

# Beta-blocker therapy in elderly patients with renal dysfunction and heart failure

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## ABSTRACT

**OBJECTIVE** To assess the role of beta-blockers (BB) in patients with chronic kidney disease (CKD) aged  $\geq 75$  years.

**METHODS AND RESULTS** From January 2008 to July 2014, we included 390 consecutive patients  $\geq 75$  years of age with ejection fraction  $\leq 35\%$  and glomerular filtration rate (GFR)  $\leq 60$  mL/min per  $1.73$  m<sup>2</sup>. We analyzed the relationship between treatment with BB and mortality or cardiovascular events. The mean age of our population was  $82.6 \pm 4.1$  years. Mean ejection fraction was  $27.9\% \pm 6.5\%$ . GFR was 60–45 mL/min per  $1.73$  m<sup>2</sup> in 50.3% of patients, 45–30 mL/min per  $1.73$  m<sup>2</sup> in 37.4%, and  $< 30$  mL/min per  $1.73$  m<sup>2</sup> in 12.3%. At the conclusion of follow-up, 67.4% of patients were receiving BB. The median follow-up was 28.04 (IR: 19.41–36.67) months. During the study period, 211 patients (54.1%) died and 257 (65.9%) had a major cardiovascular event (death or hospitalization for heart failure). BB use was significantly associated with a reduced risk of death (HR = 0.51, 95% CI: 0.35–0.74;  $P < 0.001$ ). Patients receiving BB consistently showed a reduced risk of death across the different stages of CKD: stage IIIa (GFR = 30–45 mL/min per  $1.73$  m<sup>2</sup>; HR = 0.47, 95% CI: 0.26–0.86,  $P < 0.0001$ ), stage IIIb (GFR 30–45 mL/min per  $1.73$  m<sup>2</sup>; HR = 0.55, 95% CI: 0.26–1.06,  $P = 0.007$ ), and stages IV and V (GFR  $< 30$  mL/min per  $1.73$  m<sup>2</sup>; HR = 0.29, 95% CI: 0.11–0.76;  $P = 0.047$ ).

**CONCLUSIONS** The use of BB in elderly patients with HFrEF and renal impairment was associated with a better prognosis. Use of BB should be encouraged when possible.

Heart failure (HF) is one of the most prevalent cardiovascular (CV) disorders worldwide. Approximately half of all patients with HF have reduced or mid-range ejection fraction.<sup>[1,2]</sup> Due to their negative inotropic action, for many years beta-blockers (BB) were contraindicated in patients with HF. Toward the end of the last century, however, these drugs were shown to have highly positive effects in patients with HF. Since then, they have become a cornerstone in the treatment of HF with systolic dysfunction,<sup>[3]</sup> and the most recent clinical practice guidelines encourage

BB use to reduce mortality and CV events.<sup>[4,5]</sup>

Despite such advances, data remain scarce on the role of these drugs in elderly patients with chronic kidney disease (CKD). Classically, both elderly and CKD patients have been underrepresented in clinical trials, creating a gap in the evidence base. In addition, CKD is highly prevalent among elderly patients with HF and reduced ejection fraction (HFrEF).<sup>[6]</sup> As a result, though HF drugs (e.g., Angiotensin-Converting Enzyme inhibitors (ACEi)/Angiotensin Receptor Blockers (ARB), BB, Mineralocorticoid Receptor Antagonist (MRA), An-

giotensin Receptor-Nepriylsin Inhibitors (ARNI) provide a substantial cardiovascular (CV) benefit, the underrepresentation of elderly patients with CKD in the primary clinical trials and the existence of side effects may limit their use.<sup>[6,7]</sup> As well as ACEi/ARB and MRA,<sup>[8]</sup> the elderly may be less likely to receive BB than other populations with HFrEF, particularly in cases with associated CKD, despite the fact that there is no clear reason to avoid this medication.<sup>[9]</sup> Our study analyzes the role of BB therapy in elderly patients with HFrEF and CKD.

## METHODS

### Patients

We carried out a single-center, observational cohort study. From January 2008 to July 2014, we consecutively enrolled 802 patients 75 years of age or older with left ventricular ejection fraction (LVEF)  $\leq$  35% as measured by 2-dimensional echocardiography. Of the total population, 390 had renal impairment, defined as a glomerular filtration rate (GFR)  $<$  60 mL/min per 1.73 m<sup>2</sup>.

A specific database compiled in the cardiac imaging department of Hospital Fundación Jiménez Díaz (Madrid, Spain) was used to screen for patients meeting both criteria. All patients underwent regular medical supervision according to their symptoms and the indications of their physician (cardiologists or general practitioners) to optimize treatment.

Data including baseline clinical characteristics, cardiovascular risk factors, comorbidities, GFR calculated by CKD-EPI equation, electrocardiographic findings (rhythm, heart rate, and QRS complex width), New York Heart Association (NYHA) functional class, and type and dose of cardiovascular drugs at the start of follow-up were collected from patients' electronic health records. Data analysis was performed in 2019.

This investigation was carried out in accordance with the principles outlined in the Declaration of Helsinki.

### Outcomes and Follow-up

The outcomes analyzed in our study were the rate of all-cause death and major CV events. Here, CV events included death from any cause or admis-

sion due to HF. HF admission was defined as admission to a health-care facility lasting  $>$  24 h due to the worsening of HF symptoms and followed by specific treatment for HF (regardless of the cause of cardiac decompensation). Data on clinical events and death during follow-up were collected from patients' electronic health records or, if unavailable, from telephone interviews with patients or relatives.

### Statistical Analysis

Data were subjected to descriptive statistical analysis via frequency measurements (absolute frequencies and percentages) for qualitative variables and using mean and standard deviation for quantitative variables. The magnitude of the effects of the variables was expressed as hazard ratio (HR) and 95% confidence interval (95% CI). Univariate analysis of the quantitative variables was performed using the Student *t* test when the variables were normally distributed, and the Mann-Whitney U test when distribution was not normal. Qualitative variables were analyzed using the  $\chi^2$  or the Fisher exact test.

Because observational studies do not allow for randomization, we planned 2 different approaches to avoid potential confounding factors: multivariate Cox proportional hazard and propensity score (PS)-matched analysis. These two analyses were used to determine significant predictors of CV events and mortality. First, we performed a multivariate analysis with Cox (backward stepwise) regression. Of all the baseline variables collected, we selected those with the potential to act as confounding factors. The selection criteria were as follows: first, clinical and biological plausibility and, second, the statistical criterion of Mickey, excluding all those variables that returned a *P* value  $>$  0.20 on univariate analysis. Second, we performed a PS-matched analysis. The PS was calculated by means of an ordered logistic regression model, taking the BB group as the dependent variables and adopting a parsimonious approach. In a first step, all the following variables were included in the univariate analysis: age, gender, hypertension, diabetes mellitus, obesity, GFR, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, any degree of cognitive impairment, any degree of functional disability, ischemic origin of reduced EF, pre-

vious HF admission, sinus rhythm, wide QRS complex, LVEF, and New York Heart Association (NYHA) Class I or II (vs. III, IV, or not available) at initiation of follow-up. All variables with a  $P$ -value  $< 0.2$  were entered into a multivariate binary logistic regression model, which served to estimate the PS of every patient. Patient matching was performed at a 1:1 ratio with the nearest neighbor method (caliper =  $0.2 \times SD$  [logitPs]).

Results are expressed as hazard ratio (HR) and 95% CI. Statistical analyses were performed with SPSS version 22.0 (SPSS, Inc, Chicago IL, USA).

## RESULTS

### Baseline Characteristics

During the study period, 802 consecutive patients with LVEF  $\leq 35\%$  were assessed for eligibility. Of these, 390 patients were included due to associated renal impairment. Table 1 shows the baseline characteristics of our population. In terms of sex, 62.3% were male, and the mean age was  $82.6 \pm 4.1$  years. Mean LVEF was  $27.9\% \pm 6.5\%$ . An ischemic etiology was found in 50.6% of cases. GFR was between 60 and 45 mL/min per  $1.73 \text{ m}^2$  in 50.3% of patients, 45–30 mL/min per  $1.73 \text{ m}^2$  in 37.4%, and  $< 30$  mL/min per  $1.73 \text{ m}^2$  in 12.3%.

At the end of follow-up ( $32 \pm 23$  months), 263 (67.4%) patients were undergoing treatment with BB. The most commonly used BB by type was bisoprolol once daily in 143 (54.4%) patients followed by carvedilol twice daily in 111 (42.2%) patients, metoprolol twice daily in 6 (2.3%) patients, and nebivolol once daily in 3 (1.1%) patients. Chronic lung disease (32.4%), followed by bradycardia (9.0%), asthma (4.5%), and deterioration of HF (4.5%) were the most frequent reasons why study subjects did not take BB; however, in 29.7% of these patients no formal contraindication was found. Dose levels of BB used are shown in Table 2 for both the entire population and according to GFR.

### Outcomes

After a median follow-up of 28.04 (IR: 19.41–36.67) months, 211 patients (54.1%) died and 257 patients (65.9%) developed a major CV event (death or hospitalization for HF). Of the patients who died, the cause of death was CV in 56 cases (26.5%), and

non-CV causes accounted for 73 deaths (34.6%). We were unable to determine the cause of death in 82 patients (38.9%). Regarding HF hospitalization alone, 146 patients (37.4%) of the total study population were admitted due to HF decompensation. We performed a multivariate analysis (Cox regression) of our study population in order to identify significant predictors of total mortality, following the methodology described above. In similar fashion, we performed another multivariate analysis (Cox regression) to determine significant predictors of CV events. Tables 3 and 4 show the results of univariate and multivariate analyses of overall mortality (Table 3) and CV events (Table 4). A multivariate Cox regression analysis revealed that the use of BB was significantly associated with lower mortality rates (HR = 0.53, 95% CI: 0.37–0.78,  $P$  log-rank  $< 0.001$ ), as compared with patients not receiving BB (Figure 1A). However, BB use was not significantly associated with differences in CV events. When we used propensity score matching specifically aimed at analyzing the role of BB in our population, we found that BB had benefited our population, producing a difference that reached statistical significance (HR = 0.45, 95% CI: 0.27–0.75,  $P = 0.002$ ) (Figure 1B). Similarly, we found no relationship between BB and CV events. Finally, a multivariate Cox analysis considering HF hospitalization alone revealed no relation between BB and a reduction in HF admissions; only ACEi/ARBs played a protective role in this regard (HR = 0.467; 95% CI: 0.313–0.696).

When we analyze the role of BB according to eGFR, we see similar results throughout the study population. In the subgroup of patients with stage IIIa CKD (GFR 45–60/mL/min per  $1.73 \text{ m}^2$ ), BB significantly reduced mortality (HR = 0.47; 95% CI: 0.26–0.86;  $P$  log-rank  $< 0.0001$ ); the same was true for patients with stage IIIb (GFR = 30–45/mL/min per  $1.73 \text{ m}^2$ ; HR = 0.55, 95% CI: 0.26–1.06;  $P$  log-rank = 0.007) and stages IV and V disease (GFR  $< 30$  mL/min per  $1.73 \text{ m}^2$ ; HR = 0.29, 95% CI: 0.11–0.76;  $P$  log-rank = 0.047) (Figure 2).

When we analyzed the population by BB dose, no differences in the mean dose of bisoprolol and carvedilol were found between the different glomerular filtration groups. A similar analysis was not done for metoprolol and nebivolol because of their low rate of use in our population.

Table 1 Baseline characteristics.

Total population (n = 390)	BB (after propensity score matching) (n = 178)			P value
	Yes (n = 89)	No (n = 89)		
Age, yrs	82.6 ± 4.1	82.9 ± 5.0	82.8 ± 5.1	NS
Male	243 (42.3%)	51 (57.3%)	55 (61.8%)	NS
High blood pressure	322 (82.8%)	79 (88.8%)	73 (82.0%)	NS
Diabetes mellitus	129 (33.2%)	26 (29.2%)	32 (36.0%)	NS
Hyperlipidemia	180 (46.3%)	47 (52.8%)	30 (33.7%)	0.015
Current smoker	27 (6.9%)	6 (5.6%)	12 (13.5%)	NS
BMI > 30 kg/m <sup>2</sup>	31 (8.0%)	9 (10.1%)	7 (7.9%)	NS
Chronic lung disease	84 (21.6%)	28 (31.5%)	30 (33.7%)	NS
Stroke/TIA	60 (15.4%)	11 (12.4%)	16 (18.0%)	NS
Peripheral artery disease	78 (20.1%)	15 (16.9%)	20 (22.5%)	NS
Chronic liver disease	11 (2.8%)	1 (1.1%)	1 (1.1%)	NS
Severe osteoarthritis	69 (17.8%)	24 (27.0%)	18 (20.2%)	NS
Cognitive impairment	42 (10.9%)	14 (15.7%)	9 (10.1%)	NS
Functional disability	56 (14.5%)	15 (16.8%)	16 (18.0%)	NS
LVEF	27.9% ± 6.5%	27.8% ± 6.7%	27.9% ± 7.0%	NS
Ischemic LV dysfunction	197 (50.6%)	50 (70.4%)	37 (56.9%)	NS
Previous HF admission	230 (59%)	50 (56.2%)	51 (57.3%)	NS
QRS > 120 ms	213 (54.6%)	46 (54.1%)	51 (62.2%)	NS
Sinus rhythm	238 (61%)	57 (66.3%)	55 (64.7%)	NS
GFR, mL/min per 1.73 m <sup>2</sup>	42.8 ± 11.8			
45–60	196 (50.3%)	48 (53.9%)	41 (46.1%)	NS
30–44	146 (37.4%)	26 (29.2%)	39 (43.8%)	NS
< 30	48 (12.3%)	15 (16.9%)	9 (10.1%)	NS
Hemodialysis	12 (3.1%)	0 (0.0%)	4 (4.5%)	NS
NYHA III–IV	66 (17.9%)	19 (21.3%)	19 (21.3%)	NS
Betablockers	263 (67.4%)	–	–	–
ACEi/ARB	268 (68.7%)	62 (69.7%)	58 (65.2)	–
MRA	156 (41.6%)	36 (40.4%)	44 (49.4%)	NS
Diuretics	313 (83.7%)	75 (84.3%)	76 (85.4%)	NS
Digoxin	52 (13.9%)	9 (10.1%)	19 (21.3%)	NS
Ivabradine	22 (5.9%)	1 (1.1%)	11 (12.4%)	0.005
Amiodarone	63 (16.8%)	15 (16.9%)	19 (21.3%)	NS
Anticoagulation	167 (44.7%)	39 (43.8%)	32 (36.0%)	NS
ICD/CRT	65 (16.6%)	16 (18.0%)	7 (7.8%)	NS

Data are presented as mean ± SD or n (%). ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; BMI: body mass index; CRT: cardiac resynchronization therapy; GFR: glomerular filtration rate; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; MRA: mineral-corticoid receptor antagonist; NYHA: New York Heart Association class; TIA: transient ischemic attack.

## DISCUSSION

Blocking the adrenergic system with BB has proven effectiveness in patients with HFREF,<sup>[3]</sup> and

this treatment is currently included in clinical guidelines.<sup>[4,5]</sup> A closer look at the studies reporting evidence in support of using these drugs, however,

Table 2 Daily doses of beta-blockers used.

	Overall population	GFR60–45 mL/min/ 1.73 m <sup>2</sup>	GFR45–30 mL/min/ 1.73 m <sup>2</sup>	GFR < 30 mL/min/ 1.73 m <sup>2</sup>
Carvedilol (N, mean dose (mg))	111, 16.9 ± 14.0	52, 17.1 ± 13.3	44, 16.7 ± 14.7	15, 17.3 ± 15.2
Bisoprolol (N, mean dose (mg))	143, 4.0 ± 2.8	81, 3.8 ± 2.6	46, 4.7 ± 3.1	16, 3.0 ± 2.4
Metoprolol (N, mean dose (mg))	6, 79.2 ± 33.2	3, 66.7 ± 28.9	27, 5.0 ± 35.4	11, 25.0 ± 0.0
Nebivolol (N, mean dose (mg))	3, 4.2 ± 2.4	1, 5.0 ± –	1, 5.0 ± –	1, 2.5 ± –

Data are presented as mean ± SD. GFR: glomerular filtration rate; SD: standard deviation.

Table 3 Univariate and multivariate analysis of overall mortality.

	Univariate analysis		Multivariate analysis	
	HR	95% CI	HR	95% CI
Age	1.11	1.05–1.11	1.08	1.04–1.12
Sex	1.09	0.84–1.78		
High blood pressure	1.16	0.76–1.77		
Diabetes mellitus	1.11	0.88–1.54		
Hyperlipidemia	0.94	0.72–1.24		
Chronic lung disease	1.22	0.89–1.67		
Stroke/TIA	1.62	1.15–2.28	1.84	1.19–2.85
Ischemic LV dysfunction	1.57	1.11–2.24	1.96	1.32–2.92
Previous HF admission	1.38	1.04–1.83	1.65	1.13–2.13
QRS > 120 ms	0.84	0.64–1.11		
Sinus rhythm	1.01	0.76–1.34		
LVEF	0.96	0.95–0.98	0.96	0.94–0.98
NYHA III–IV	1.91	1.34–2.69	1.87	1.20–2.00
Beta-blockers	0.47	0.36–0.63	0.53	0.37–0.78
ACEi/ARB	0.76	0.56–1.01		NS
MRA	1.09	0.83–1.44		
ICD/CRT	0.45	0.24–0.84	0.46	0.23–0.93

ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association class; TIA: transient ischemic attack. Variables included in the multivariate analysis: age, cerebrovascular disease, previous heart failure, ischemic left ventricle dysfunction, New York Heart Association class, angiotensin converting enzyme inhibitors/angiotensin receptor blocker, beta-blocker therapy, left ventricular ejection fraction, and implantable cardioverter defibrillator/cardiac resynchronization therapy.

reveals that the populations studied present a relatively low number of comorbidities, with few patients over 75 years of age (average age commonly under 65 years),<sup>[10,11]</sup> making these studies unrepresentative of routine clinical practice.<sup>[12]</sup> Elderly patients make up a substantial portion of the population with severe left ventricular dysfunction,<sup>[9]</sup> and the rate of renal failure in this cohort is often 3-fold higher than that of the general population.<sup>[13]</sup> In addition, these patients have a higher proportion of other comorbidities and polypharmacy, and more than 70% of HF patients older than 80 years fulfil frailty criteria.<sup>[14,15]</sup> These differences are important to bear in mind when interpreting the results of ran-

domized clinical trials on BB, and nowadays, specific data remain limited and controversial.<sup>[16]</sup>

Although the available evidence on BB therapy in patients > 70 years with HFrEF is limited, recent studies support the use of these drugs. The SENIORS trial compared the use of BB against a placebo in patients over 70 years of age with HF;<sup>[17]</sup> all patients included in the study had a clinical history of chronic HF with one or both of the following features: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive HF or documented LVEF ≤ 35% within the previous 6 months. The trial demonstrated a correlation between nebivolol use and a significant

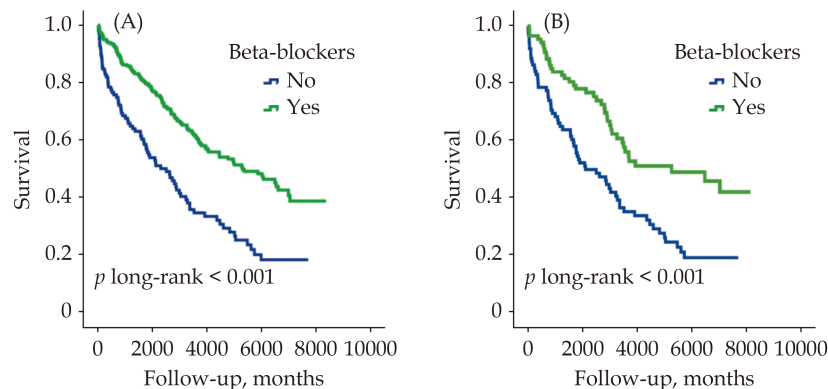




**Table 4** Univariate and multivariate analysis of cardiovascular events.

	Univariate analysis		Multivariate analysis	
	HR	95% CI	HR	95% CI
Age	1.06	1.04–1.09	1.07	1.03–1.10
Sex	1.17	0.90–1.51		
High blood pressure	1.27	0.91–1.76		NS
Diabetes mellitus	1.11	0.86–1.43		
Hyperlipidemia	1.01	0.79–1.29		
Chronic lung disease	1.48	1.12–1.96	1.58	1.12–2.25
Stroke/TIA	1.45	1.06–2.00	1.59	1.06–2.39
Ischemic LV dysfunction	1.78	1.29–2.44	1.67	1.19–2.33
Previous HF admission	1.44	1.11–1.86	1.65	1.13–2.13
QRS > 120 ms	0.83	0.65–1.07		
Sinus rhythm	1.14	0.88–1.47		
LVEF	0.98	0.97–1.00		NS
NYHA III–IV	1.59	1.15–2.19		NS
Beta-blockers	0.71	0.54–0.92		NS
ACEi/ARB	0.68	0.52–0.87	0.71	0.50–0.98
MRA	1.08	0.84–1.38		NS
ICD/CRT	0.74	0.45–1.21		NS

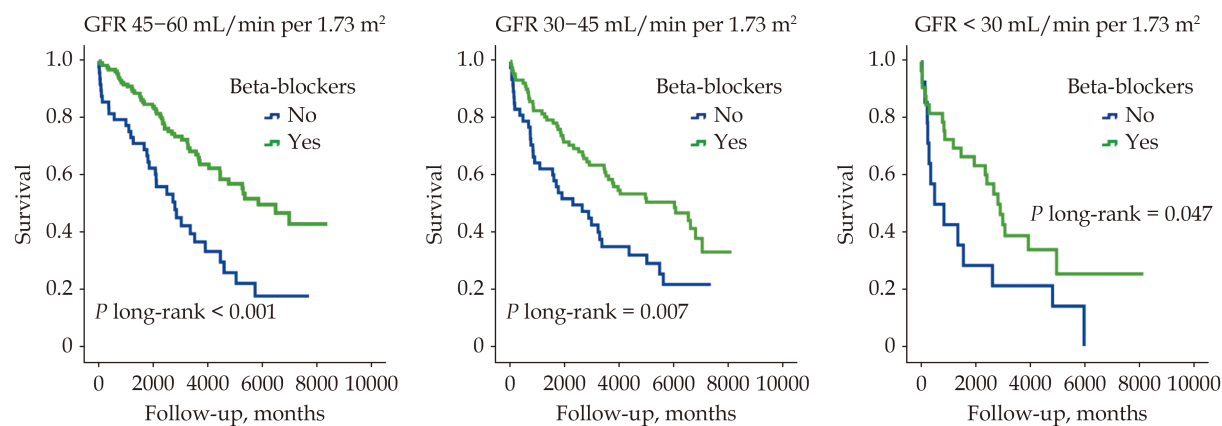
ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; CRT: cardiac resynchronization therapy; GRF: glomerular filtration rate; HF: heart failure; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; MRA: mineral-corticoid receptor antagonist; NYHA: New York Heart Association class; TIA: transient ischemic attack. Included variables in the multivariate analysis: age, high blood pressure, chronic obstructive pulmonary disease, New York heart Association class, angiotensin converting enzyme inhibitors/angiotensin receptor blocker, previous heart failure, betablocker therapy, left ventricular ejection fraction, mineral-corticoid receptor antagonist therapy, cerebrovascular disease, and implantable cardioverter defibrillator/cardiac resynchronization therapy.



**Figure 1** All-cause mortality in overall population. (A): Kaplan-Meier curve showing all-cause mortality in the overall population, comparing the group under beta-blocker therapy (green) against the group not receiving this treatment (blue); (B): Kaplan-Meier curve showing all-cause mortality, comparing the group under beta-blocker therapy (green) versus the group that did not use beta-blockers (blue), after propensity score matching.

(14%) reduction of the primary end-point, a composite of all-cause mortality or cardiovascular hospital admission. Though a secondary end-point, no favorable impact of nebivolol on all-cause mortality was demonstrated (HR = 0.88, 95% CI: 0.71–1.08;  $P = 0.21$ ).<sup>[18]</sup> We believe that the main difference between the SENIORS study and both our study and pivotal

clinical trials is the inclusion of patients with preserved LVEF, since 35% of patients were reported to have LVEF > 35%. In fact, no treatment has demonstrated a clear survival benefit among patients with preserved LVEF-HF.<sup>[4,5]</sup> There is a lack of robust data evidencing decreased mortality associated with BB administration in the elderly population. Hernandez



**Figure 2** Kaplan-Meier curves showing all-cause mortality, comparing the group under beta-blocker therapy (green) versus the group with no use of beta-blockers (blue) in the different subgroups according to glomerular filtration rate (GFR).

*et al.*, in the OPTIMIZE-HF registry, suggest that BB are beneficial in elderly patients with HFrEF.<sup>[16]</sup> Few studies have reported clear benefit of BB in elderly population in terms of mortality. Our group conducted a retrospective, observational study in elderly patients (> 75 years) with HFrEF, concluding that BB therapy improves survival in patients with LVEF lesser than or equal to 0.35, although this effect seems unrelated to the dose received ( $P = 0.025$ ).<sup>[18]</sup>

Another issue to take into account when evaluating these patients is CKD status. We know this disorder is more prevalent in patients with HF and has an important influence on prognosis.<sup>[19,20]</sup> In addition, we know that the presence of CKD in HF patients affects the prescription, dosage, and maintenance of therapies that have demonstrated benefits in HFrEF.<sup>[4,5]</sup> In addition, advanced-stage CKD was an exclusion criterion in many of the clinical trials analyzing the role of BB therapy in patients with HFrEF.<sup>[21]</sup> Furthermore, those studies that have examined the role of BB therapy in this group of patients are mostly observational in design, and the endpoints used are less relevant (i.e., other than major factors or non-fatal clinical events).<sup>[22,23]</sup> Despite this lack in the knowledge base, presence of CKD is one of the primary factors associated with increased mortality.<sup>[22]</sup>

Most clinical trials carried out to date use exclusion criteria based on glomerular filtration rate (GFR), and as a result patients with Stage I and II kidney disease are well-represented (GFR > 90 mL/min per 1.73 m<sup>2</sup> and 60–89 mL/min per 1.73 m<sup>2</sup>, respectively).<sup>[24,25]</sup> However, this representativeness decreases at lower GFR, and the available data on patients at stage IV and V are scant.

This pattern can be seen in the classical studies investigating the role of BB therapy in HFrEF patients with associated Stage-IIIa, Stage-IIIb, and Stage-IV-V CKD(25). Although there is no strong evidence of the effect of BB in CKD, stage III is better represented in the different clinical trials. In the MERIT-HF trial (metoprolol vs placebo), which included patients with HFrEF, there was a significant relative risk reduction in the composite endpoint of CV hospitalization/all-cause mortality in patients with GFR of 45–60 mL/min per 1.73 m<sup>2</sup> (HR = 0.68 (0.52–0.90)) and even in patients with GFR < 45 mL/min per 1.73 m<sup>2</sup>.<sup>[26]</sup>

In the CIBIS-II trial on the effect of bisoprolol in patients with HFrEF, BB significantly reduced the mortality and HF-related hospital stay in the subgroup of patients with GFR < 60 mL/min per 1.73 m<sup>2</sup> as well as those with GFR < 45 mL/min per 1.73 m<sup>2</sup>.<sup>[27]</sup> As in the SENIORS trial in patients with reduced GFR, the effect of BB was not different from the effect in patients with GFR above 60 mL/min per 1.73 m<sup>2</sup>.<sup>[28]</sup> Finally, a meta-analysis of the effect of carvedilol in the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) and CAPRICORN (Carvedilol Post Infarct Survival Control in LV Dysfunction) trials showed that this BB significantly improved outcome in patients with eGFR between 45 and 60 mL/min per 1.73 m<sup>2</sup>. There was no interaction between the effect of carvedilol treatment and eGFR categories (< 45 vs. 45 to 60 mL/min per 1.73 m<sup>2</sup>).<sup>[29]</sup>

Stages IV and V are not well-represented, though data from both the MERIT-HF and CIBIS-II trials suggest that BB are effective in patients with CKD

stage IIIb-V(26,27). Specially, in the MERIT-HF study, the metoprolol/placebo hazard ratio was 0.41 (95% CI: 0.25 to 0.68) in the 493 patients with eGFR < 45 mL/min per 1.73 m<sup>2</sup> (12% of the whole study population). This subgroup had a mean eGFR of 36.6 ± 6.8 mL/min per 1.73 m<sup>2</sup>, which included patients with eGFR < 30 mL/min per 1.73 m<sup>2</sup>.<sup>[26]</sup> In the SENIORS study, only 3.1% of patients had stage IV CKD, but no subgroup analysis has been performed on these patients.<sup>[28]</sup> However, only 8% of all patients in these studies had stage 4 CKD. In a small trial of hemodialysis patients with HF, carvedilol significantly improved the secondary combined endpoint of all-cause mortality and CV death.<sup>[30]</sup>

Recently, Kotecha, *et al.*<sup>[31]</sup> published the largest meta-analysis including patients with left ventricular dysfunction and CKD. The authors considered 10 double blind placebo-controlled trials that included more than 16,000 patients. They found that BB reduced the relative risk of all-cause mortality by 27% (95% CI: 0.62–0.86) in patients with GFR of 45–60 mL/min per 1.73 m<sup>2</sup> and 29% (95% CI: 0.58–0.87) in those with a GFR of 30–44 mL/min per 1.73 m<sup>2</sup>. This benefit was only seen in patients in sinus rhythm. In patients with GFR < 30 mL/min per 1.73 m<sup>2</sup> there were not enough patients to draw conclusions due to the exclusion criteria of the different trials.<sup>[31]</sup>

Concern for increased toxicity often leads clinicians to undertreat these patients with CKD, causing less therapeutic resources to be devoted to individuals with myocardial infarction and concomitant CKD.<sup>[32]</sup> However, it has been shown that these therapeutic measures are beneficial in this population.<sup>[33]</sup>

Our population is particularly elderly (mean age, 82.6 ± 4.1 years), and as such is representative of the individuals we treat in our daily practice. There is currently no solid evidence on the role of BB in the elderly population with HF and CKD. Given this lack of data about the role of BB in this common population: elderly with HF and CKD. For this reason, we believe that our findings are relevant for overall practice. We found a significant reduction in all-cause mortality, and this benefit was maintained when separately assessing the role of BB treatment in advanced CKD patients (< 45 mL/min per 1.73 m<sup>2</sup>), as the protective effect of this treatment continues to be statistically significant in

terms of all-cause mortality. The effect of treatment with BB is neutral, however, when we isolate the variable of mortality. The high rate of associated cardiovascular co-morbidities may have attenuated the beneficial effect of BB therapy in our study population in terms of CV events.

In sum, according to our data, treatment with BB in elderly patients presenting HF<sub>r</sub>EF and CKD was associated with a lower rate of all-cause mortality. Our data thus show that BB therapy could improve the prognosis of this selected population when there is no formal contraindication for its use.

## STUDY LIMITATIONS

Our study has certain limitations. First, the study population is relatively small, which could influence the statistical results. In addition, it is a retrospective, non-randomized study using a historical cohort from a single center. A third limitation is the relatively short follow-up period, potentially masking a long-term benefit of BB in reduction of CV events. Nevertheless, this last issue is less relevant due to the short life expectancy of elderly patients and the higher number of CV events they present. Lastly, we were unable to discern the cause of death in 82 (38.7%) patients as this information was lacking from their clinical records.

## CONCLUSIONS

According to our results, use of BB is significantly associated with a reduction in all-cause mortality in elderly patients with HF<sub>r</sub>EF and CKD irrespective of GFR. As a result, these drugs may be beneficial for these patients provided there are no formal contraindications. Nevertheless, this is an observational study and that residual confounding may exist.

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## REFERENCES

- [1] Gheorghiane M, Sopko G, Luca L De, *et al.* Navigating the crossroads of coronary artery disease and heart failure. *Circulation* 2006; 114: 1202–1013.





- [2] Khatibzadeh S, Farzadfar F, Oliver J, *et al.* Worldwide risk factors for heart failure: A systematic review and pooled analysis. *Int J Cardiol* 2013; 168: 1186–1194.
- [3] Martinez-Milla J, Raposeiras-Roubin S, Pascual-Figal DA, Ibanez B. Role of Beta-blockers in Cardiovascular Disease in 2019. *Rev Esp Cardiol (Engl Ed)* 2019; 72: 844–852.
- [4] Ponikowski P, Voors AA, Anker SD, *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129–2200.
- [5] Yancy CW, Jessup M, Bozkurt B, *et al.* 2013 ACCF/AHA guideline for the management of heart failure: A report of the American college of cardiology foundation/american heart association task force on practice guidelines. *J Am Coll Cardiol* 2013; 62: e147–e239.
- [6] Tamirisa KP, Aaronson KD, Koelling TM. Spironolactone-induced renal insufficiency and hyperkalemia in patients with heart failure. *Am Heart J* 2004; 148: 971–978.
- [7] Navis G, Faber HJ, de Zeeuw D, de Jong PE. ACE inhibitors and the kidney. A risk-benefit assessment. *Drug Saf* 1996; 15: 200–211.
- [8] Martinez-Milla J, Garcia MC, Urquia MT, *et al.* Blockade of Renin-Angiotensin-Aldosterone System in Elderly Patients with Heart Failure and Chronic Kidney Disease: Results of a Single-Center, Observational Cohort Study. *Drugs Aging* 2019; 36: 1123–1131.
- [9] Komajda M, Hanon O, Hochadel M, *et al.* Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II. *Eur Heart J* 2009; 30: 478–486.
- [10] Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002; 162: 1682–1688.
- [11] Patel P, White DL, Deswal A. Translation of clinical trial results into practice: temporal patterns of beta-blocker utilization for heart failure at hospital discharge and during ambulatory follow-up. *Am Heart J* 2007; 153: 515–522.
- [12] Tsutsui H, Tsuchihashi-Makaya M, Kinugawa S, *et al.* Characteristics and outcomes of patients with heart failure in general practices and hospitals. *Circ J* 2007; 71: 449–454.
- [13] Kottgen A, Russell SD, Loehr LR, *et al.* Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol* 2007; 18: 1307–1315.
- [14] Vidan MT, Blaya-Novakova V, Sanchez E, *et al.* Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure. *Eur J Heart Fail* 2016; 18: 869–875.
- [15] Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007; 93: 1137–1146.
- [16] Hernandez AF, Hammill BG, O'Connor CM, *et al.* Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. *J Am Coll Cardiol* 2009; 53: 184–192.
- [17] Lainscak M, Duengen H-D, Anker SD. Beta-blockers in elderly patients with heart failure ready for prime time? *J Am Coll Cardiol* 2009; 54: 2202.
- [18] Franco Pelaez JA, Cortes Garcia M, Romero Daza AM, *et al.* Relationship between different doses of beta-blockers and prognosis in elderly patients with reduced ejection fraction. *Int J Cardiol* 2016; 220: 219–225.
- [19] Lofman I, Szummer K, Hagerman I, *et al.* Prevalence and prognostic impact of kidney disease on heart failure patients. *Open Hear* 2016; 3: e000324.
- [20] Damman K, Valente MAE, Voors AA, *et al.* Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J* 2014; 35: 455–469.
- [21] Chatterjee S, Biondi-Zoccai G, Abbate A, *et al.* Benefits of blockers in patients with heart failure and reduced ejection fraction: Network meta-analysis. *BMJ* 2013; 346: 1–10.
- [22] Hawwa N, Schreiber MJJ, Tang WHW. Pharmacologic management of chronic reno-cardiac syndrome. *Curr Heart Fail Rep* 2013; 10: 54–62.
- [23] Heywood JT, Fonarow GC, Yancy CW, *et al.* Influence of renal function on the use of guideline-recommended therapies for patients with heart failure. *Am J Cardiol* 2010; 105: 1140–1146.
- [24] Damman K, Tang WHW, Felker GM, *et al.* Current evidence on treatment of patients with chronic systolic heart failure and renal insufficiency: practical considerations from published data. *J Am Coll Cardiol* 2014; 63: 853–871.
- [25] K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39(2 Suppl 1): S1–S266.
- [26] Ghali JK, Wikstrand J, Van Veldhuisen DJ, *et al.* The influence of renal function on clinical outcome and response to beta-blockade in systolic heart failure: insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF). *J Card Fail* 2009; 15: 310–318.
- [27] Castagno D, Jhund PS, McMurray JJ V, *et al.* Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the cardiac insufficiency bisoprolol study II (CIBIS-II) trial. *Eur J Heart Fail* 2010; 12: 607–616.
- [28] Cohen-Solal A, Kotecha D, van Veldhuisen DJ, *et al.* Efficacy and safety of nebivolol in elderly heart failure patients with impaired renal function: insights from the SENIORS trial. *Eur J Heart Fail* 2009; 11: 872–880.
- [29] Wali RK, Iyengar M, Beck GJ, *et al.* Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease: a meta-analysis of randomized trials. *Circ Heart Fail* 2011; 4: 18–26.
- [30] Cice G, Ferrara L, D'Andrea A, *et al.* Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. *J Am Coll Cardiol* 2003; 41: 1438–1444.
- [31] Kotecha D, Gill SK, Flather MD, *et al.* Impact of Renal



Impairment on Beta-Blocker Efficacy in Patients With Heart Failure. *J Am Coll Cardiol* 2019; 74: 2893–2904.

- [32] Beattie JN, Soman SS, Sandberg KR, *et al.* Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. *Am J Kidney Dis*

2001; 37: 1191–1200.

- [33] McCullough PA, Sandberg KR, Borzak S, *et al.* Benefits of aspirin and beta-blockade after myocardial infarction in patients with chronic kidney disease. *Am Heart J* 2002; 144: 226–232.

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