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Improved survival with bisoprolol in patients with heart failure and renal impairment. An analysis of the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II) trial.

Castagno: Bisoprolol in heart failure and renal impairment

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Abstract

Background

Information on the effectiveness of beta-blockade in patients with heart failure (HF) and concomitant renal impairment is scarce and beta-blockers are underutilized in these patients.

Methods and Results

The Cockcroft-Gault formula normalized for body surface-area was used to estimate renal function ($eGFR_{BSA}$) in 2622 patients with HF, LVEF ≤35%, NYHA class III/IV and serum creatinine <300μmol/L (3.4mg/dL) in the second Cardiac Insufficiency Bisoprolol Study (CIBIS-II). They were divided into 4 sub-groups according to baseline $eGFR_{BSA}$ (< 45, 45-60, 60-75 and ≥ 75ml/min per 1.73m^2). Cox proportional-hazards models adjusted for pre-specified confounders were used to assess the effect of bisoprolol and potential heterogeneity of effect across the $eGFR_{BSA}$ sub-groups. Older age, female-sex, diabetes and ischemic-etiology were more common in those with reduced $eGFR_{BSA}$. The hazard associated with bisoprolol use for all-cause mortality, the composite of all-cause mortality or heart failure-hospitalization and heart failure-hospitalization alone was consistently <1.0 across $eGFR_{BSA}$ categories with no treatment by renal-function interaction (p=0.81, p=0.66, p=0.71 respectively). The rate of bisoprolol discontinuation was higher in patients with $eGFR_{BSA}$ <45ml/min per1.73 m^2. Nevertheless the absolute benefit of bisoprolol was greater for patients with chronic kidney disease compared to those without.

Conclusions

The beneficial effects of bisoprolol on mortality and hospitalization for worsening heart-failure were not modified by baseline $eGFR_{BSA}$. Renal impairment should not prevent the use of bisoprolol in patients with HF.

Key words

Heart failure

Kidney

Drugs

Receptors, adrenergic, beta

Nervous system, sympathetic

Introduction

Renal insufficiency is a common co-morbidity amongst patients with chronic heart failure (HF). It is associated with a worse prognosis and complicates therapeutic management. Indeed renal impairment, independently of left ventricular ejection fraction (LVEF), is associated with neurohormonal activation and worse fatal and non-fatal outcomes in patients with both ischemic and non-ischemic HF[1,2].

In clinical trials the relative benefit of several treatments is similar in patients with and without renal dysfunction. As a result, these treatments provide a large absolute benefit in patients with heart failure and renal insufficiency. This has been shown for ACE inhibitors[3], digoxin[4] and the combination of hydralazine and isosorbide dinitrate[5]. In clinical practice, however, HF patients with renal insufficiency are less likely to receive efficacious therapies than patients with normal or near normal renal function[6,7]. The explanation for this is uncertain, but may be due to a real or perceived increased risk of treatment-related adverse effects in patients with renal impairment. There is limited evidence about the efficacy and tolerability of beta-blockers in patients with heart failure and renal dysfunction, originally arising from observational studies[7,8,9], and more convincingly from two recent post hoc analyses of randomized clinical trials addressing these questions[10,11]. Bisoprolol was the first beta-blocker to show beneficial effects on outcomes in patients with HF and left ventricular systolic dysfunction taking part in the second Cardiac Insufficiency Bisoprolol Study (CIBIS-II)[12]. A report from the CIBIS-II[13] failed to answer thoroughly whether the treatment effect in heart failure of this selective β_1 antagonist with dual renal and hepatic routes of excretion varies by renal function. In our study we sought to expand and extend that analysis adjusting for potential confounders and taking in consideration the non linear relationship

between renal function and outcomes in the assessment of treatment by renal function interaction.

Methods

Source population

The design, baseline characteristics of the participants in and the principal findings of CIBIS-II have been published elsewhere[12,14]. In brief, CIBIS-II was a double-blind, randomized comparison of bisoprolol and placebo in 2647 ambulatory patients with New York Heart Association (NYHA) class III and IV HF and a left-ventricular ejection fraction of 35% or less. Patients were treated with a diuretic and an ACE-inhibitor (other vasodilators were allowed in the case of ACE-inhibitor intolerance) for at least two weeks before randomization. Eligible patients were commenced on bisoprolol 1.25 mg or placebo once daily, and the dose increased progressively to 2.5 mg, 3.75 mg, 5.0 mg, 7.5 mg and 10.0 mg according to tolerance. The trial was stopped prematurely, after a mean follow-up of 1.3 years, as β-blocker treatment led to a highly significant reduction in the primary endpoint of all-cause mortality, with a bisoprolol:placebo hazard ratio (and 95% confidence intervals) of 0.66 (0.54, 0.81), $p<0.0001$.

Baseline renal function

Renal function impairment, quantified as a serum creatinine (SCr) $\geq$ 300 μmol/L (3.4 mg/dL) at baseline, was an exclusion criterion from CIBIS-II. Because SCr alone is inaccurate in the assessment of renal function[15], we estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault formula[16] (recommended for estimation of GFR, together with the Modification of Diet in Renal Disease [MDRD] formula[17], by the Kidney Disease Outcome Quality Initiative guidelines[18]). Furthermore, to improve eGFR accuracy, we used normalization to body surface area[19,20] (BSA) that was calculated according to the Du Bois

height-weight formula[21]. In summary: $eGFR_{cg}$ = [(140 – age in years) x (body weight in kg)] / (SCr in μmol/L) x (0.85 if female), BSA = 0.007184 x body weight (in kg)$^{0.425}$ x height (in cm)$^{0.725}$, $eGFR_{BSA}$ ($eGFR_{cg}$ corrected for BSA) = $eGFR_{cg}$ x (1.73/BSA) = ml/min per 1.73 m^2.

In keeping with prior studies of the effect of captopril[3] and valsartan[22] according to renal function, in patients with left ventricular dysfunction, heart failure or both after myocardial infarction (MI), we divided patients into four $eGFR_{BSA}$ categories: < 45, 45 to <60, 60 to < 75 and ≥ 75 ml/min per 1.73 m^2.

Outcomes evaluated

In addition to the original study primary endpoint of all-cause mortality, we examined the effect of bisoprolol on the *post hoc* composite outcome of all-cause mortality or heart failure hospitalization, a commonly used endpoint in HF trials. We also evaluated the effect of bisoprolol on heart failure hospitalization alone. To evaluate tolerability and safety, we evaluated permanent premature treatment withdrawals (a secondary endpoint in the original study) and the *post hoc* composite outcome of all-cause mortality or all-cause hospitalization. All medical events, including treatment withdrawals, were blindly reviewed and classified by members of an independent Critical Event Committee according to standardized definitions.

Statistical Analysis

Continuous variables are expressed as medians (with interquartile ranges) and categorical variables as counts and percentages. To assess differences in baseline characteristics among $eGFR_{BSA}$ categories we used the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. Kaplan-Meier analyses, stratified according to the $eGFR_{BSA}$, for death from any cause and for all the other end points were determined and presented as event

curves, compared by means of log-rank test. Cox proportional hazard models were used to compare each clinical outcome according to treatment intervention across $eGFR_{BSA}$ groups. Multivariable analysis adjusted for age (years), sex, presence of diabetes mellitus, HF etiology (ischemic, idiopathic, others), baseline systolic blood pressure and ejection fraction. The proportional hazards assumption was checked using scaled Schoenfeld residuals. To ascertain potential heterogeneity of the effect of bisoprolol across the entire spectrum of renal function, evidence of treatment by $eGFR_{BSA}$ categories interaction was investigated. Analyses were conducted modeling $eGFR_{BSA}$ as a categorical and linear continuous variable. To explore the nonlinear relationship between renal function and event free survival, we also modeled $eGFR_{BSA}$ as a restricted cubic spline.

All p values were 2 sided, and $p < 0.05$ was used to determine statistical significance. Analyses were all based on intention-to-treat and were performed with STATA, version 10.1 (StataCorp LP, College Station, TX, USA).

Results

Baseline characteristics

A baseline $eGFR_{BSA}$ could be calculated for 2622 participants (99.1% of CIBIS-II patients). The 25 subjects without a baseline $eGFR_{BSA}$ did not differ significantly in terms of demographic/clinical characteristics, treatment received and major outcomes from the population analyzed (data not shown).

The median $eGFR_{BSA}$ was 64.5 ml/min per 1.73 m^2 (IQR 49.9, 81.5). 863 (32.9%) patients had an $eGFR_{BSA}$ of at least 75 ml/min per 1.73 m^2, 640 (24.4%) had an $eGFR_{BSA}$ of 60 to 74.9 ml/min per 1.73 m^2, 669 (25.5%) had an $eGFR_{BSA}$ of 45 to 59.9 ml/min per 1.73 m^2 and 450 (17.2%) had an $eGFR_{BSA}$ below 45 ml/min per 1.73 m^2. The difference between the

lowest and highest $eGFR_{BSA}$ category was 52 ml per minute per 1.73 m^2 and the difference in creatinine was 49 μmol/L (0.6 mg/dL).

Baseline demographic and clinical characteristics for patients in the four $eGFR_{BSA}$ categories are shown in Table 1. Lower $eGFR_{BSA}$ was associated with older age, female sex, higher frequency of co-morbidities (hypertension, diabetes, coronary artery disease, peripheral and cerebrovascular disease) and ischemic etiology. There was no significant difference in the severity of HF (expressed as NYHA class), and, although statistically significant, the difference in ejection fraction (2%) between $eGFR_{BSA}$ groups was small. There was no difference in the allocation of randomized treatment across eGFR categories.
Among each $eGFR_{BSA}$ group no difference was found in the concomitant treatment with diuretic, ACE inhibitors, digoxin and antiplatelet agents whereas patients with lower $eGFR_{BSA}$ more often received amiodarone and anticoagulants.

Outcomes

All cause mortality

Death occurred in 379 patients during follow up. Figure 1 shows all-cause mortality for each $eGFR_{BSA}$ category. Reduced $eGFR_{BSA}$ at baseline was associated with higher mortality. Patients in the lowest $eGFR_{BSA}$ category (<45 ml/min per 1.73 m^2) had a 2.4 fold higher adjusted risk compared with subjects with an $eGFR_{BSA} \geq 75$ ml/min per 1.73 m^2. Patients in the other categories had an intermediate risk: 1.4-fold higher in those with an $eGFR_{BSA}$ between 45 and 59.9 ml/min per 1.73 m^2 and 1.2-fold higher in those with an $eGFR_{BSA}$ between 60 and 74.9 ml/min per 1.73 m^2. The adjusted bisoprolol:placebo hazard ratio for each $eGFR_{BSA}$ category is shown in table 2. The effect of bisoprolol on all-cause mortality was not modified by baseline $eGFR_{BSA}$ category (p for $eGFR_{BSA:}$ treatment interaction = 0.81).

Treating $eGFR_{BSA}$ as a linear continuous variable there was a 13% adjusted risk accrual for each 10-unit decrease in baseline renal function (p for $eGFR_{BSA}$: treatment interaction = 0.85). The non-significant interaction between $eGFR_{BSA}$ transformed as a restricted cubic spline and treatment with bisoprolol and its effect on all-cause mortality is represented graphically in figure 2a.

All cause mortality or heart failure hospitalization

The risk of the composite outcome of all-cause mortality or heart failure hospitalization was also associated with renal impairment (figure 3). When compared with patients with normal or near normal renal function (≥ 75 ml/min per 1.73 m^2) patients with $eGFR_{BSA}$ < 45, between 45 and 59.9, between 60 and 74.9 ml/min per 1.73 m^2 had 2.5, 1.5 and 1.3 fold higher adjusted risks respectively. After multivariable adjustment, the effect of bisoprolol on the composite outcome was consistent across renal function groups (table 2) and was not influenced by baseline renal function (p for interaction = 0.66).

Modeling $eGFR_{BSA}$ as a linear continuous variable the adjusted risk accrual for each 10-unit decrease in renal function was 14% (p for interaction = 0.62). The graphical representation of interaction between bisoprolol and $eGFR_{BSA}$ transformed as a restricted cubic spline, for the composite endpoint is presented in figure 2b.

Heart failure hospitalization

Overall, 386 (14.7%) patients were hospitalized for worsening symptoms of heart failure during follow up. Patients in the lowest $eGFR_{BSA}$ category had a 2.9 fold higher adjusted risk of being hospitalized for worsening heart failure compared with subjects with $eGFR_{BSA} \geq 75$ ml/min per 1.73 m^2 whereas the risk of hospital admission was 1.8 fold and 1.3 fold higher for patients with an $eGFR_{BSA}$ of 45 to 59.9 and 60 to 74.9 ml/min per 1.73 m^2 respectively. The adjusted bisoprolol:placebo hazard ratios for each $eGFR_{BSA}$ category are shown in table

2. The hazard ratio appeared to fall further as $eGFR_{BSA}$ increased into the near normal range, an impression reinforced by the graphical representation of interaction between bisoprolol and $eGFR_{BSA}$ transformed as a restricted cubic spline (figure 2c). However, the test for interaction was not statistically significant whether $eGFR_{BSA}$ was tested as a categorical (p=0.71) or a continuous (p=0.47) variable.

Tolerability and safety

During the entire duration of follow up the average daily dose of both bisoprolol and placebo was significantly lower for patients with baseline renal impairment (table 1). Moreover the dose of bisoprolol was significantly lower than the dose of placebo across all the $eGFR_{BSA}$ categories. Nonetheless, after 3 months of follow up there was a trend towards a greater reduction in heart rate in patients in the lowest $eGFR_{BSA}$ category amongst those allocated to bisoprolol, compared with placebo (p for treatment-$eGFR_{BSA}$ interaction = 0.14) [table 3]. Similarly, there was trend for more of a reduction of diastolic blood pressure with bisoprolol, compared with placebo, in the lowest $eGFR_{BSA}$ category (p for treatment:$eGFR_{BSA}$ interaction = 0.18). The greatest fall in systolic blood pressure between baseline and 3 months was in patients with the worst baseline renal function but there was no between-treatment difference in this change (treatment-$eGFR_{BSA}$ interaction p value = 0.40).

In patients with a baseline $eGFR_{BSA} < 45$ ml/min per 1.73 m^2 there was a substantially higher rate of permanent discontinuation of bisoprolol than placebo (HR 1.54, CI 95% 1.01 to 2.33), as shown in figure 4 and table 2. Conversely, in those with baseline $eGFR_{BSA} \geq 75$ ml/min per 1.73 m^2, the risk of drug discontinuation was lower for patients allocated to bisoprolol than among those allocated to placebo (HR 0.54, CI 95% 0.35 to 0.85). The relationship between baseline $eGFR_{BSA}$ on the risk of drug discontinuation (transformed as a restricted cubic spline) is illustrated further in figure 2d.

The effect of bisoprolol on the outcome of our *post hoc* global safety outcome of all-cause mortality or all-cause hospitalization was consistent across each $eGFR_{BSA}$ category (table 2) and unmodified by baseline renal function (p for interaction = 0.81). No significant interaction was observed when $eGFR_{BSA}$ was modeled as a linear continuous variable (p for interaction = 0.77).

Discussion

The main finding from the present analysis of CIBIS-II was the consistency of clinical benefit derived from bisoprolol across the entire spectrum of renal function as quantified using the body surface area adjusted Cockcroft and Gault formula. The role of renal insufficiency as a predictor of negative outcomes in patients with HF was also confirmed. As a consequence, the absolute benefit attributable to bisoprolol was higher for the primary and post hoc composite outcomes in patients with a reduced compared to a normal or near normal $eGFR_{BSA}$. This benefit was realized despite patients with worse renal function achieving a lower dose of and having a higher rate of discontinuation of bisoprolol.

Renal function in heart failure

While renal insufficiency is a common and challenging co-morbidity in patients with HF in every day clinical practice[6,7], such patients have been underrepresented in clinical trials, most of which excluded patients with a serum creatinine >2.0-2.5mg/dL[23,24,25,26]. Consequently, the efficacy and tolerability of treatments in this large and high risk subgroup of patients has not been well documented. Understanding the tolerability and efficacy of beta-blockers in such patients is very relevant. Although over-activation of the sympathetic nervous system is thought to contribute to disease progression and poor outcomes in both HF[27] and chronic kidney disease[28] (CKD), acute administration of a beta-blocker can result in initial

depression of ventricular function[29] and may also reduce renal blood flow, potentially leading to worsening of kidney function[30]. However in the longer term, beta-blockers improve ventricular function and clinical outcomes in patients with HF[12,31,32,33,34,35].

CIBIS-II had a less stringent renal exclusion criterion than many trials, allowing enrolment of patients with a creatinine of up to 3.4 mg/dL (300 μmol/L). As a result, more than 40% of patients in CIBIS-II had moderate to severe renal dysfunction, namely an $eGFR_{BSA} < 60$ ml/min per 1.73 m^2 according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative[18].

Effects of bisoprolol according to renal function

Our analysis has shown that in stable patients with moderate to severe heart failure caused by reduced left ventricular systolic function, addition of the selective β_1 antagonist bisoprolol which has a dual route of excretion to standard treatment with a diuretic and an ACE inhibitor reduced all-cause mortality, regardless of baseline renal function. Although there was some suggestion that the effect of bisoprolol to reduce the risk of heart failure hospitalization was greater in patients with a near normal $eGFR_{BSA}$ the test for interaction was not statistically significant.

Only two other studies have examined the effects of beta blockade in the setting of HF and concomitant renal insufficiency. A *post hoc* analysis from the Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF) focused on the efficacy of metoprolol, a beta-1 selective blocker with a predominantly hepatic route of excretion, according to different baseline renal function. Interestingly and in contrast to what we found with bisoprolol, the relative risk reduction with metoprolol was greater in patients in the lowest compared to highest eGFR category[10]. Why this should be is not clear but may be due to differences between the studies. The proportion of patients in the lowest eGFR category was higher in CIBIS-II than MERIT-HF (17.2% versus 12.4% of patients, respectively). For

patients allocated to placebo the mortality rate was also higher in the lowest eGFR category in CIBIS-II compared to MERIT-HF: in CIBIS-II 61/235 (26.0%) of patients with an eGFR <45 ml/min per 1.73 m^2 died compared to 44/224 (19.6%) of these patients in MERIT-HF. Another post hoc analysis from the SENIORS trial (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure) recently suggested that the efficacy of nebivolol was not reduced in elderly HF patients with mild or moderate renal impairment. Similar to our findings, a non significant interaction between baseline renal function and the effect of nebivolol was found[11]. Like metoprolol, metabolism and elimination of nebivolol is almost entirely hepatic with a minimal amount of the drug excreted unchanged in the urine. Nevertheless, some important differences between SENIORS and CIBIS-II design must be considered. In SENIORS patients were excluded if their baseline serum creatinine was higher than 2.8 mg/dL (250 μmol/L). Moreover, the enrollment of patients with mildly symptomatic HF (more than 50% were in NYHA class I-II) and with an ejection fraction >35% (more than one third of the entire population) was permitted.

We found a trend towards a greater reduction in heart rate and diastolic blood pressure with bisoprolol (compared to placebo) in patients with the most reduced renal function. This might be explained by greater sympathetic over-activity in patients with the worst renal function (although baseline heart rate did not vary notably across $eGFR_{BSA}$ categories, similar to what was reported in MERIT-HF) or could be due to bisoprolol accumulation in those patients. In keeping with this latter hypothesis was the higher rate of permanent treatment withdrawals observed in the lowest $eGFR_{BSA}$ category amongst patients allocated to bisoprolol. Of note, the rate of discontinuation of metoprolol (compared to placebo), for adverse events, was not increased in the lowest eGFR category in MERIT-HF, although overall discontinuation rates were not reported. It is possible that accumulation of bisoprolol could have led to a decline in

renal function and sodium and water retention. Although this has been demonstrated to occur acutely in response to a single large intravenous dose of bisoprolol in patients with hypertension[30], we do not know if this occurs chronically in patients with heart failure and serial measurement of renal function was not performed in CIBIS-II. It needs to be re-iterated, however, that a larger absolute benefit was obtained with bisoprolol in patients in the lowest (compared to the highest) $eGFR_{BSA}$ category in CIBIS-II.

The only other relevant study we know of is a small placebo-controlled trial in which the effects of carvedilol on mortality and morbidity were investigated in 114 patients with end-stage renal disease and associated dilated cardiomyopathy receiving regular hemodialysis. After one year of carvedilol therapy left ventricular function improved compared to placebo. At two years follow up, the number of deaths in the carvedilol group was 30 (51.7%) compared to 41 (73.2%) in the placebo group ($p < 0.01$). Moreover, significantly fewer patients receiving carvedilol were admitted to hospital[36].Unfortunately, because of the design of this study we cannot compare dose of treatment achieved, hemodynamic effects and discontinuation rates according to the degree of renal dysfunction at baseline.

Our study has a number of strengths. To the best of our knowledge no previous report has investigated the interaction between renal dysfunction and the effect of bisoprolol on mortality and heart failure hospitalization in patients with HF in advanced NYHA class. Moreover, we also investigated the tolerability and safety of bisoprolol in this clinical setting. In CIBIS-II, given the high serum creatinine threshold allowed for enrolment, almost half of the entire population presented moderate to severe renal impairment. A number of limitations should also be noted. Renal function was estimated and not measured by means of reference method (e.g. iothalamate clearance). We used the Cockcroft-Gault formula to estimate glomerular filtration rate as done in several previous studies[1,2,37]. Furthermore, we

normalized for body surface area to increase the accuracy of the original equation[19,38]. We found that 43% of patients had an eGFR < 60 ml/min whilst in a previous analysis of CIBIS-2 this proportion was 32%[13]. This discrepancy is due to the different equations used and we believe that our analysis better represents the true renal function in this cohort. Measurement of renal function was made on only one occasion in the present study, thus limiting our ability to examine the impact of bisoprolol on renal function during follow up. Other potential prognostic confounders such as hemoglobin were not measured. Nevertheless, their association with impaired estimated renal function makes it unlikely that important distortions of the effect of bisoprolol have occurred.

Clinical implications

Among patients with HF due to left ventricular systolic dysfunction bisoprolol was effective, regardless baseline renal impairment. Therefore, the value of beta-blockers should be reinforced amongst those with HF and CKD, especially as the absolute gains may be higher.

Disclosures

All authors have no conflicts of interest to declare

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Figure Legends

Figure 1. Title: Kaplan-Meier survival function for all-cause mortality according to renal function. **Caption:** plotted lines: *Bisoprolol* (———), *Placebo* (———); A) $eGFR_{BSA}$ < 45 ml/min per 1.73 m^2, B) $eGFR_{BSA}$ 45 to < 60 ml/min per 1.73 m^2, C) $eGFR_{BSA}$ 60 to < 75 ml/min per 1.73 m^2, D) $eGFR_{BSA} \geq 75$ ml/min per 1.73 m^2. **Legend:** $eGFR_{BSA}$ = estimated glomerular filtration rate corrected for body surface area

Figure 2. Title: Unadjusted effect of treatment according to $eGFR_{BSA}$ modeled as a restricted cubic spline. **Caption:** *Bisoprolol effect* (———), *95% confidence interval* (– – – –), *hazard ratio 1* (– · – · –). **Legend:** $eGFR_{BSA}$ = estimated glomerular filtration rate corrected for body surface area, HR = hazard ratio, WHFH = worsening heart failure hospitalization

Figure 3. Title: Kaplan-Meier survival function for all-cause mortality or hospital admissions for worsening heart failure according to renal function. **Caption:** plotted lines: *Bisoprolol* (———), *Placebo* (———); A) $eGFR_{BSA}$ < 45 ml/min per 1.73 m^2, B) $eGFR_{BSA}$ 45 to < 60 ml/min per 1.73 m^2, C) $eGFR_{BSA}$ 60 to < 75 ml/min per 1.73 m^2, D) $eGFR_{BSA} \geq 75$ ml/min per 1.73 m^2 **Legend:** $eGFR_{BSA}$ = estimated glomerular filtration rate corrected for body surface area, WHFH = worsening heart failure hospitalization

Figure 4. Title: Kaplan-Meier survival function for permanent treatment withdrawals according to renal function. **Caption:** plotted lines: *Bisoprolol* (———), *Placebo* (———); A) $eGFR_{BSA}$ < 45 ml/min per 1.73 m^2, B) $eGFR_{BSA}$ 45 to < 60 ml/min per 1.73 m^2, C) $eGFR_{BSA}$ 60 to < 75 ml/min per 1.73 m^2, D) $eGFR_{BSA} \geq 75$ ml/min per 1.73 m^2 **Legend:** $eGFR_{BSA}$ = estimated glomerular filtration rate corrected for body surface area

Table 1. Baseline characteristics according to $eGFR_{BSA}$

Variable		$eGFR_{BSA}$ < 45.0 ml/min per 1.73 m^2 N=450	$eGFR_{BSA}$ 45.0 – 59.9 ml/min per 1.73 m^2 N=669	$eGFR_{BSA}$ 60.0 – 74.9 ml/min per 1.73 m^2 N=640	$eGFR_{BSA}$ ≥75.0 ml/min per 1.73 m^2 N=863	p value
Randomized treatment	Placebo	235 (52.2%)	308 (46.0%)	320 (50.0%)	447 (51.8%)	0.10
	Bisoprolol	215 (47.8%)	361 (54.0%)	320 (50.0%)	416 (48.2%)	
Median age (IQR), years		71 (66, 75)	67 (61, 72)	61 (56, 67)	53 (46, 59)	< 0.001
Sex	Female	204 (45.3%)	177 (26.5%)	79 (12.3%)	50 (5.8%)	< 0.001
	Male	246 (54.7%)	492 (73.5%)	561 (87.7%)	813 (94.2%)	
Median BMI* (IQR)		24.8 (22.6, 27.3)	25.7 (23.7, 28.1)	26.4 (24.3, 29.0)	28.0 (25.5, 30.7)	< 0.001
Smoking history	Never	218 (48.4%)	285 (42.8%)	214 (33.4%)	271 (31.4%)	
	Former	189 (42.0%)	300 (45.0%)	310 (48.4%)	393 (45.5%)	< 0.001
	Current	43 (9.6%)	81 (12.2%)	116 (18.2%)	199 (23.1%)	

Medical history						
Hypertension		225 (50.0%)	303 (45.3%)	268 (41.9%)	346 (40.1%)	0.004
Diabetes mellitus		74 (16.4%)	88 (13.2%)	61 (9.5%)	85 (9.8%)	0.001
Coronary artery disease		328 (72.9%)	452 (67.6%)	426 (66.6%)	496 (57.5%)	< 0.001
Valve disease		77 (17.1%)	84 (12.6%)	64 (10.0%)	54 (6.3%)	< 0.001
Cerebrovascular disease		43 (9.6%)	55 (8.2%)	56 (8.8%)	43 (5.0%)	0.006
Peripheral arterial disease		45 (10.0%)	71 (10.6%)	41 (6.4%)	36 (4.2%)	< 0.001
Percutaneous coronary intervention		19 (4.2%)	32 (4.8%)	25 (3.9%)	40 (4.6%)	0.86
Cardiac surgery		88 (19.6%)	109 (16.3%)	96 (15.0%)	80 (9.3%)	< 0.001
Heart Failure Etiology	Ischemic	248 (55.1%)	346 (51.7%)	325 (50.8%)	386 (44.7%)	
	PDCM	28 (6.2%)	69 (10.3%)	77 (12.0%)	140 (16.2%)	0.03
	Others**	174 (38.7%)	254 (38.0%)	238 (37.2%)	337 (39.1%)	
NYHA¶ Class	III	370 (82.2%)	558 (83.4%)	531 (83.0%)	719 (83.3%)	0.95

	IV	80 (17.8%)	111 (16.6%)	109 (17.0%)	144 (16.7%)	
Median HR‖ (IQR), beats/min		78 (70, 88)	77 (69, 88)	78 (68, 89)	80 (70, 91)	0.08
Atrial Fibrillation		90 (20.0%)	129 (19.3%)	133 (20.8%)	166 (19.2%)	0.87
Median SBP# (IQR), mmHg		126 (112, 140)	130 (115, 140)	128 (115, 140)	130 (120, 140)	0.77
Median DBP† (IQR), mmHg		80 (70, 80)	80 (70, 86)	80 (70, 90)	80 (70, 90)	< 0.001
Median creatinine (IQR), µmol/L		133 (111, 159)	113 (97.2, 124)	99 (89, 108.7)	84 (75, 94)	< 0.001
Median $eGFR_{BSA}$§ (IQR) ml/min/1.73 m^2		38.4 (32.9, 42.1)	52.4 (48.9, 56.2)	67.0 (63.6, 71.0)	90.4 (81.6, 102.3)	< 0.001
Median left ventricular EF‡ (IQR), %		28 (22.7, 32)	28 (23, 32)	28.9 (24.1, 32.1)	29.6 (24.1, 33)	< 0.001
Average daily dose (mg)	Placebo	6.8 (2.8)	7.1 (2.7)	7.4 (2.6)	7.6 (2.5)	0.007
	Bisoprolol	5.6 (3.2)	6.0 (3.1)	6.1 (3.0)	6.8 (2.8)	< 0.001
Median daily dose (mg)	Placebo	8.3 (4.7, 9.2)	8.8 (4.9, 9.3)	8.9 (5.5, 9.3)	9.0 (6.7, 9.3)	0.007
	Bisoprolol	6.1 (2.4, 9.0)	7.0 (2.8, 9.1)	6.6 (3.4, 9.2)	7.7 (4.2, 9.2)	< 0.001
Co-medication						

Diuretic	448 (99.6%)	661 (98.8%)	634 (99.1%)	858 (99.4%)	0.44
Spironolactone	47 (10.4%)	72 (10.8%)	63 (9.8%)	88 (10.2%)	0.32
ACE Inhibitor	423 (94.0%)	634 (94.8%)	602 (94.1%)	827 (95.8%)	0.37
Digoxin	227 (50.4%)	353 (52.8%)	320 (50.0%)	451 (52.3%)	0.70
Amiodarone	90 (20.0%)	103 (15.4%)	102 (15.9%)	93 (10.8%)	< 0.001
Anticoagulants	154 (34.2%)	204 (30.5%)	182 (28.4%)	220 (25.5%)	0.008
Antiplatelet agents	173 (38.4%)	286 (42.8%)	271 (42.3%)	344 (40.0%)	0.06

* BMI = body mass index, † DBP = diastolic blood pressure, ‡ EF = ejection fraction, § $eGFR_{BSA}$= estimated glomerular filtration rate corrected for body surface area, ‖ HR = heart rate, ¶ NYHA = New York Heart Association, # = systolic blood pressure

To convert creatinine values to mg/dl, divide by 88.4.

** Others : patients with valvular disease or hypertension, together with those with suspected but unproved ischaemic heart disease or cardiomyopathy

Table 2. Proportional hazards ratios for all the outcomes under study across $eGFR_{BSA}$ categories

Outcome		Creatinine Clearance Category (ml/min per 1.73 m^2)				Test for interaction ‡
		< 45	**45 to < 60**	**60 to < 75**	**≥ 75**	
		N=450	N=669	N=640	N=863	
All-cause mortality	*No of events (%)*	105 (23.3%)	98 (14.6%)	87 (13.6%)	89 (10.3%)	0.81 (0.85)
	Bisoprolol /Placebo HR (95% CI†)*	0.71 (0.48 – 1.05)	0.69 (0.46 – 1.04)	0.53 (0.34 – 0.82)	0.64 (0.42 – 0.99)	
All-cause mortality or hospital admissions for worsening heart failure	*No of events (%)*	165 (36.7%)	169 (25.3%)	148 (23.1%)	156 (18.1%)	0.66 (0.62)
	Bisoprolol /Placebo HR (95% CI)	0.72 (0.53 to 0.99)	0.66 (0.49 to 0.91)	0.55 (0.39 to 0.77)	0.56 (0.40 to 0.78)	
Heart failure hospitalization	*No of events (%)*	99 (22.0%)	112 (16.7%)	82 (12.8%)	93 (10.8%)	0.71 (0.47)
	Bisoprolol /Placebo HR (95% CI)	0.76 (0.51 to 1.14)	0.66 (0.45 to 0.97)	0.54 (0.34 to 0.85)	0.52 (0.34 to 0.80)	

All-cause mortality or all-cause hospital admission	*No of events (%)*	261 (58.0%)	286 (42.7%)	256 (40.0%)	286 (33.1%)	0.81 (0.77)
	Bisoprolol /Placebo HR (95% CI)	0.82 (0.64 to 1.05)	0.72 (0.57 to 0.92)	0.69 (0.54 to 0.89)	0.77 (0.61 to 0.98)	
Permanent treatment withdrawals	*No of events (%)*	95 (21.1%)	114 (17.0%)	81 (12.7%)	89 (10.3%)	0.01 (<0.001)
	Bisoprolol /Placebo HR (95% CI)	1.54 (1.01 to 2.33)	1.05 (0.71 to 1.55)	0.76 (0.48 to 1.19)	0.54 (0.35 to 0.85)	

* HR = hazard ratio, † CI = confidence interval

‡ For interaction test, value in brackets is for test using continuous rather than categorical variable.

Table 3. Median (interquartile range) change in heart rate, systolic blood pressure (BP) and diastolic BP between baseline and 3 months of follow-up.

Change from baseline to 3 months follow-up	**Randomized Treatment**	**$eGFR_{BSA}$* < 45.0 ml/min per 1.73 m^2**	**$eGFR_{BSA}$ 45.0 – 59.9 ml/min per 1.73 m^2**	**$eGFR_{BSA}$ 60.0 – 74.9 ml/min per 1.73 m^2**	**$eGFR_{BSA}$ ≥75.0 ml/min per 1.73 m^2**	**p value**	**Interaction p value**
Heart rate	Placebo	0 (-7, 10)	2 (-5, 10)	-0.5 (-8, 8)	-2 (-6, 10)	0.5	0.14
	Bisoprolol	-15 (2, 25.5)	-12 (2, 22)	-11 (2, 20)	-10 (1, 20)	0.04	
Systolic BP †	Placebo	-10 (-10, 30)	-5 (-5, 21)	-4 (-10, 20)	-4 (-10, 20)	0.04	0.40
	Bisoprolol	-10 (-5, 50)	-5 (-10, 20)	-5 (-5, 20)	-2 (-8, 20)	0.02	
Diastolic BP	Placebo	0 (-6, 8)	0 (-5, 10)	0 (-5, 10)	0 (-5, 10)	0.36	0.18
	Bisoprolol	-3 (-2, 10)	0 (-5, 10)	0 (-5, 10)	0.5 (-5, 10)	0.38	

* $eGFR_{BSA}$ = estimated glomerular filtration rate corrected for body surface area, † BP = blood pressure

Figure 1.

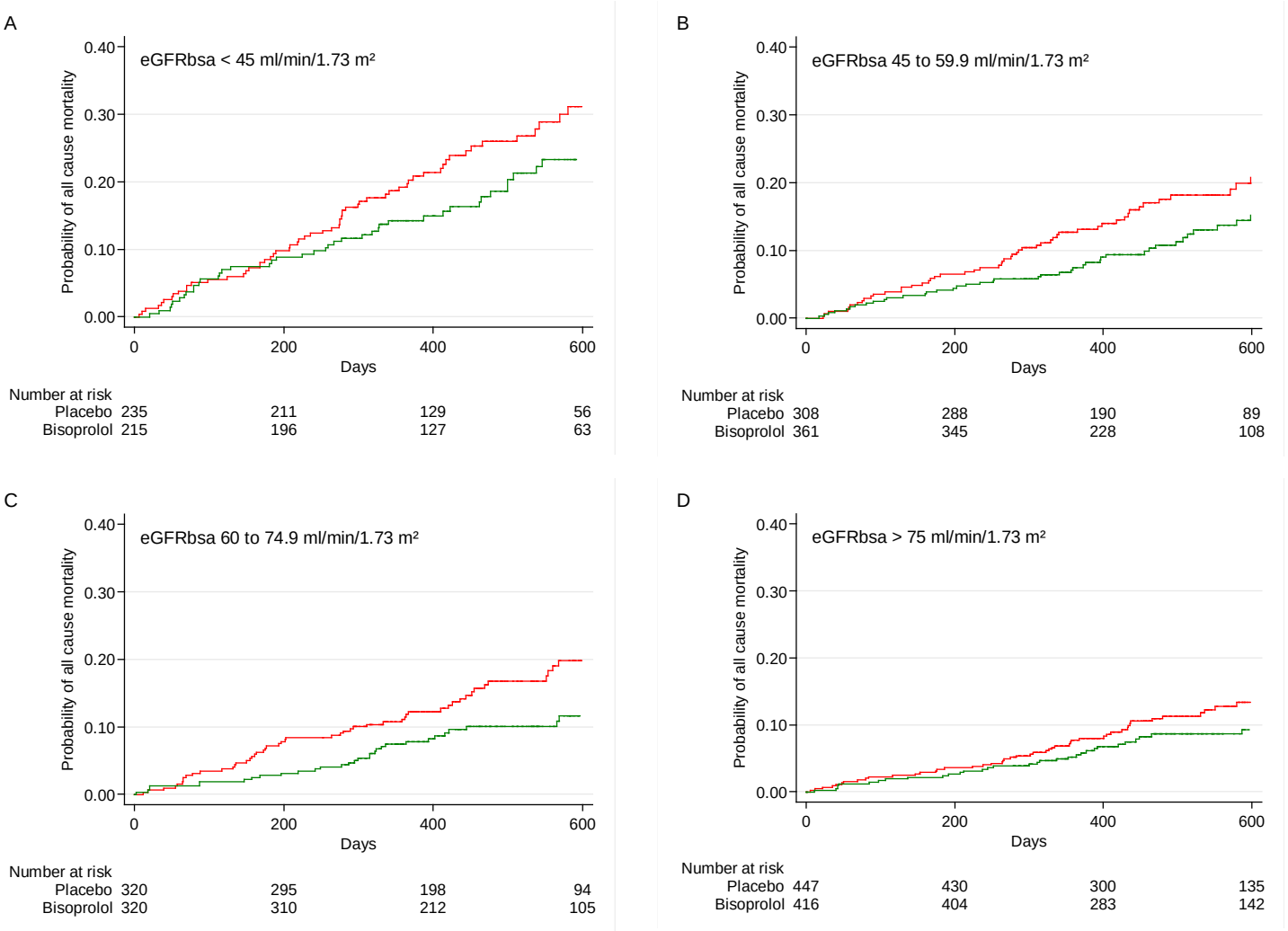

A
eGFRbsa < 45 ml/min/1.73 m²
Probability of all cause mortality
0.00
0.10
0.20
0.30
0.40
0
200
400
600
Days
Number at risk
Placebo 235 211 129 56
Bisoprolol 215 196 127 63
B
eGFRbsa 45 to 59.9 ml/min/1.73 m²
Probability of all cause mortality
0.00
0.10
0.20
0.30
0.40
0
200
400
600
Days
Number at risk
Placebo 308 288 190 89
Bisoprolol 361 345 228 108
C
eGFRbsa 60 to 74.9 ml/min/1.73 m²
Probability of all cause mortality
0.00
0.10
0.20
0.30
0.40
0
200
400
600
Days
Number at risk
Placebo 320 295 198 94
Bisoprolol 320 310 212 105
D
eGFRbsa > 75 ml/min/1.73 m²
Probability of all cause mortality
0.00
0.10
0.20
0.30
0.40
0
200
400
600
Days
Number at risk
Placebo 447 430 300 135
Bisoprolol 416 404 283 142

Figure 2.

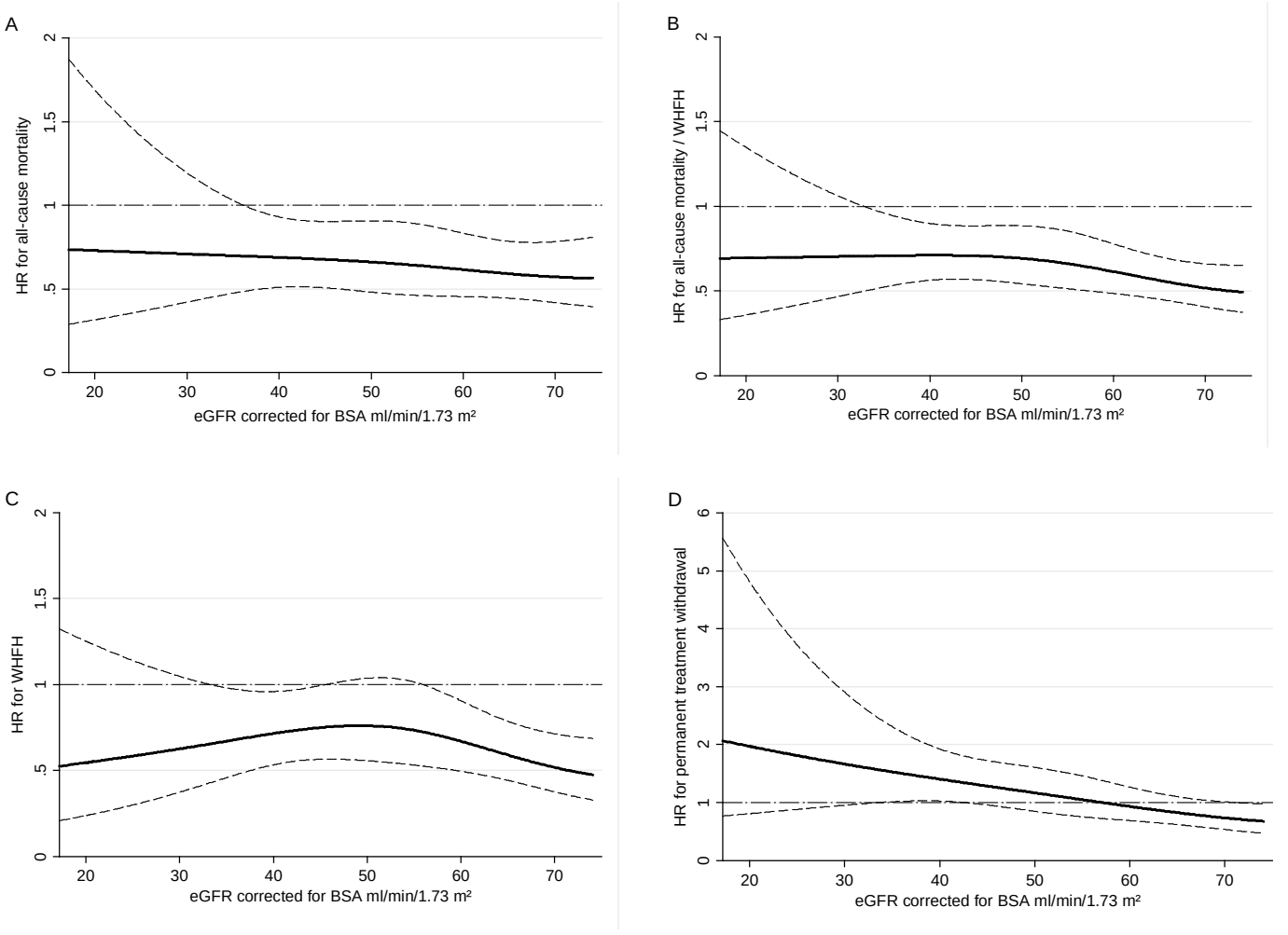

A
HR for all-cause mortality
0
.5
1
1.5
2
20
30
40
50
60
70
eGFR corrected for BSA ml/min/1.73 m²
B
HR for all-cause mortality / WHFH
0
.5
1
1.5
2
20
30
40
50
60
70
eGFR corrected for BSA ml/min/1.73 m²
C
HR for WHFH
0
.5
1
1.5
2
20
30
40
50
60
70
eGFR corrected for BSA ml/min/1.73 m²
D
HR for permanent treatment withdrawal
0
1
2
3
4
5
6
20
30
40
50
60
70
eGFR corrected for BSA ml/min/1.73 m²

Figure 3.

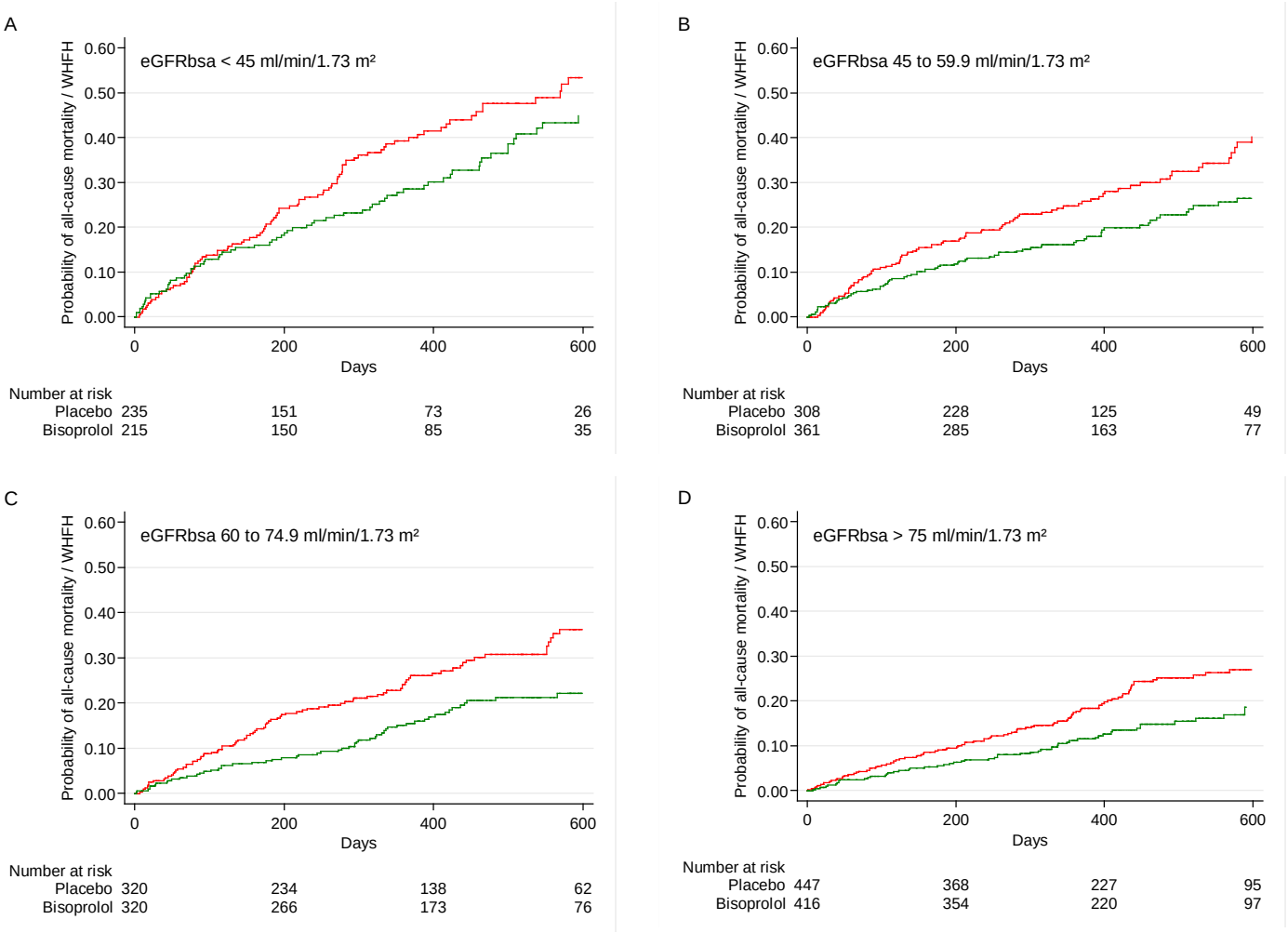
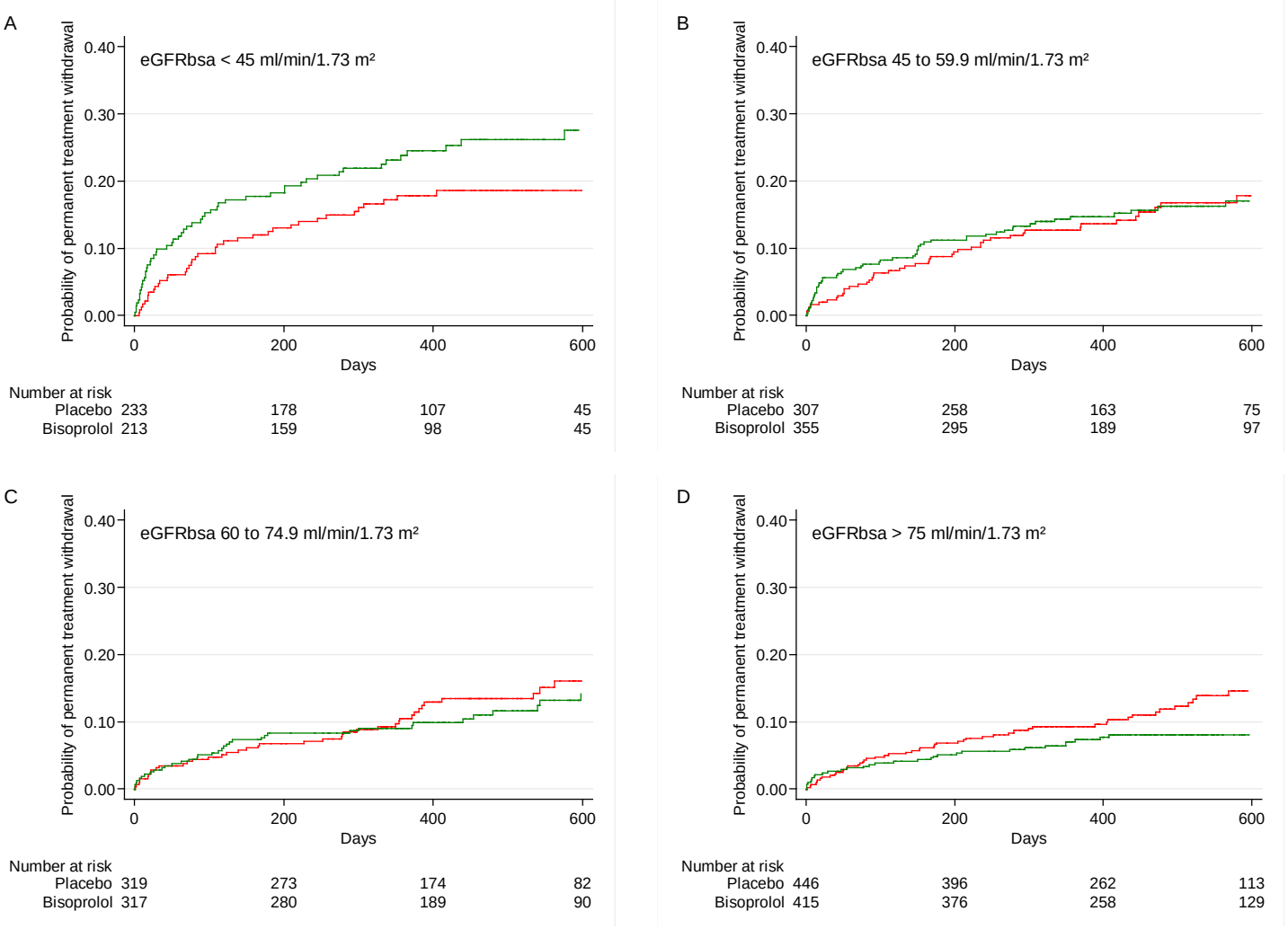

A
eGFRbsa < 45 ml/min/1.73 m²
Probability of all-cause mortality / WHFH
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0
200
400
600
Days
Number at risk
Placebo 235 151 73 26
Bisoprolol 215 150 85 35
B
eGFRbsa 45 to 59.9 ml/min/1.73 m²
Probability of all-cause mortality / WHFH
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0
200
400
600
Days
Number at risk
Placebo 308 228 125 49
Bisoprolol 361 285 163 77
C
eGFRbsa 60 to 74.9 ml/min/1.73 m²
Probability of all-cause mortality / WHFH
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0
200
400
600
Days
Number at risk
Placebo 320 234 138 62
Bisoprolol 320 266 173 76
D
eGFRbsa > 75 ml/min/1.73 m²
Probability of all-cause mortality / WHFH
0.00
0.10
0.20
0.30
0.40
0.50
0.60
0
200
400
600
Days
Number at risk
Placebo 447 368 227 95
Bisoprolol 416 354 220 97

Figure 4.


A
eGFRbsa < 45 ml/min/1.73 m²
Probability of permanent treatment withdrawal
0.00
0.10
0.20
0.30
0.40
0
200
400
600
Days
Number at risk
Placebo 233 178 107 45
Bisoprolol 213 159 98 45
B
eGFRbsa 45 to 59.9 ml/min/1.73 m²
Probability of permanent treatment withdrawal
0.00
0.10
0.20
0.30
0.40
0
200
400
600
Days
Number at risk
Placebo 307 258 163 75
Bisoprolol 355 295 189 97
C
eGFRbsa 60 to 74.9 ml/min/1.73 m²
Probability of permanent treatment withdrawal
0.00
0.10
0.20
0.30
0.40
0
200
400
600
Days
Number at risk
Placebo 319 273 174 82
Bisoprolol 317 280 189 90
D
eGFRbsa > 75 ml/min/1.73 m²
Probability of permanent treatment withdrawal
0.00
0.10
0.20
0.30
0.40
0
200
400
600
Days
Number at risk
Placebo 446 396 262 113
Bisoprolol 415 376 258 129