF.

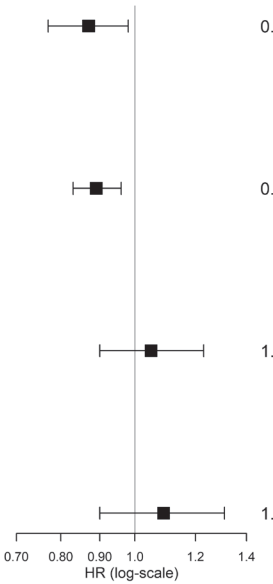
A. All-cause mortality

	No. of events	Person-years	Incidence rate (95% CI)	HR (95% CI)
HFrEF (EF ≤39) + advanced CKD				
Overall	2849	6138	46.4 (44.7-48.2)	
No BB	329	514	64 (57.2-71.3)	
BB	2520	5623	44.8 (43.1-46.6)	0.85 (0.75-0.96)
HFrEF (EF ≤39) + moderate CKD (positive control)				
Overall	7468	40121	18.6 (18.2-19)	
No BB	888	3351	26.5 (24.8-28.3)	
BB	6580	36769	17.9 (17.5-18.3)	0.88 (0.82-0.95)
HFpEF (EF ≥50) + advanced CKD				
Overall	1405	3515	40 (37.9-42.1)	
No BB	269	561	47.9 (42.4-54)	
BB	1136	2953	38.5 (36.3-40.8)	0.88 (0.77-1.02)
HFmrEF (EF 40-49) + advanced CKD				
Overall	1073	2605	41.2 (38.8-43.7)	
No BB	167	325	51.5 (43.9-59.9)	
BB	906	2280	39.7 (37.2-42.4)	0.95 (0.79-1.14)



B. Composite CV death/HF hospitalization

	No. of events	Person-years	Incidence rate (95% CI)	HR (95% CI)
HFrEF (EF ≤39) + advanced CKD				
Overall	2779	3981	69.8 (67.2-72.5)	
No BB	313	339	92.3 (82.3-103.1)	
BB	2466	3642	67.7 (65.1-70.4)	0.87 (0.77-0.98)
HFrEF (EF ≤39) + moderate CKD (positive control)				
Overall	8945	28248	31.7 (31-32.3)	
No BB	942	2387	39.5 (37-42.1)	
BB	8003	25861	30.9 (30.3-31.6)	0.89 (0.83-0.96)
HFpEF (EF ≥50) + advanced CKD				
Overall	1301	2415	53.9 (51-56.9)	
No BB	223	411	54.2 (47.3-61.8)	
BB	1078	2004	53.8 (50.6-57.1)	1.05 (0.90-1.23)
HFmrEF (EF 40-49) + advanced CKD				
Overall	1006	1803	55.8 (52.4-59.3)	
No BB	149	257	58 (49.1-68.1)	
BB	857	1547	55.4 (51.8-59.3)	1.09 (0.90-1.31)



Legend: Analyses were adjusted for age, sex, NYHA class, ejection fraction, mean arterial pressure, heart rate, eGFR, smoking, atrial fibrillation, anemia, COPD, dilated cardiomyopathy, diabetes, hypertension, ischemic heart disease, peripheral artery disease, stroke/TIA, valvular disease, cancer, dementia, coronary revascularization, devices (CRT or ICD), RAS inhibitor, 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 40-49% and HFpEF ≥50%. EF: ejection fraction.

Figure 2. Standardized survival curves for the association between beta-blocker use and all-cause mortality and the composite outcome cardiovascular mortality or heart failure hospitalization. Legend: Panels A and B: patients with HFrEF and advanced CKD. Panels C and D: patients with HFrEF and moderate CKD (positive control analysis). HR = hazard ratio; CI = confidence interval; ARD = absolute risk difference at 5 years.

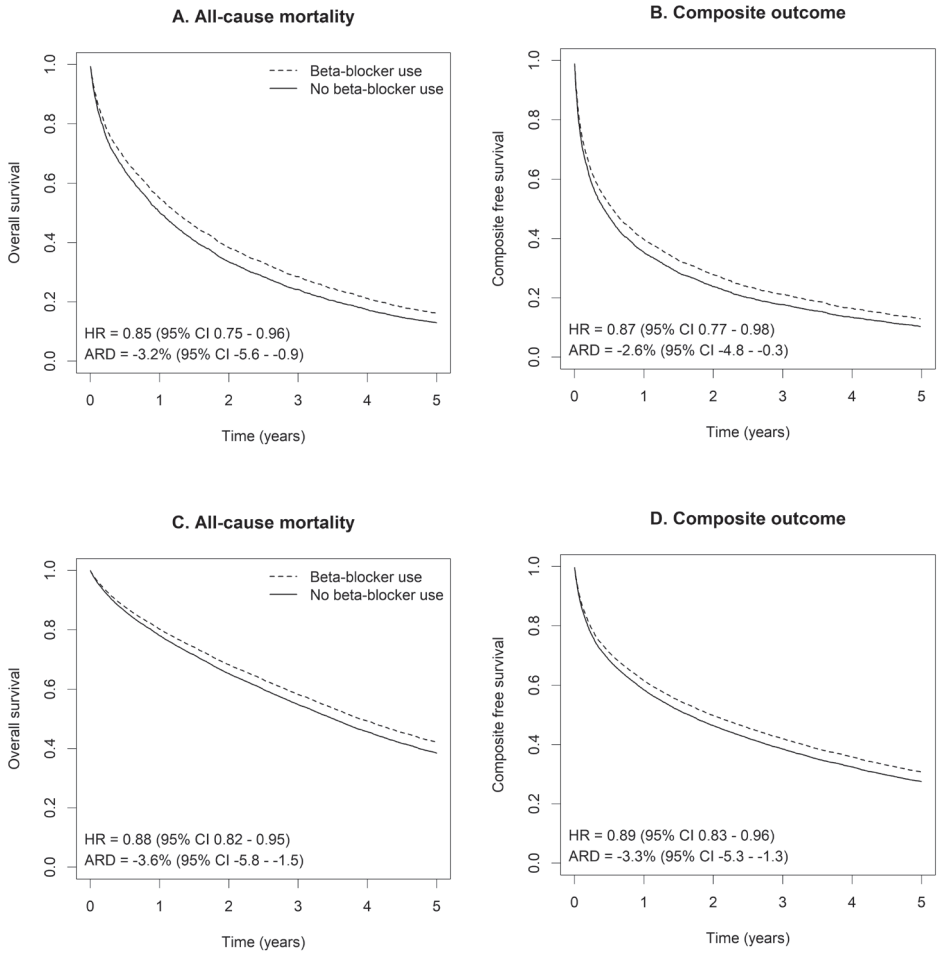
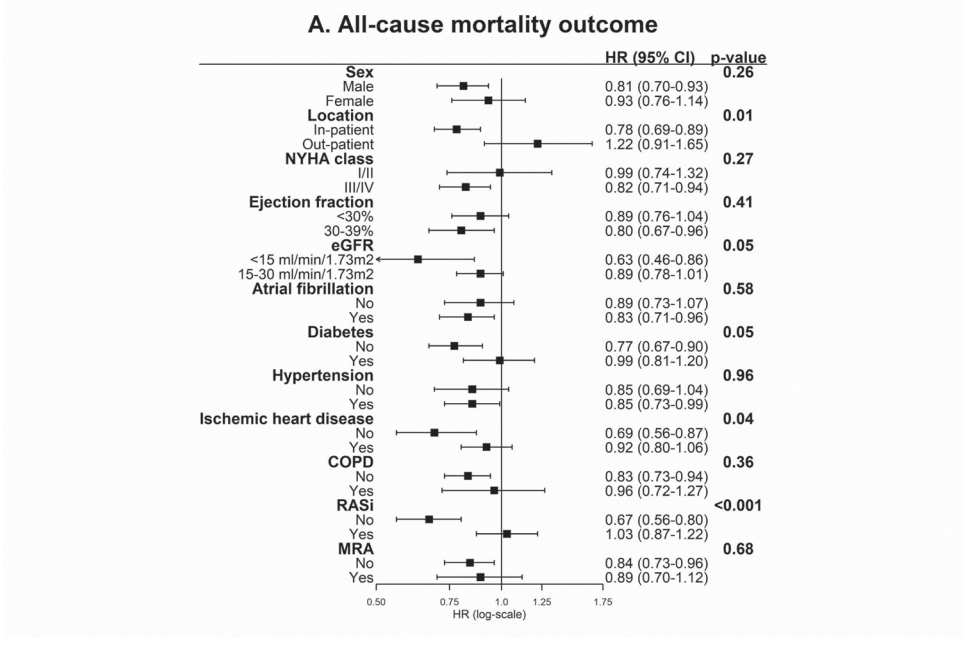
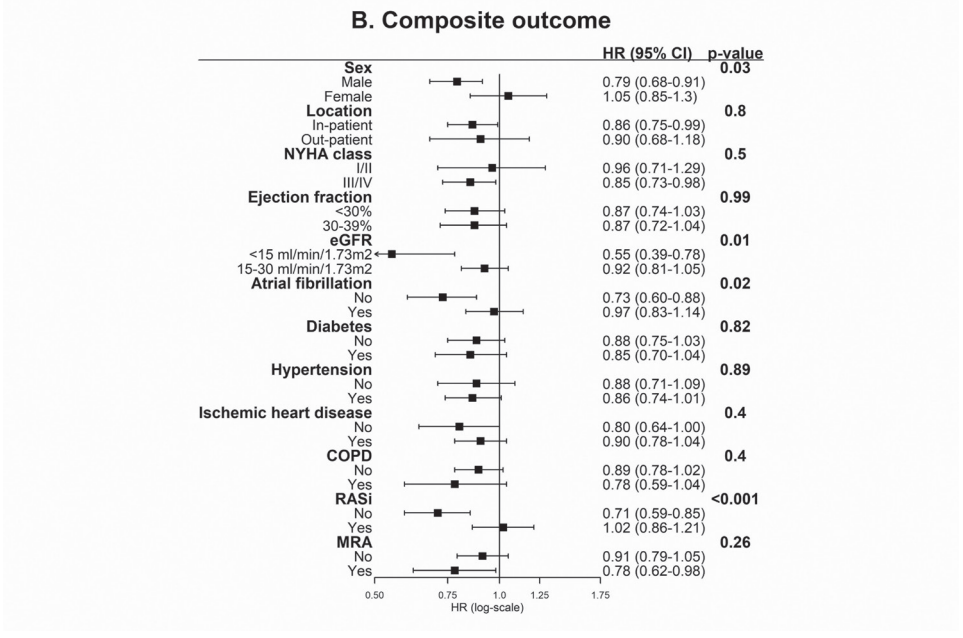


Figure 3. Association between beta-blocker use, 5-year all-cause mortality (A) and the composite of cardiovascular mortality and heart failure hospitalization (B) in subgroups of patients with HFrEF and advanced CKD.





Positive control cohort: Beta 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 beta-blockers. Median eGFR was 48 ml/min/1.73m^2 (IQR 40-54), 60.2% had CKD G3a and 39.8% CKD G3b (**Supplemental Table S11**). The pattern of beta-blocker drug class use was similar to that observed for patients with advanced CKD (**Supplemental Table S4**). 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 non-users and 42.0% for beta-blocker users (**Figure 2**, **Supplemental Table S6**). Compared to no-use, patients receiving beta-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 CV death/HF hospitalization was also lower among beta-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 heart failure hospitalization risk (HR 0.88; 0.81-0.96) (**Supplemental Figure S3**).

Secondary analyses: Beta blockers in HFpEF and HFmrEF with advanced CKD

We identified 2,009 individuals with HFpEF and 1,514 individuals with HFmrEF and advanced CKD. In patients with HFpEF, 1,649 (82.1%) used beta-blockers, and 1,297 (85.7%) patients with HFmrEF used beta-blockers. Their characteristics are shown in **Supplemental Tables S12-13**, and the number of outcomes during follow up in **Figure 1** and **Supplemental Figure S3**. The pattern of specific beta-blocker class and recommended target dose within each class were similar to our primary analysis (**Supplemental Table S4**). In patients with HFpEF the use of beta-blockers did not significantly associate with the risk of death (0.88; 0.77-1.02) or CV death/HF hospitalization (1.05; 0.90-1.23) (**Figure 1**). The association was neither observed in beta-blocker users with HFmrEF (HR 0.95; 95% CI 0.79-1.14 for death and 1.09; 0.90-1.31 for CV death/HF hospitalization) (**Supplemental Figure S3**).

Discussion

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

Between 10-15% 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) 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 CV 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 beta-blocker use may actually be largest in individuals with the lowest kidney function, similarly to what has been observed for RASi-inhibitors in HFrEF and advanced CKD (38) or older age (39).

Beta-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 trials, reported consistency in the death risk reduction of beta-blockers for persons with moderate CKD (eGFR 30-60 ml/min/1.73m^2), reporting a HR of 0.73 (95% CI 0.62-0.86) for patients with an eGFR of 45-59 ml/min/1.73m^2 and of 0.71 (95% CI 0.58-0.87) for patients with eGFR 30-44 ml/min/1.73m^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 vs. 68 years, respectively) and used different medications (MRA use 38% in our cohort vs. 10% in the trials, respectively) than the patients included in those trials.

Beta-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 16,740 patients (2.7%) were identified to have advanced CKD at inclusion (22). Due to this low number the authors were unable to comment on the efficacy of beta-blockers in this population. Despite a lack of trial evidence, the majority (89%) of advanced CKD patients in our register used beta-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 beta-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 CV mortality/HF hospitalization also extended to those with the lowest level of kidney function

(eGFR <15 ml/min/1.73m^2) and indicated no increased risk for syncope, although confidence intervals 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 beta-blocker use with regard to CV 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 beta-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 beta-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/1.73m^2 and 0.83 (0.58-1.19; N = 458) for those with an eGFR between 30-44 ml/min/1.73m^2 (22). It may be that patients with advanced CKD and heart failure benefit from beta-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 beta-blocker use in certain subgroups such as those not receiving RASi needs replication in future studies.

Beta-blocker use in HFpEF or HFmrEF and advanced CKD

Information on ejection fraction further allowed us to evaluate the potential effectiveness of beta-blockers separately according to LVEF strata. We found that the observed benefit associated with beta-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 beta-blockers conferred similar (cardiovascular) mortality benefit in persons with LVEF between 40-49% compared to LVEF <40% (adjusted HR 0.59; 95% CI 0.34-1.03 for mortality and 0.48; 0.24-0.97 for CV 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), MRAs (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 beta-blockers in the small subgroup of 244 patients with LVEF >50% in sinus rhythm. The absence of an effect of beta-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 3,775 patients with HFrEF and advanced CKD is the largest evaluation to date of beta-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 beta-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 beta-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, beta-blocker use was associated with improved survival. Our analyses support current guideline recommendations on beta-blocker therapy in HFrEF patients regardless of kidney function.

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Supplementary Material

Table S1. Variable definitions of comorbidities and outcomes.

Table S2. Percentage of missingness for all variables in all cohorts.

Table S3. Baseline characteristics of all individuals with advanced CKD (eGFR<30 ml/min/1.73m^2) regardless of ejection fraction, stratified by beta-blocker use.

Table S4. Guideline recommended beta-blocker agents and doses for patients with HFrEF, HFpEF and HFmrEF.

Table S5. Overall survival, composite-free survival and risk differences for all-cause mortality and the composite outcome cardiovascular mortality or heart failure hospitalization after 1, 3 and 5 years of follow-up in patients with HFrEF and advanced CKD.

Table S6. Overall survival, composite-free survival and risk differences for all-cause mortality and the composite outcome cardiovascular mortality or heart failure hospitalization after 1, 3 and 5 years of follow-up in the positive control cohort of patients with HFrEF and moderate CKD.

Table S7. Number of events, incidence rates, crude and adjusted hazard ratios for the association between beta-blocker use and 1-year all-cause mortality, CV mortality/HF hospitalization for individuals with HFrEF and advanced CKD.

Table S8. Number of events, incidence rates, crude and adjusted hazard ratios for the association between beta-blocker use and the negative control outcome cancer.

Table S9. Incidence rates and adjusted hazard ratios for mortality according to prescribed target dose of beta-blockers in patients with HFrEF and advanced CKD.

Table S10. Incidence rates and adjusted hazard ratios for the composite outcome CV death or HF hospitalization according to prescribed target dose of beta-blockers in patients with HFrEF and advanced CKD.

Table S11. Baseline characteristics in the positive control cohort of individuals with HFrEF and moderate CKD stratified by beta-blocker use.

Table S12. Baseline characteristics of individuals with HFpEF and advanced CKD (eGFR<30 ml/min/1.73m^2) stratified by beta-blocker use.

Table S13. Baseline characteristics of individuals with HFmrEF and advanced CKD (eGFR<30 ml/min/1.73m^2) stratified by beta-blocker use.

Figure S1. Flow chart of patient selection from the Swedish Heart Failure Registry.

Figure S2. Density plot of beta-blocker dose levels (% of recommended dose) used in patients with HFrEF and advanced CKD from the Swedish Heart Failure Registry.

Figure S3. Number of events, incidence rates and adjusted hazard ratios for the association between beta-blocker use and 5-year cardiovascular mortality, and heart failure hospitalization in patients with HFrEF, positive control cohort, HFpEF and HFmrEF.