Mortality Reduction Associated With β-Adrenoceptor Inhibition in Chronic Heart Failure Is Greater in Patients With Diabetes

Klaus K. Witte,[1] Michael Drozd,[1] Andrew M.N. Walker,[1] Peysh A. Patel,[1] Jessica C. Kearney,[1] Sally Chapman,[1] Robert J. Sapsford,[2] John Gierula,[1] Maria F. Paton,[1] Judith Lowry,[1] Mark T. Kearney,[1] and Richard M. Cubbon[1]

Diabetes Care 2018;41:136–142 | https://doi.org/10.2337/dc17-1406

OBJECTIVE

Diabetes 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 ACE inhibitors (ACEIs) 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 1,797 patients with CHF recruited between 2006 and 2014, with mean follow-up of 4 years. β-Blocker dose was expressed as the equivalent dose of bisoprolol (mg/day) and ACEI dose as the equivalent dose of ramipril (mg/day). Cox regression analysis was used to examine the interaction between diabetes and drug dose on all-cause mortality.

RESULTS

Patients with diabetes were prescribed larger doses of β-blockers and ACEIs 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).

CONCLUSIONS

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

Chronic heart failure (CHF) associated with left ventricular systolic dysfunction is a global health care problem affecting more than 26 million individuals (1,2). More than one-third of these people will also suffer from diabetes (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 a significant prognostic disadvantage to patients with established CHF (6–8). In a large prospective cohort study specifically designed to examine prognostic factors in CHF associated with

[1]Leeds Institute for Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, U.K.
[2]Cardiology Department, Leeds Teaching Hospitals NHS Trust, Leeds, U.K.

Corresponding author: Mark Kearney, m.t.kearney@leeds.ac.uk.

Received 13 July 2017 and accepted 10 September 2017.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-1406/-/DC1.

This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.

K.K.W. and M.D. are joint first authors.

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See accompanying articles, pp. 11, 14, 143, 150, and 156.

left ventricular systolic dysfunction (LVSD), we showed that diabetes increases the risk of death threefold (8).

During the last three decades, disease-modifying therapies have led to a substantial reduction in mortality in patients with CHF associated with LVSD (9). Two of the principal disease-modifying agents, ACE inhibitors (ACEIs) (10) and β-adrenoceptor antagonists (β-blockers) (11), have been shown to reduce death in patients with CHF. Although ACEIs 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 analyzing data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) 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 used a highly characterized cohort of unselected, prospectively recruited patients with CHF secondary to LVSD to examine the association of ACEIs 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 [LVEF] ≤45%) who were 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 an LVEF of ≤45% on transthoracic echocardiography. Between June 2006 and December 2014, consecutive patients attending specialist cardiology clinics in four U.K. hospitals were approached to participate. In total, 1,802 patients provided written informed consent, although 5 had missing medication doses and 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 U.K. Office of Population Censuses and Surveys, which provided details of time of death; follow-up censorship occurred on 8 May 2016.

As described previously (8,9), details of medical history, including diabetes status, were collected at recruitment, and symptomatic status was defined using the New York Heart Association (NYHA) Functional Classification. Venous blood was collected for measurement of electrolyte concentrations, assessment of renal function, and hematological 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 previously 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 diuretics, ACEIs, angiotensin receptor blockers (ARBs), 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 resynchronization therapy (CRT) or implantable cardioverter-defibrillator (ICD) was assessed during the 6-month period after recruitment (9).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 21 software (IBM Corporation, Armonk, NY). Normal distribution of data was confirmed using skewness and kurtosis tests. Continuous data are presented as mean (SEM), and categorical data are shown as percentage (*n*). 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 1,797 patient cohort, 28% of patients (*n* = 503) also had diabetes; these had a mean (SEM) HbA_{1c} of 61.5 (0.8) mmol/mol (7.8% [0.1]) and used the following glycemic control strategies: diet alone in 30.2%, sulfonylureas in 30.2%, metformin in 38.8%, insulin in 19.9%, dipeptidyl-peptidase 4 inhibition in 3.4%, thiazolidinediones in 2.6%, sodium–glucose cotransporter 2 inhibition in 0.2%, and glucagon-like peptide 1 receptor agonists 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 they were more likely to have an ischemic 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 rates were comparable to patients without diabetes. After a mean follow-up period of 4 years (7,227 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, 1,523 patients (84.8%) were prescribed a β-blocker; of these, 1,276 (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 into groups receiving no β-blocker or receiving bisoprolol equivalent doses of <2.5 mg/day (low dose), 2.5–7.4 mg/day (medium dose), or ≥7.5 mg/day (high dose) (Table 2). There were clear associations between β-blocker dose group and patient characteristics, such as age, heart rate, and 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). Although the decline in heart rate with escalating β-blocker dose (in patients

Table 1—Characteristics of total patient cohort and of cohort divided into patients with and without type 2 diabetes

	Total cohort (*n* = 1,797)	No diabetes (*n* = 1,294)	Diabetes (*n* = 503)	*P* value
Age (years)	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 × mmHg)	9,152 (73)	9,091 (86)	9,321 (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/1.73 m^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 (1,315)	72 (932)	76.1 (383)	0.077
Ischemic etiology (% [*n*])	59.2 (1,064)	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

Data are presented as mean (SEM) or as indicated. *P* value compares groups with and without diabetes with unpaired *t* tests or χ^2 tests. BP, blood pressure; LVEDD, left ventricular end-diastolic diameter; RPP, rate-pressure product.

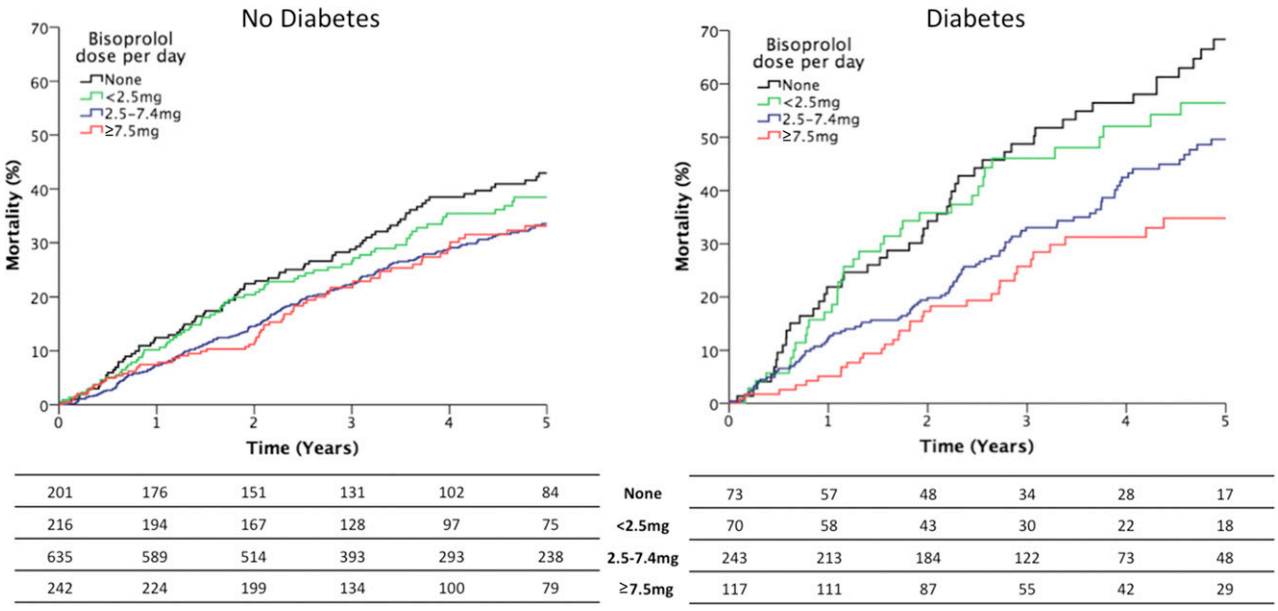
with and without diabetes) was statistically significant, the apparently modest effect probably reflects the use of CRT devices in more than 25% of the cohort.

Increasing β-blocker dose was associated with lower all-cause mortality in patients without and with diabetes (Fig. 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 (1,825 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, whereas ≥7.5 mg/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, and ≥7.5 mg/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.

Table 2—Characteristics of patient cohort divided into patients with and without diabetes, according to β-blocker (bisoprolol) daily dose

	No diabetes				Diabetes			
	None (*n* = 201)	<2.5 mg/day (*n* = 216)	2.5–7.4 mg/day (*n* = 635)	≥7.5 mg/day (*n* = 242)	None (*n* = 73)	<2.5 mg/day (*n* = 70)	2.5–7.4 mg/day (*n* = 243)	≥7.5 mg/day (*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 × mmHg)	9,609 (216)**	9,482 (218)	8,924 (124)	8,768 (180)	9,649 (444)*	9,771 (337)	9,753 (172)	9,321 (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/1.73 m^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 class 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)

Data are presented as mean (SEM) or as indicated. *P* value separately compares dose groups for patients with and without diabetes with ANOVA or χ^2 tests. BP, blood pressure; IHD, ischemic heart disease; LVEDD, left ventricular end-diastolic diameter; RPP, rate-pressure product. *$P < 0.05$; **$P < 0.005$.



201	176	151	131	102	84	None	73	57	48	34	28	17
216	194	167	128	97	75	<2.5mg	70	58	43	30	22	18
635	589	514	393	293	238	2.5-7.4mg	243	213	184	122	73	48
242	224	199	134	100	79	≥7.5mg	117	111	87	55	42	29

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

For every milligram per 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 correction for factors associated with β-blocker dose, including age, sex, ACEI dose, the presence of an 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 into groups above and below the median LVEF of 32% and noted that the interaction between diabetes and β-blocker dose only persisted in those with an LVEF of <32% (Fig. 2*A*). We then studied just the patients with diabetes to ask whether glycemic control or management was 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 noninsulin therapy (Fig. 2*B*). After dividing the patients with diabetes according to median HbA_{1c} (57 mmol/mol), we again noted no interaction between glycemic control and β-blocker dose ($P = 0.67$), indicating a similar β-blocker dose-effect size in patients with better and worse glycemic control (Fig. 2*B*).

Diabetes and the Relationship Between ACEI Dose and Mortality

We divided patients with and without diabetes into groups receiving no ACEI (or ARB) or ramipril equivalent doses of <2.5 mg/day (low dose), 2.5–7.4 mg/day (medium dose) and ≥7.5 mg/day (high dose) (Supplementary Table 1). Clear associations were found between the 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 (Supplementary Fig. 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 (1,825 days) of follow-up (i.e., the area under Kaplan-Meier mortality curves). In patients without diabetes, not taking an ACEI was associated with 478 (95% CI 344–611) days lost, whereas ≥7.5 mg/day was associated with 287 (95% CI 220–355) days lost. In patients with diabetes, not taking an ACEI was associated with 774 (95% CI 534–1,013) days lost, and ≥7.5 mg/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 milligram per day increment in the 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.

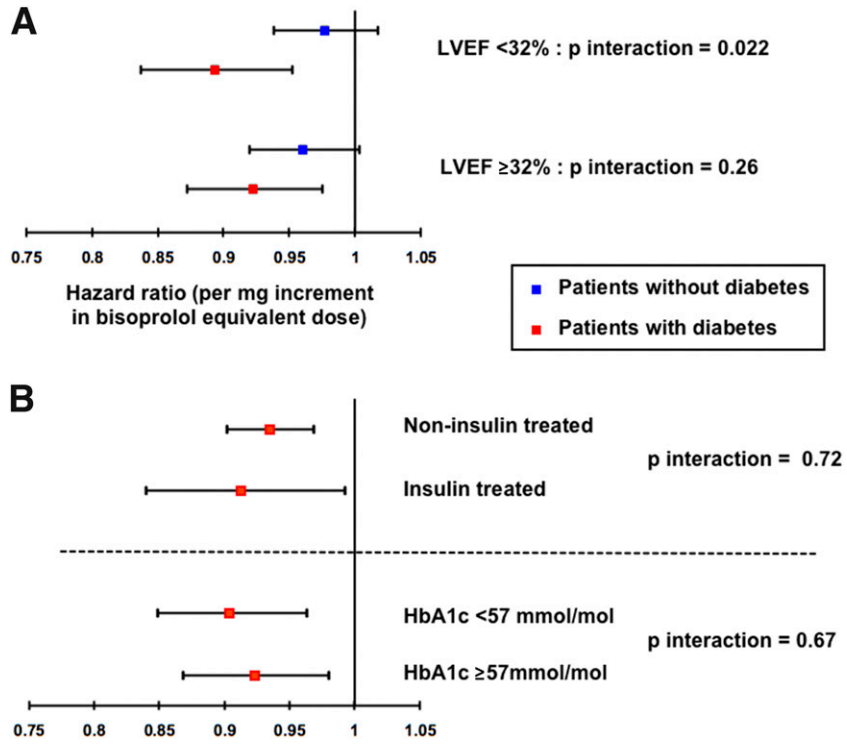


Figure 2—Forest plots illustrate hazard ratios and 95% CIs for mortality per milligram per day increase in the bisoprolol-equivalent dose. Values <1 indicate reduced risk of death. *A*: The stronger association of the bisoprolol dose with mortality in patients with diabetes (i.e., *P* interaction <0.05) is only apparent in the context of LVEF <32%. *B*: Forest plot, restricted to patients with diabetes, shows the association of the bisoprolol dose with mortality was similar in patients stratified by insulin treatment or by glycemic control.

CONCLUSIONS

The present report provides important new information for health care professionals caring for patients suffering from CHF with reduced LVEF 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 ACEIs were 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.
- Among patients with diabetes, the relationship between β-blocker dose and mortality was not associated with glycemic control or insulin therapy.

Data From the ACCORD and BARI-2D Trials: Effects of β-Blockers on Outcome in Patients With CHF and Diabetes

Tsujimoto et al. (13) recently published reports examining the effect of β-blockers on mortality in patients with diabetes and reduced LVEF. The report from the ACCORD data set raised concerns about β-blocker use in intensively treated patients suffering from type 2 diabetes with LVSD, and the authors attributed this to increased hypoglycemia in β-blocker–treated patients. The almost simultaneous report using the BARI-2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) data set from the same group was more reassuring (15), supporting the use of β-blockers in patients with ischemic heart disease and reduced LVEF. However, both of these well-performed retrospective analyses should be considered in the context of the highly selected patients studied. Unlike our data set, neither report provided detailed drug dose and LVEF 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 the clinical trials described by Tsujimoto et al. (13,15). Of relevance to this, the prevalence of ischemic heart disease in our study was greater in patients with diabetes, as seen in other large CHF cohorts (e.g., 16,17), probably reflecting an excess of atherosclerosis risk factors in patients with diabetes (4).

Potential Mechanisms Underlying the Favorable Effect of β-Blockers on Outcome in Patients With Chronic Heart Failure and Diabetes

The current 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 Supplementary Fig. 2). We previously showed that β-blocker–naïve patients with CHF and diabetes (taking ACEIs) have increased basal sympathetic neural outflow, assessed using muscle sympathetic nerve activity, compared with CHF patients without diabetes (18). Moreover, peak sympathoactivation in these patients in response to a high carbohydrate load was also higher than in CHF patients without diabetes. Heightened muscle sympathetic nerve activity has been linked to increased mortality in patients with CHF (19). We also recently demonstrated that patients with the combination of CHF and diabetes who are optimally treated have evidence of excessive sympathoactivation using measurements of heart rate turbulence and heart rate variability (20), both of which we have shown to be markers of increased risk of death (21,22). Although we did not examine the effect of β-blockers on these variables in the current 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 an LVEF below the median value of 32%, suggesting that 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 Strengths 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 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 because although of interest, these 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. Fourthly, our work predominantly describes patients with type 2 diabetes, and we do not have data on hypoglycemic episodes. Fifthly, the assessment of drug dose was taken at a single point in time, so the current study cannot account for previous exposure to β-blockers or ACEIs or a 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-blockers or ACEIs per se result in lower mortality; instead, the ability to tolerate greater doses of such agents could identify intrinsically lower risk patients. However, the contrasting data for β-blockers versus ACEIs, 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 the Present Study

Although 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. (23), β-blocker dosing in community CHF services is significantly lower than in randomized clinical trials, especially when prescribed by noncardiologists. Across many health care settings, the achieved β-blocker doses are often less than those achieved in clinical trials (24). Data that quantify the value of each increment in β-blocker dose in mortality risk (and survival gain) may help patients and care providers when discussing β-blocker titration. Here we show that each milligram per day increment in the equivalent bisoprolol 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. (25) recently demonstrated that improvements in outcome with higher β-blocker doses may be more attributable to dose than heart rate reduction, 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 health care providers and encourage careful but determined uptitration of β-blockers in this high-risk group of patients.

Funding. This work was supported by the British Heart Foundation (PG/08/020/24617). K.K.W. is a National Institute of Health Research (NIHR) Clinician Scientist, A.M.N.W. and P.A.P. are British Heart Foundation Clinical Research Fellows, J.G. and M.F.P. are NIHR PhD fellows, M.T.K. is British Heart Foundation Professor of Cardiovascular and Diabetes Research, and R.M.C. is supported by a British Heart Foundation Intermediate Research Fellowship.

Duality of Interest. K.K.W. has received speaker fees from Medtronic, Livanova, St. Jude Medical, Pfizer, Bayer, and Bristol-Myers Squibb. M.T.K. has received speaker fees from Merck and Novo Nordisk and unrestricted research awards from Medtronic. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. K.K.W., M.D., A.M.N.W., P.A.P., R.J.S., and M.T.K. collected data, recruited patients, and reviewed and edited the manuscript. J.C.K. collected data and wrote the manuscript. S.C., J.G., M.F.P., and J.L. collected data and reviewed the manuscript. R.M.C. collected data, recruited patients, performed statistical analyses, and reviewed and edited the manuscript. M.T.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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