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Mortality reduction associated with beta-adrenoceptor inhibition in chronic heart failure is greater in patients with diabetes mellitus

Abbreviated title: Diabetes, heart failure, and beta-blockers

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Abstract

Objective. Diabetes mellitus increases mortality in patients with chronic heart failure (CHF) and reduced left ventricular ejection fraction. Studies have questioned the safety of β-adrenoceptor blockers (β-blockers) in some patients with diabetes and reduced left ventricular ejection fraction. We examined whether β-blockers and angiotensin converting enzyme inhibitors (ACEI) are associated with differential effects on mortality in CHF patients with and without diabetes.

Research Design and Methods. We conducted a prospective cohort study of 1797 patients with CHF recruited between 2006 and 2014, with mean follow-up of 4 years. β-blocker dose was expressed as equivalent dose of bisoprolol (mg/day), and ACEI dose as equivalent dose of ramipril (mg/day). Cox regression analysis was used to examine the interaction between diabetes and drug dose upon all-cause mortality.

Results. Patients with diabetes were prescribed larger doses of β-blocker and ACEI than were patients without diabetes. Increasing β-blocker dose was associated with lower mortality in patients with diabetes (8.9% per mg/day; 95% CI 5-12.6%) and without diabetes (3.5% per mg/day; 95% CI 0.7-6.3%), although the effect was larger in people with diabetes (interaction p=0.027). Increasing ACEI dose was associated with lower mortality in patients with diabetes (5.9% per mg/day; 95% CI 2.5-9.2%) and without diabetes (5.1% per mg/day; 95% CI 2.6-7.6%), with similar effect size in these groups (interaction p=0.76).

Conclusion. Increasing β-blocker dose is associated with a greater prognostic advantage in CHF patients with diabetes than without diabetes.

Chronic heart failure (CHF) associated with left ventricular systolic dysfunction is a global healthcare problem affecting over 26 million individuals (1,2). Of these people, over one third will also suffer from diabetes mellitus (3,4). A recent study of 1.9 million individuals demonstrated that CHF was second only to peripheral artery disease as a cardiovascular complication of type 2 diabetes (5). In addition to being an important risk factor for the development of CHF, diabetes also imparts significant prognostic disadvantage to patients with established CHF (6,7,8). In a large prospective cohort study specifically designed to examine prognostic factors in CHF associated with left ventricular systolic dysfunction (LVSD), we showed that diabetes increases risk of death threefold (8).

Over the last three decades, disease-modifying therapies have led to a substantial reduction in mortality in patients with CHF associated with left ventricular systolic dysfunction (9). Two of the principal disease modifying agents, angiotensin converting inhibitors (ACEI) (10) and β-adrenoceptor antagonists (β-blockers) (11), have been shown to reduce death in patients with CHF. While ACEI and β-blockers are well established as the cornerstone of CHF treatment (12), no contemporary study has compared the effect of these agents in patients with and without diabetes. A recent publication retrospectively analysing data from the ACCORD trial raised concerns around the safety of β-blockers in intensively treated patients suffering from type 2 diabetes with LVSD (13). In the present analysis we utilised a highly characterised cohort of unselected, prospectively recruited patients with CHF secondary to LVSD, to examine the association of ACEI and β-blockers with all-cause mortality in patients with and without diabetes. In particular, we present the first investigation of the relationship between ACEI and β-blocker dose and mortality

in patients with CHF and LVSD, stratified by diabetes status. We hypothesized that higher doses of these therapies would be associated with differential reductions in mortality in people with and without diabetes.

Research Design and Methods

We conducted a prospective cohort study with the a priori defined aim of identifying prognostic markers in patients with CHF secondary to LVSD (left ventricular ejection fraction ≤45%), receiving contemporary evidence-based therapies (8,9). Inclusion in the study required the presence of stable signs and symptoms of CHF for at least 3 months, age ≥18 years, and left ventricular ejection fraction ≤45% on transthoracic echocardiography. Between June 2006 and December 2014, consecutive patients attending specialist cardiology clinics in four UK hospitals were approached to participate. In total, 1802 patients provided written informed consent, although 5 had missing medication doses so were excluded from the current analysis. The Leeds West Research Ethics Committee gave ethical approval and the investigation conforms to the principles outlined in the Declaration of Helsinki. All patients were registered with the UK Office of Population Censuses and Surveys, which provided details of time of death; follow-up censorship occurred on 8th May 2016.

As described previously (8,9), details of medical history, including diabetes status, were collected at recruitment, and symptomatic status defined using the New York Heart Association (NYHA) classification. Venous blood was collected for measurement of electrolyte concentrations, assessment of renal function and haematological parameters; these were performed in the local hospital chemical pathology laboratories. Estimated glomerular filtration rate (eGFR) was calculated

using the Modification of Diet in Renal Disease method as we described (8). Two-dimensional echocardiography was performed according to The American Society of Echocardiography recommendations (14). Resting heart rate was measured using 12-lead electrocardiograms. Prescribed doses of loop diuretic, ACEI, angiotensin receptor blockers (ARB) and β-blockers were collected at study recruitment. The prescribed daily doses of β-blocker, ACEI (or ARB if used instead of ACEI) and loop diuretic were expressed relative to the maximal licensed dose of bisoprolol, ramipril and furosemide, respectively, as we have previously published (9). Receipt of cardiac resynchronisation therapy (CRT) or implantable cardioverter-defibrillator (ICD) was assessed during the six-month period after recruitment (9).

Statistical analysis

All statistical analyses were performed using IBM SPSS statistics version 21 (IBM Corporation, Armonk, NY, USA). Normal distribution of data was confirmed using skewness and kurtosis tests. Continuous data are presented as mean (standard error of the mean [SEM]) and categorical data are shown as percentage (number). Groups were compared using two-sided Student t-tests or ANOVA for continuous data and two-sided Pearson χ^2 tests for categorical data. Survival of groups was compared with Kaplan-Meier curves and log-rank tests, or Cox proportional hazards regression analysis. Statistical significance was defined as $p<0.05$.

Results

Patient characteristics. Within the 1797 patient cohort, 28% (n=503) also had diabetes; these had a mean HbA1c of 61.5mmol/mol (SEM 0.8) [7.8% (SEM 0.1%)], and used the following glycaemic control strategies: diet alone in 30.2%;

sulphonylurea in 30.2%; metformin in 38.8%; insulin in 19.9%; dipeptidyl-peptidase 4 (DPP4) inhibition in 3.4%; thiazolelidinedione in 2.6%; sodium-glucose co-transporter-2 (SGLT2) inhibition in 0.2%; glucagon-like peptide-1 receptor agonist in 0.2%. Only 1.2% (n=6) of cases of diabetes were classified as type 1, with the remainder being type 2. Descriptive data contrasting patients with and without diabetes are presented in **Table 1**. Patients with diabetes had similar age and sex distribution**,** although were more likely to have an ischaemic etiology underlying their CHF, had lower hemoglobin and eGFR, were more often in NYHA class III/IV, had less impaired left ventricular function, and yet were prescribed higher doses of loop diuretic. Patients with diabetes received higher doses of β-blocker and ACEI, although their heart rate was comparable to patients without diabetes. After a mean follow-up period of 4 years (7227 patient-years), 494 patients without diabetes and 241 patients with diabetes had died.

Diabetes and the relationship between β-blocker dose and mortality. Within the entire study cohort, 1523 patients (84.8%) were prescribed a β-blocker; of these 1276 (83.8%) received bisoprolol, 165 (10.8%) received carvedilol, and 82 (5.4%) received other β-blockers (predominantly metoprolol or nebivolol). The distribution of these β-blockers was comparable in patients with and without diabetes (χ^2 p=0.68). We divided patients with and without diabetes in to groups receiving no β-blocker, or bisoprolol equivalent doses of <2.5mg/day (low dose), 2.5-7.4mg/day (medium dose) and ≥7.5mg/day (high dose) (**Table 2**). There were clear associations between β-blocker dose group and patient characteristics, such as age, heart rate, and implantable cardioverter defibrillator (ICD) provision. However, the pattern of these associations did not statistically differ between groups with or without diabetes (i.e.

no significant interaction was present with diabetes status). Whilst the decline in heart rate with escalating β-blocker dose (in patients with and without diabetes) was statistically significant, the apparently modest effect probably reflects the use of cardiac resynchronisation devices in over 25% of the cohort.

Increasing β-blocker dose was associated with lower all-cause mortality in patients without and with diabetes (**Figure 1**); however, the magnitude of this association appeared more pronounced in patients with diabetes. To quantify this, we calculated the days of survival lost per patient during the first 5 years (1825 days) of follow-up (i.e. the area under Kaplan-Meier mortality curves). In patients without diabetes, taking no β-blocker was associated with 448 (95% CI 347-549) days lost, whilst ≥7.5mg/day was associated with 326 (95% CI 239-413) days lost. In patients with diabetes, taking no β-blocker was associated with 712 (95% CI 527-896) days lost, whilst ≥7.5mg/day was associated with 355 (95% CI 227-482) days lost. To explore this further, Cox regression analysis was used to define the association between β-blocker dose, as a continuous variable, and mortality in people without and with diabetes. For every mg/day increment in bisoprolol dose, patients without diabetes exhibited a 3.5% (95% CI 0.7-6.3%) reduction in mortality, which was significantly lower (interaction p=0.027) than the 8.9% (95% CI 5-12.6%) reduction in mortality noted in patients with diabetes. This interaction persisted (p=0.026) after correcting for factors associated with β-blocker dose, including age, gender, ACEI dose, the presence of ICD, and clinical status (NYHA class III/IV symptoms). However, the interaction lost statistical significance (p=0.086) if heart rate was also included in the multivariate analysis, suggesting differential heart rate reduction may account for some of the greater association with mortality reduction in people with diabetes.

Exploring the interaction between diabetes and β-blocker dose. Subgroup analyses were used to explore potential mechanisms of greater β-blocker dose effect size in patients with diabetes. First, we asked whether the interaction between diabetes and β-blocker dose persisted in patients with more or less pronounced LVSD. To do this, we split the cohort in to groups above and below the median left ventricular ejection fraction (LVEF) of 32%, and noted that the interaction between diabetes and β-blocker dose only persisted in those with LVEF<32% (**Figure 2A**). We then studied just the cohort of patients with diabetes, to ask whether glycemic control or management were associated with the relationship between mortality and β-blocker dose. We found no interaction between insulin treatment and β-blocker dose (p=0.72), suggesting similar β-blocker dose-effect size in patients receiving insulin or non-insulin therapy (**Figure 2B**). After dividing the cohort of patients with diabetes according to median HbA1c (of 57mmol/mol), we again noted no interaction between glycemic control and β-blocker dose (p=0.67), indicating similar β-blocker dose-effect size in patients with better and poorer glycemic control (**Figure 2B**).

Diabetes and the relationship between ACEI dose and mortality. We divided patients with and without diabetes in to groups receiving no ACEI (or ARB), or ramipril equivalent doses of <2.5mg/day (low dose), 2.5-7.4mg/day (medium dose) and ≥7.5mg/day (high dose) (**Supplemental Table 1**). There were clear associations between ACEI dose group and patient characteristics, such as age, renal dysfunction, and symptomatic status. However, the pattern of these associations did not statistically differ between groups with or without diabetes (i.e. no significant

interaction was present with diabetes status), other than for NYHA class (interaction p=0.012), which fell more steeply with rising ACEI dose in people with diabetes.

Increasing ACEI dose was associated with lower all-cause mortality in patients without and with diabetes (**Supplemental Figure 1**), although the magnitude of this association appeared more comparable in patients with and without diabetes, than for β-blocker dose. To quantify this, we calculated the days of survival lost per patient during the first 5 years (1825 days) of follow-up (i.e. the area under Kaplan-Meier mortality curves). In patients without diabetes, taking no ACEI was associated with 478 (95% CI 344-611) days lost, whilst ≥7.5mg/day was associated with 287 (95% CI 220-355) days lost. In patients with diabetes, taking no ACEI was associated with 774 (95% CI 534-1013) days lost, whilst ≥7.5mg/day was associated with 391 (95% CI 282-499) days lost. To further corroborate a similar effect size of ACEI dose in patients with and without diabetes, Cox regression analysis was used to define the association between ACEI dose, as a continuous variable, and all-cause mortality. For every mg/day increment in ramipril dose, patients without diabetes exhibited a 5.1% (95% CI 2.6-7.6%) reduction in mortality, which was similar to (interaction p=0.76) the 5.9% (95% CI 2.5-9.2%) reduction in mortality noted in patients with diabetes.

Conclusions

The present report provides important new information for healthcare professionals caring for patients suffering from CHF with reduced ejection fraction per se, and patients with the lethal combination of CHF and diabetes. We present the first

quantification of the association between CHF modifying agent dose and all-cause mortality in people with and without diabetes. Our most important findings are:

- Higher dose β-blockers are associated with lower mortality in patients with CHF and LVSD, but patients with diabetes may derive more benefit from higher dose β-blockers.
- Higher dose ACEI was associated with comparable mortality reduction in people with and without diabetes.
- The association between higher β-blocker dose and reduced mortality is most pronounced in patients with diabetes who have more severely impaired left ventricular function.
- Amongst patients with diabetes, the relationship between β-blocker dose and mortality was not associated with glycemic control or insulin therapy.

Data from the Action to Control Cardiovascular Risk in Diabetes and Bypass Angioplasty Revascularization Investigation 2 Diabetes trials: effects of β-blockers on outcome in patients with CHF and diabetes. Tsujimoto and colleagues recently published reports examining the effect of β-blockers on mortality in patients with diabetes and reduced left ventricular ejection fraction. The report from the ACCORD dataset raised concerns around β-blocker use in intensively treated patients suffering from type 2 diabetes with LVSD (13); the authors attributed this to increased hypoglycaemia in β-blocker treated patients. The almost simultaneous report using the BARI-2D dataset from the same group was more reassuring (15), supporting the use of β-blockers in patients with ischaemic heart disease and reduced ejection fraction. However, both of these well-performed retrospective analyses should be taken in the context of the highly selected patients

studied. Unlike our dataset, neither report provided detailed drug dose and left ventricular ejection fraction data; moreover, BARI-2D excluded patients with NYHA class III/IV heart failure symptoms. Importantly, our study population is representative of very large population studies (16), unlike the patients recruited to clinical trials described by Tsujimoto et al (13,15). Of relevance to this, in our study the prevalence of ischemic heart disease was greater in patients with diabetes mellitus, as seen other large CHF cohorts (e.g. 16,17), probably reflecting an excess of atherosclerosis risk factors in patients with diabetes (18).

Potential mechanisms underlying the favorable effect of β-blockers on outcome in patients with chronic heart failure and diabetes. The present study was not designed to examine disease mechanisms, but the more favorable effect of β-blockers on mortality in patients with diabetes and CHF warrants some discussion (see also **Supplemental Figure 2**). We have previously shown that β-blocker naïve patients with CHF and diabetes (taking ACEI) have increased basal sympathetic neural outflow, assessed using muscle sympathetic nerve activity (MSNA), compared to CHF patients without diabetes (19). Moreover, peak sympathoactivation in these patients in response to a high carbohydrate load was also higher than in CHF patients without diabetes. Heightened MSNA has been linked to increased mortality in patients with CHF (20). We also recently demonstrated that optimally treated patients with the combination of CHF and diabetes have evidence of excessive sympathoactivation using measurements of heart rate turbulence and heart rate variability (21), both of which we have shown are markers of increased risk of death (22,23). Whilst we did not examine the effect of β-blockers on these variables in the present study, it is tempting to speculate that the stronger

association of β-blocker dose with outcome in patients with diabetes is linked to an important reduction in the detrimental effects of excessive sympathoactivation caused by diabetes.

Our exploratory analyses also provide some potentially relevant clues to underpinning mechanisms, but these data should be viewed as hypothesis generating. The interaction between diabetes and β-blocker dose was only noted in patients with left ventricular ejection fraction below the median value of 32%, suggesting heart failure phenotype is an important part of the interaction. However, the comparable association of β-blocker dose with mortality in patients with diabetes divided by insulin treatment, or by glycemic control, may suggest that glycemic management is less relevant to our observations about β-blocker dose.

Study stengths and limitations. Our investigation is the first to describe the association between dose of standard heart failure medical therapies and mortality in a large unselected contemporary cohort, and may have important implications for the management of CHF in people with diabetes. However, a number of potential limitations of our study should be also be considered. Firstly, our study did not include patients with CHF and preserved ejection fraction, so the data are not generalizable to this group of patients. Secondly, we elected not to analyze the association between β-blocker and ACEI dose and mode of death in CHF patients with and without diabetes, as whilst of interest, this data would not strengthen the overall key message of the manuscript. Thirdly, the nature of the study does not allow us to provide a mechanism for the differential effect of β-blockers on mortality in patients with CHF with and without diabetes, although our exploratory analyses

provide useful data to guide future research. Fourth, our work predominantly describes patients with type 2 diabetes, and we do not have data on hypoglycaemic episodes. Fifth, the assessment of drug dose was taken at a single point in time so the present study cannot account for previous exposure to β-blocker or ACEI, or subsequent titration of these drugs. Finally, the observational nature of our analysis means that we cannot infer causality in the associations we have demonstrated. In particular, this means we cannot be certain that higher doses of β-blocker or ACEI per se result in lower mortality, and instead the ability to tolerate greater doses of such agents could identify intrinsically lower risk patients. However, the contrasting data for β-blockers versus ACEI, along with our adjusted analyses including disease severity measured by NYHA class, provide support for direct benefits of higher β-blocker dose.

Clinical implications of present study. While β-blockers are well-established as a cornerstone of the treatment of patients suffering from CHF associated with LVSD (11), there is often a reluctance to prescribe the doses achieved in clinical trials. As reported by Fowler et al, β-blocker dosing in community CHF services is significantly lower than in randomized clinical trials (24), especially when prescribed by non-cardiologists. Across many healthcare settings, achieved β-blocker dose is often less than those achieved in clinical trials (25). Data that quantify the value of each increment in β-blocker dose in terms of mortality risk (and survival gain) may help patients and care providers when discussing β-blocker titration. Here we show that each mg/day increment in bisoprolol equivalent dose is associated with a 3.5% mortality reduction in CHF patients without diabetes, but an almost 9% reduction in CHF patients with diabetes. Of relevance to our report, Fiuzat et al recently

demonstrated that improvements in outcome with higher β-blocker may be more attributable to dose than heart rate reduction (26), although our data may suggest some role for heart rate reduction.

In conclusion, this study is the first to use a prospectively recruited cohort of unselected patients with CHF to examine mortality reduction associated with greater β-blocker and ACEI dose in people with and without diabetes. We make the important observation that patients with diabetes may derive more prognostic benefit from higher β-blocker doses than patients without diabetes. These data should provide reassurance to patients and healthcare providers, and encourage careful but determined up titration of β-blockers in this high-risk group of patients.

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	Total cohort (n=1797)	No Diabetes (n=1294)	Diabetes (n=503)	P value
Age (yrs)	69.6 (0.3)	69.4 (0.4)	70.2 (0.5)	0.2
Heart Rate (bpm)	75.3 (0.4)	75.3 (0.5)	75.3 (0.8)	0.99
Systolic BP (mmHg)	122 .4 (0.6)	121.5 (0.7)	125 (1)	0.004
RPP (bpm x mmHg)	9152 (73)	9091 (86)	9321 (137)	0.16
QRS duration (ms)	123 (1)	124 (1)	122 (1)	0.22
Hemoglobin (g/dL)	13.4 (0.1)	13.6 (0.1)	13 (0.1)	<0.001
eGFR (ml/min/1.73m^2)	57.7 (0.5)	59.1 (0.5)	54.4 (0.9)	<0.001
LVEDD (mm)	57.2 (0.2)	57.5 (0.3)	56.3 (0.4)	0.01
LVEF (%)	32 (0.2)	31.5 (0.3)	33.1 (0.4)	0.001
Bisoprolol dose (mg/day)	3.9 (0.1)	3.8 (0.1)	4.2(0.2)	0.01
Ramipril dose (mg/day)	4.9 (0.1)	4.8 (0.1)	5.3 (0.2)	0.004
Furosemide dose (mg/day)	51.2 (1.2)	44.6 (1.3)	68.3 (2.5)	<0.001
Male sex (% [n])	73.2 (1315)	72 (932)	76.1 (383)	0.077
Ischaemic etiology (% [n])	59.2 (1064)	54.9 (710)	70.4 (354)	<0.001
ICD in situ (% [n])	11.7 (210)	11.7 (152)	11.5 (58)	0.9
CRT in situ (% [n])	25.3 (455)	25.5 (330)	24.9 (125)	0.78
NYHA Class III/IV (% [n])	30.8 (554)	28.4 (367)	37.2 (187)	<0.001

Table 1. Characteristics of patient cohort and cohort divided into patients with and without type 2 diabetes mellitus. Data presented as mean (SEM) or % (n). P value compares groups with and without diabetes with unpaired t-tests or chi-squared tests. BP=blood pressure, RPP=rate-pressure product, eGFR=estimated glomerular filtration rate, LVEDD=left ventricular end diastolic diameter, LVEF=left ventricular ejection fraction, ICD=implantable cardioverter defibrillator, CRT=cardiac resynchronisation therapy, NYHA=New York Heart Association.

	No Diabetes				Diabetes			
Bisoprolol equivalent dose (mg/day)	**None (n=201)**	**<2.5mg (n=216)**	**2.5-7.4mg (n=635)**	**≥7.5mg (n=242)**	**None (n=73)**	**<2.5mg (n=70)**	**2.5-7.4mg (n=243)**	**≥7.5mg (n=117)**
Age (years)	71.7 (0.8)**	70.4 (0.9)	69.5 (0.5)	66.4 (0.9)	70.9 (1.3)	70.1 (1.4)	70.8 (0.7)	68.6 (0.9)
Heart Rate (bpm)	77.1 (1.3)**	78.6 (1.4)	73.7 (0.7)	75 (1.3)	79.6 (2.7)*	79.6 (2.1)	73 (1)	75.4 (1.8)
Systolic BP (mmHg)	123.8 (1.6)	121.7 (1.7)	121.3 (1)	119.7 (1.3)	126.3 (2.8)	124.5 (2.5)	123.8 (1.6)	127.2 (1.9)
RPP (bpm x mmHg)	9609 (216)**	9482 (218)	8924 (124)	8768 (180)	9649 (444)*	9771 (337)	9753 (172)	9321 (137)
QRS duration (ms)	123 (2)	123 (2)	125 (1)	120 (2)	124 (4)	122 (4)	120 (2)	122 (3)
Hemoglobin (g/dL)	13.6 (0.1)	13.5 (0.1)	13.6 (0.1)	13.9 (0.1)	12.8 (0.2)	12.8 (0.2)	12.9 (0.1)	13.2 (0.2)
eGFR (ml/min/1.73m^2)	58.6 (1.3)	60.6 (1.4)	58.6 (0.8)	59.3 (1.2)	53.1 (2.2)	55.4 (2.5)	53 (1.4)	57.3 (1.8)
LVEDD (mm)	56 (1)	57 (1)	58 (1)	58 (1)	56 (1)	55 (1)	56 (1)	57 (1)
LVEF (%)	33 (1)*	31 (1)	31 (1)	31 (1)	34 (1)	32 (1)	33 (1)	33 (1)
Bisoprolol (mg/day)	0**	1.2 (0.01)	3.6 (0.05)	9.6 (0.11)	0**	1.3 (0.01)	3.7 (0.08)	9.6 (0.16)
Ramipril (mg/day)	4.2 (0.2)**	4 (0.2)	4.8 (0.1)	6 (0.2)	4.7 (0.4)**	3.9 (0.4)	5.3 (0.2)	6.6 (0.3)
Furosemide (mg/day)	45 (4)	43 (3)	45 (2)	45 (3)	74 (7)	63 (6)	69 (3)	66 (6)
Male sex (% [n])	68 (137)	71 (154)	72 (459)	75 (182)	70 (51)	71 (50)	78 (189)	80 (93)
IHD etiology (% [n])	59 (119)	52 (112)	54 (341)	57 (138)	60 (44)	77 (54)	73 (341)	67 (78)
ICD in situ (% [n])	9.5 (19)**	6.9 (15)	11.7 (74)	18.2 (44)	5.5 (4)*	5.7 (4)	12.8 (31)	16.2 (19)
CRT in situ (% [n])	22.9 (46)	24.5 (53)	26 (165)	27.3 (66)	28.8 (21)	12.9 (9)	25.1 (61)	29.1 (34)
NYHA III/IV (% [n])	38 (76)**	31.9 (69)	26.9 (171)	21.1 (51)	56.2 (41)**	40 (28)	33.3 (81)	31.6 (37)

Table 2. Characteristics of patient cohort divided into patients with and without diabetes, according to β-blocker (Bisoprolol) daily dose. Data presented as mean (SEM) or % (n). P value separately compares dose groups for patients with and without diabetes with ANOVA or chi-squared tests (*P<0.05, **P<0.005). BP=blood pressure, RPP=rate-pressure product, eGFR=estimated

glomerular filtration rate, LVEDD=left ventricular end diastolic diameter, IHD = ischaemic heart disease, LVEF=left ventricular ejection fraction, ICD=implantable cardioverter defibrillator, CRT=cardiac resynchronisation therapy, NYHA=New York Heart Association.

Figure legends

Figure 1. Kaplan-Meier curves showing 5-year all-cause mortality according to dose of β-blocker in patients with ($p<0.001$ across groups by log-rank test) and without diabetes ($p=0.004$ across groups by log-rank test)**.** The number of patients remaining in each group (i.e. those alive and non-censored) after each year of follow-up is listed below the corresponding figure.

Figure 2. A) Forest plot illustrating hazard ratios and 95% confidence intervals for mortality per mg/day increase in bisoprolol equivalent dose. Values below 1 indicate reduced risk of death. The stronger association of bisoprolol dose with mortality in patients with diabetes (i.e. p interaction<0.05) is only apparent in the context of left ventricular ejection fraction <32%. **B)** Forest plots, restricted to patients with diabetes, illustrating hazard ratios and 95% confidence intervals for mortality per mg/day increase in bisoprolol equivalent dose. Values below 1 indicate reduced risk of death. The association of bisoprolol dose with mortality was similar in patients stratified by insulin treatment, or by glycemic control. In panels A and B, red markers denote patients with diabetes, and blue markers patients without diabetes.