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Effects of β-blockers on all-cause mortality in patients with type 2 diabetes and coronary heart disease

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Aims: To assess whether the use of beta-blockers influences mortality and the incidence of major cardiovascular events in patients with diabetes and coronary heart disease (CHD).

Materials and methods: Using data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial, we performed Cox proportional hazards analysis to assess the effects of β-blockers on all-cause mortality in 2244 patients with type 2 diabetes who had stable CHD with and without a history of myocardial infarction (MI)/heart failure with reduced left ventricular ejection fraction (HFrEF).

Results: All-cause mortality in patients with MI/HFrEF was significantly lower in those receiving β-blockers than in those not receiving β-blockers (adjusted hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.37-0.98; P = .04), whereas that in patients without MI/HFrEF did not significantly differ (adjusted HR 0.91, 95% CI 0.76-1.32; P = .64). Among patients with MI/HFrEF, all-cause mortality in those who received intensive medical therapy alone for CHD was significantly lower in those on β-blockers than in those not on β-blockers (adjusted HR 0.45, 95% CI 0.23-0.88; P = .02); however, mortality in patients who received early revascularization for CHD was not significantly lower in those on β-blockers (adjusted HR 0.81, 95% CI 0.40-1.65; P = .57). The risk of major cardiovascular events in patients without MI/HFrEF was not significantly different between those on and those not on β-blocker treatment.

Conclusions: In patients with diabetes and CHD, the use of β-blockers was effective in reducing all-cause mortality in those with MI/HFrEF but not in those without MI/HFrEF.

KEYWORDS

β-blocker, BARI 2D trial, heart failure with reduced left ventricular ejection fraction, mortality, myocardial infarction, type 2 diabetes

1 | INTRODUCTION

The main aim of diabetes management is to prevent diabetes-related complications. Although appropriate glycaemic control reduces the risk of microvascular complications,[1] recent trials have shown that intensive glycaemic therapy may not prevent cardiovascular events.[2–4] In addition, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial reported that intensive glycaemic therapy was associated with increased risk of all-cause and cardiovascular deaths.[2] Possible explanations for higher mortality in patients with diabetes receiving intensive glycaemic therapy may be severe

hypoglycaemia and weight gain, which are associated with increased risk of death and cardiovascular events.[5,6]

Current guidelines recommend the use of β-blockers in patients with coronary heart disease (CHD);[7–10] however, there is no evidence supporting improved survival in patients with stable CHD without a history of myocardial infarction (MI) or heart failure with reduced left ventricular ejection fraction (HFrEF). In addition, based on the potential risk of hypoglycaemia and weight gain attributable to β-blockers,[11,12] the disadvantages of β-blockers may outweigh the benefits in patients with diabetes and CHD. The aim of the present study, therefore, was to assess whether the use of β-blockers

influences mortality and the incidence of major cardiovascular events in patients with diabetes and CHD. Recent observational studies have suggested that early β-blocker use in patients with acute MI was associated with reduced mortality, but prolonged β-blocker treatment beyond 1 year after acute MI was unlikely to improve survival.[13,14] The results of these studies suggest a progressively decreasing benefit of β-blocker treatment over time; therefore, we also assessed whether the use of β-blockers is effective in patients with diabetes and CHD who underwent early revascularization and had ameliorated ischaemia.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

We used data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial to evaluate the association between the use of β-blockers and all-cause mortality and cardiovascular events in patients with type 2 diabetes who had stable CHD. A detailed description of the BARI 2D study design, protocol and patient characteristics has been reported previously.[15–19] Briefly, BARI 2D was a multicentre, international, randomized, clinical trial comparing two major strategies in patients with type 2 diabetes and CHD: (1) an initial elective coronary revascularization (percutaneous coronary intervention or bypass surgery) combined with aggressive medical therapy vs an initial strategy of aggressive medical therapy alone; and (2) a strategy of providing more insulin (endogenous or exogenous) vs a strategy of increasing sensitivity to insulin (reducing insulin resistance), with a target glycated haemoglobin (HbA1c) level of <7.0% for each strategy. Patients were eligible for the BARI 2D study if they were aged ≥25 years and had a diagnosis of both type 2 diabetes and CHD. Type 2 diabetes was diagnosed based on the need for treatment with insulin or oral hypoglycaemic drugs, a confirmed diagnosis of diabetes by record review, or elevated fasting plasma glucose levels (≥7.0 mmol/L [126/mg/dL]). CHD was diagnosed based on documentation on angiography (≥50% stenosis of a major epicardial coronary artery associated with a positive stress test or ≥70% stenosis of a major epicardial coronary artery and classic angina). Patients were excluded if they required immediate coronary revascularization, had undergone revascularization within 12 months before study entry, or had stenosis ≥50% of the left main coronary artery, serum creatinine >2.0 mg/dL (176.8 μmol/L), HbA1c >13.0%, New York Heart Association functional class III or IV congestive heart failure, or hepatic disease. After randomization, all patients were treated at least with intensive management of dyslipidaemia (LDL cholesterol level <100 mg/dL (2.59 mmol/L)) and hypertension (blood pressure <130/80 mm Hg). In addition, all patients received counselling regarding smoking cessation, regular physical exercise and weight loss. The study was approved by the institutional review board of the National Centre for Global Health and Medicine, and the National Heart, Lung, and Blood Institute (NHLBI) approved our use of BARI 2D data.

In the BARI 2D study, 2368 patients with type 2 diabetes and CHD were enrolled at 49 clinical sites in the USA, Canada, Brazil, Mexico, Czech Republic and Austria between January 1, 2001 and March 31, 2005. Patients aged ≥80 years or for whom information was lacking on use of β-blockers or a history of MI or HFrEF were excluded from the study, resulting in a final sample size of 2244 patients. MI was defined as having a history of MI and HFrEF as having a history of congestive heart failure and left ventricular ejection fraction <50%.

2.2 | Outcome measurements

Similarly to a previous report of the main study,[15] the primary outcome in the present study was all-cause mortality. The secondary outcome was a composite endpoint including all-cause death, MI or stroke (major cardiovascular events). In addition, to analyse mortality in more detail, cardiovascular and cardiac mortality was assessed. Cardiac death included death as a result of cardiogenic shock, MI, primary cardiac arrest or heart failure with terminal pulmonary embolism. Cardiovascular death included cardiac death and death from stroke and other atherosclerotic vascular disease. An independent Mortality and Morbidity Classification Committee adjudicated the endpoint data in the original BARI 2D study and classified the cause of all deaths and verified all strokes. More detailed information about outcome evaluation has been reported previously.[15,20] In addition, we evaluated the incidence of severe hypoglycaemia in patients on and not on β-blockers. Severe hypoglycaemia was defined as hypoglycaemia requiring assistance with treatment and either a blood glucose level of <2.8 mmol/L (50 mg/dL) or confusion, irrational or uncontrollable behaviour, convulsions, or coma reversed by a treatment that raises blood glucose.[15] Patients were evaluated on a monthly basis for 6 months and every 3 months thereafter. Patients were followed until November 30, 2008, and the occurrence of outcomes was maximally followed for 6 years.

2.3 | Potential confounders

We extracted data on potential confounders at baseline, including age, sex, duration of diabetes, history of hypertension, hypercholesterolaemia, or stroke/transient ischaemic attack, race and ethnicity, level of education, physical activity, smoking status, body mass index (BMI, calculated as weight [kg] divided by height [m] squared), statin use, aspirin use, systolic blood pressure, and HbA1c and LDL cholesterol levels. Race and ethnicity were divided into white and non-white groups. Education was classified as lower than high school, high school graduation, or higher than high school level. Physical activity level was classified as sedentary, mild, or moderate/strenuous. Smoking status was classified as never smoked, former smoker, or current smoker. BMI was classified as <25.0, 25.0 to 29.9 or ≥30.0 kg/m². HbA1c level was classified as <6.0%, 6.0 to 6.9% or ≥7.0%.

2.4 | Statistical analysis

The patients included in the study were first divided into two groups: patients with a history of MI and/or HFrEF (MI/HFrEF) and those

without MI/HFrEF. Each group was then further divided into those on or not on β-blockers. Because the number of patients with HFrEF was small, we did not analyse the risks of all-cause death and cardiovascular events for the patients with HFrEF only. Demographic data are presented as numbers with proportions (%) or mean values with standard deviation (s.d.). We analysed hazard ratios (HRs) for primary and secondary outcomes with 95% confidence intervals (CIs) in patients on β-blockers compared with those not on β-blockers using the Cox proportional hazard models. We included age, duration of diabetes, sex, history of hypertension, hypercholesterolaemia, or stroke/transient ischaemic attack, race and ethnicity, level of education, physical activity, smoking status, BMI, statin use, aspirin use, systolic blood pressure, HbA1c level and LDL cholesterol level for adjustment. All-cause mortality was further analysed limited to the patients who received early coronary revascularization or intensive medical therapy alone for CHD. Self-reported health conditions (five categories: excellent, very good, good, fair or poor) were added for further adjustment in the analysis of all-cause mortality. Kaplan–Meier survival curves were constructed for primary and secondary outcomes in patients on and not on β-blockers.

For sensitivity analysis, we performed propensity score-matched Cox proportional hazard analysis to assess mortality and major cardiovascular events in patients on or not on β-blockers. The propensity score was used to attempt to adjust for confounding.[21] The propensity score estimated the probability that patients would have been assigned to the use of β-blockers and was derived using a logistic regression model that included use of β-blockers as the outcome variable and the following variables as predictors: age, duration of diabetes, sex, history of hypertension, hypercholesterolaemia, or stroke/transient ischaemic attack, race and ethnicity, level of education, physical activity, smoking status, BMI, statin use, aspirin use, systolic blood pressure, and HbA1c and LDL cholesterol levels.

TABLE 1 Baseline characteristics of patients with type 2 diabetes and CHD on and not on β-blockers[1]

Characteristics	MI/HFrEF (+)			MI/HFrEF (−)		
	β-blockers (−) N = 148	β-blockers (+) N = 619	P value	β-blockers (−) N = 458	β-blockers (+) N = 1019	P value
Age, years	62.0 (9.2)	60.6 (8.7)	.09	62.2 (8.6)	61.9 (8.3)	.56
Duration of diabetes, years	10.7 (8.3)	9.7 (8.6)	.23	10.7 (8.5)	10.4 (8.7)	.41
Female sex, %	22.3	26.7	.27	29.3	32.3	.24
Race and ethnicity: white, %	64.2	71.4	.08	70.5	69.7	.74
Level of education, %						
Lower than high school	38.4	40.8	.59	31.6	37.0	.04
High school	22.6	18.3	.24	23.0	23.4	.88
Above high school	39.0	40.9	.67	45.4	39.6	.03
Physical activity (%)						
Sedentary	26.0	24.9	.78	21.5	19.2	.30
Mild	42.5	40.6	.67	37.9	43.9	.03
Moderate/strenuous	31.5	34.5	.48	40.6	36.9	.17
Smoking status (%)						
Never	25.0	26.9	.63	37.2	35.6	.54
Former	55.4	57.7	.61	51.6	53.5	.50
Current	19.6	15.4	.13	11.2	10.9	.82
BMI						
<25.0 kg/m^2	16.3	9.8	.02	7.7	9.5	.28
25.0 to 29.9 kg/m^2	37.4	35.5	.65	33.1	32.2	.74
≥30.0 kg/m^2	46.3	54.7	.06	59.2	58.3	.76
Hypertension, %	76.7	83.2	.06	77.8	85.6	<.001
Hypercholesterolaemia, %	76.2	86.0	.004	75.4	82.9	.001
History of stroke/transient ischaemic attack, %	14.2	12.4	.56	7.9	8.4	.74
Statin use, %	69.6	83.0	<.001	62.7	75.9	<.001
Aspirin use, %	76.4	93.3	<.001	79.7	90.3	<.001
Systolic blood pressure, mm Hg	125.8 (19.2)	128.3 (19.2)	.15	133.0 (18.1)	133.9 (21.0)	.43
HbA1c	8.3 (0.9)	8.3 (1.0)	.84	8.3 (0.9)	8.3 (1.0)	.84
<6.0%	13.2	9.4	.17	12.1	10.9	.53
6.0% to 6.9%	27.1	29.6	.54	24.8	29.8	.05
≥7.0%	59.7	61.0	.78	63.1	59.2	.76
LDL cholesterol, mg/dL[2]	94.6 (32.7)	92.8 (31.9)	.56	100.2 (34.4)	96.7 (34.0)	.08

HbA1c: 6.0% = 42 mmol/mol; 7.0% = 53 mmol/mol.

[1] Data are presented as number of participants, percent, or mean (standard deviation).

[2] To convert LDL cholesterol to mmol/L, multiply by 0.0259.
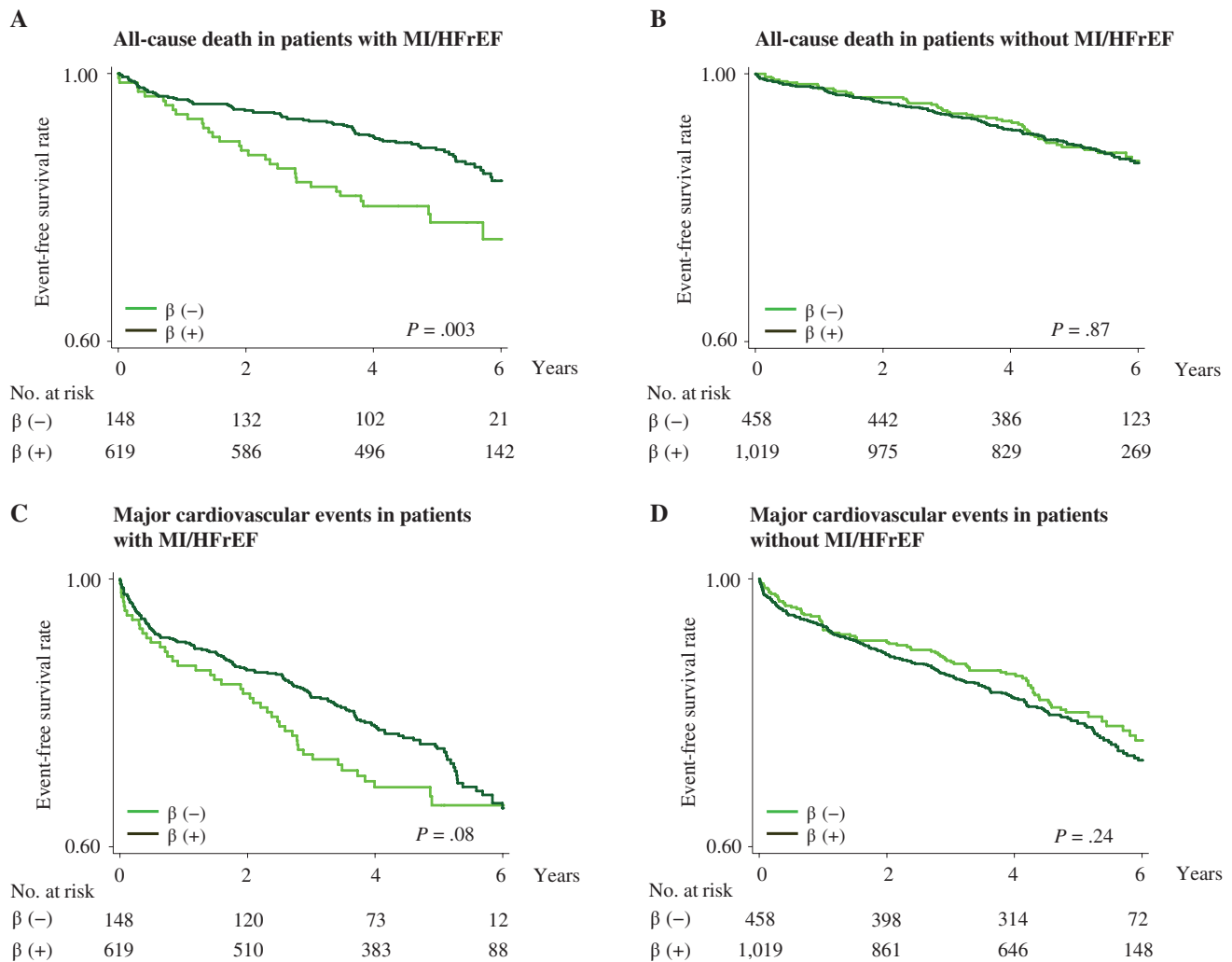
FIGURE 1 Kaplan–Meier survival curves for all-cause death and major cardiovascular events in patients on and not on β-blockers. Rates of freedom from all-cause death in patients (A) with and (B) without MI/HFrEF and from major cardiovascular events in patients (C) with and (D) without MI/HFrEF. Major cardiovascular events included all-cause death, MI and stroke. β (+), on β-blockers; β (−), not on β-blockers.

All statistical analyses were conducted using STATA software (version 14.1, Stata Corp, College Station, Texas). P values < .05 were taken to indicate statistical significance for all tests.

3 | RESULTS

3.1 | Characteristics of study patients

The baseline characteristics of patients with (n = 767) and without (n = 1477) MI/HFrEF are shown in Table 1. Among patients with MI/HFrEF, those on β-blockers had a higher prevalence of hypercholesterolaemia, there were fewer with a BMI <25 kg/m², and more patients took statins and aspirin than those not on β-blockers. Among patients without MI/HFrEF, those on β-blockers had a higher prevalence of hypertension and hypercholesterolaemia, a higher proportion of patients with an education level lower than high school and with mild levels of physical activity, and more use of statins and aspirin than those not on β-blockers.

3.2 | Primary and secondary outcomes

The mean (± s.d.) follow-up periods were 4.6 ± 1.3 years in patients with MI/HFrEF and 4.8 ± 1.2 years in those without MI/HFrEF. The Kaplan–Meier survival curves and cumulative event rates for all-cause death and major cardiovascular events in patients with and without MI/HFrEF are shown in Figure 1 and Table 2, respectively. All-cause mortality (number of events per 1000 person-years) in patients with MI/HFrEF on and not on β-blockers was 26.4 and 49.8, respectively, while that in patients without MI/HFrEF on and not on β-blockers was 22.8 and 22.3, respectively. All-cause mortality in patients with MI/HFrEF was significantly lower in those on β-blockers than those not on β-blockers (unadjusted HR 0.52, 95% CI 0.35-0.80; P = .003 [Figure 1A]), whereas that in patients without MI/HFrEF did not differ significantly between those on and not on β-blockers (unadjusted HR 1.02, 95% CI 0.73-1.43 [Figure 1B]). In addition, the adjusted HR for all-cause mortality in patients with MI/HFrEF was also significantly lower in those on β-blockers than in those not on β-blockers (adjusted HR 0.60, 95% CI 0.37-0.98; P = .04), whereas that in patients without MI/HFrEF did not differ significantly between those

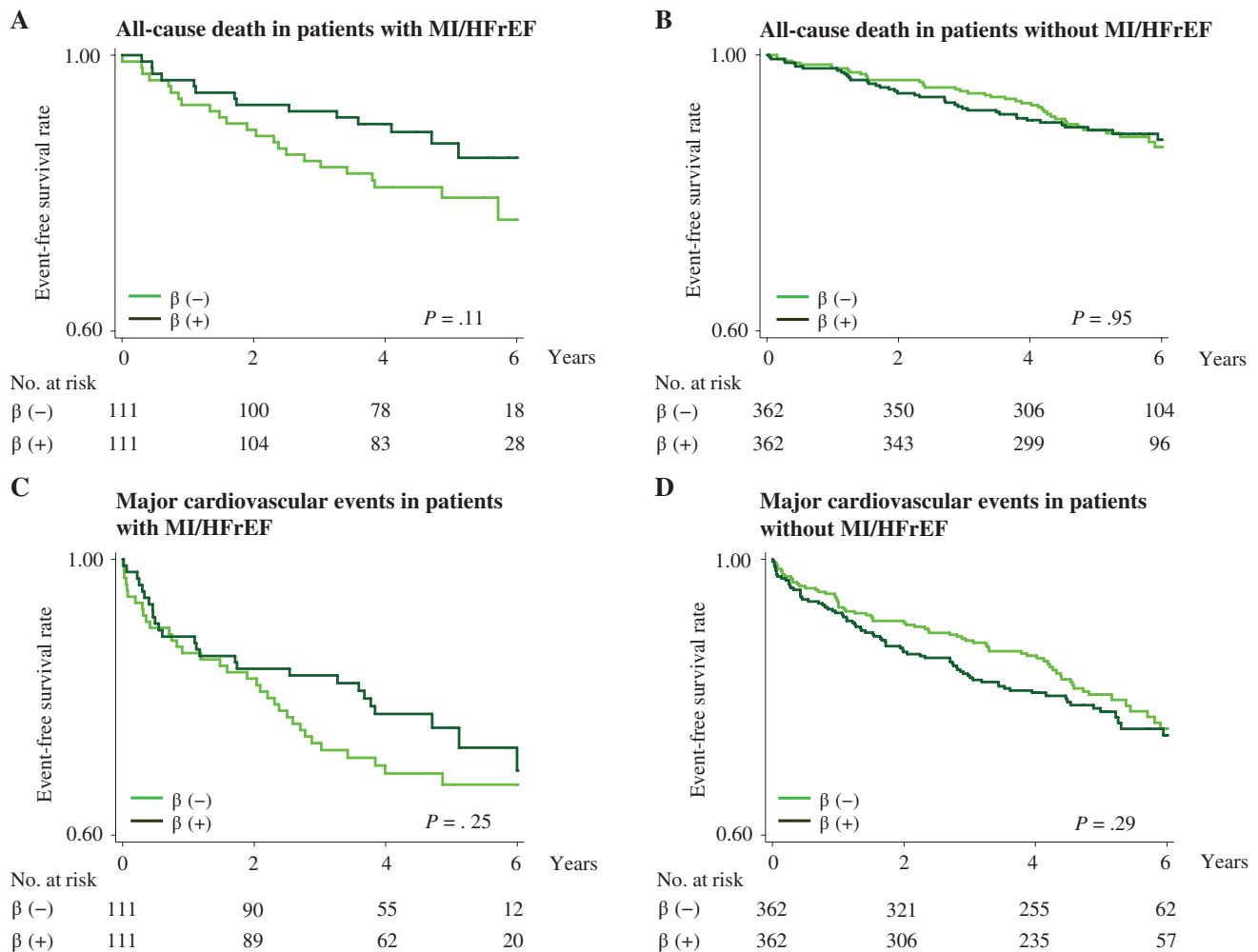**TABLE 2** Cardiovascular events and death in patients with type 2 diabetes and CHD on and not on β-blockers[2]

	MI/HFrEF (+)			MI/HFrEF (−)		
	β-blockers (−) N = 148	β-blockers (+) N = 619	P value	β-blockers (−) N = 458	β-blockers (+) N = 1019	P value
Event						
All-cause death						
No. of patients	34	86		55	113	
Event rate, per 1000 person-years	49.8	26.4		22.3	22.8	
Unadjusted HR (95% CI)	1.00 (reference)	0.52 (0.35-0.80)	.003	1.00 (reference)	1.02 (0.73-1.43)	.87
Adjusted HR (95% CI)	1.00 (reference)	0.60 (0.37-0.98)	.04	1.00 (reference)	0.91 (0.763-1.32)	.64
All-cause death, MI, or stroke						
No. of patients	47	161		87	211	
Event rate, per 1000 person-years	86.7	64.8		44.0	51.2	
Unadjusted HR (95% CI)	1.00 (reference)	0.74 (0.53-1.04)	.08	1.00 (reference)	1.16 (0.90-1.49)	.24
Adjusted HR (95% CI)	1.00 (reference)	0.81 (0.55–1.18)	.28	1.00 (reference)	1.13 (0.85-1.49)	.39
Cardiovascular death						
No. of patients	16	43		22	56	
Event rate (per 1000 person-year)	24.9	14.3		9.8	11.2	
Unadjusted HR (95% CI)	1.00 (reference)	0.58 (0.33-1.04)	.07	1.00 (reference)	1.14 (0.69-1.87)	.59
Adjusted HR (95% CI)	1.00 (reference)	0.52 (0.27-1.01)	.05	1.00 (reference)	1.04 (0.59-1.83)	.89
Cardiac death						
No. of patients	16	38		20	52	
Event rate, per 1000 person-years	24.9	12.7		8.9	10.4	
Unadjusted HR (95% CI)	1.00 (reference)	0.51 (0.28-0.93)	0.02	1.00 (reference)	1.16 (0.69-1.95)	.56
Adjusted HR (95% CI)	1.00 (reference)	0.47 (0.23-0.91)	0.02	1.00 (reference)	1.08 (0.59-1.95)	.79
Fatal or non-fatal MI						
No. of patients	21	90		42	108	
Event rate, per 1000 person-years	39.2	37.6		21.3	25.9	
Unadjusted HR (95% CI)	1.00 (reference)	0.97 (0.60-1.56)	.91	1.00 (reference)	1.20 (0.83-1.72)	.31
Adjusted HR (95% CI)	1.00 (reference)	1.05 (0.61-1.81)	.84	1.00 (reference)	1.17 (0.78-1.74)	.44
Fatal or non-fatal stroke						
No. of patients	6	19		10	26	
Event rate, per 1000 person-years	10.6	7.4		5.0	6.0	
Unadjusted HR (95% CI)	1.00 (reference)	0.68 (0.27-1.71)	.41	1.00 (reference)	1.19 (0.57-2.48)	.64
Adjusted HR (95% CI)	1.00 (reference)	0.51 (0.16-1.56)	.24	1.00 (reference)	1.07 (0.45-2.51)	.88

[1] Data are presented as number or HR (95% CI).

on and not on β-blockers (adjusted HR 0.91, 95% CI 0.76-1.32; P = .64). These results did not change after further adjustment, including self-reported health conditions (patients with MI/HFrEF: adjusted HR 0.60, 95% CI 0.37-0.97, P = .03; patients without MI/HFrEF: adjusted HR 0.89, 95% CI 0.61-1.29, P = .54). The analyses limited to patients with and without MI showed similar results (patients with MI: adjusted HR 0.60, 95% CI 0.36-1.01, P = .05; patients without MI: adjusted HR 0.89, 95% CI 0.63-1.27, P = .53). Among patients with MI/HFrEF, all-cause mortality in patients who received intensive medical therapy alone for CHD was significantly lower in those on β-blockers than in those not on β-blockers (adjusted HR 0.45, 95% CI 0.23-0.88; P = .02), whereas that in patients who underwent early revascularization for CHD did not differ significantly between those on and not on β-blockers (adjusted HR 0.81, 95% CI 0.40-1.65; P = .57). Although the incidence of major cardiovascular events in patients with MI/HFrEF was lower in those on β-blockers than in those not on β-blockers (Figure 1C), the incidence in patients

without MI/HFrEF was not significantly different between those on and not on β-blockers (unadjusted HR 1.16, 95% CI 0.90-1.49, P = .24 [Figure 1D]; adjusted HR 1.13, 95% CI 0.85-1.49, P = .39). To further verify these results, we performed sensitivity analysis using propensity score matching. Baseline characteristics of propensity score-matched patients with (n = 222) and without (n = 724) MI/HFrEF are shown in Table S1. In each group with and without MI/HFrEF, there were no significant differences in their baseline characteristics between those on and not on β-blockers. All-cause mortality and the incidence of major cardiovascular events in patients with MI/HFrEF were similarly lower in those on β-blockers than in those not on β-blockers (Figure 2A and C). In contrast, among patients without MI/HFrEF, all-cause mortality and the incidence of major cardiovascular events did not differ between those on and not on β-blockers (Figure 2B and D).

The Kaplan–Meier survival curves and cumulative event rates for cardiovascular and cardiac deaths in patients with and without

A

All-cause death in patients with MI/HFrEF

No. at risk

	0	2	4	6
β (−)	111	100	78	18
β (+)	111	104	83	28

B

All-cause death in patients without MI/HFrEF

No. at risk

	0	2	4	6
β (−)	362	350	306	104
β (+)	362	343	299	96

C

Major cardiovascular events in patients with MI/HFrEF

No. at risk

	0	2	4	6
β (−)	111	90	55	12
β (+)	111	89	62	20

D

Major cardiovascular events in patients without MI/HFrEF

No. at risk

	0	2	4	6
β (−)	362	321	255	62
β (+)	362	306	235	57

FIGURE 2 Kaplan–Meier survival curves for all-cause death and major cardiovascular events in propensity score-matched patients on and not on β-blockers. Rates of freedom from all-cause death in patients (A) with and (B) without MI/HFrEF and those from major cardiovascular events in patients (C) with and (D) without MI/HFrEF. Major cardiovascular events included all-cause death, MI and stroke. β (+), on β-blockers; β (−), not on β-blockers.

MI/HFrEF are shown in Figure 3 and Table 2, respectively. Cardiovascular and cardiac mortality in patients with MI/HFrEF was lower in those on β-blockers than in those not on β-blockers (unadjusted HR for cardiovascular mortality: 0.58, 95% CI 0.33-1.04, P = .07 [Figure 3A]; unadjusted HR for cardiac mortality: 0.51, 95% CI 0.28-0.93, P = .02 [Figure 3C]), whereas that in patients without MI/HFrEF did not differ significantly between those on and not on β-blockers (unadjusted HR for cardiovascular mortality: 1.14, 95% CI 0.69-1.87, P = .59 [Figure 3B]; and unadjusted HR for cardiac mortality: 1.16, 95% CI 0.69-1.95, P = .56 [Figure 3D]). In addition, multivariable adjusted HRs for cardiovascular and cardiac mortality were lower in patients with MI/HFrEF on β-blockers than in those not on β-blockers (adjusted HR for cardiovascular deaths: 0.52, 95% CI 0.27-1.01, P = .05; and adjusted HR for cardiac deaths: 0.47, 95% CI 0.23-0.91, P = .02), whereas that in patients without MI/HFrEF did not differ significantly between those on and not on β-blockers (adjusted HR for cardiovascular deaths: 1.04, 95% CI 0.59–1.83, P = .89; and adjusted HR for cardiac deaths: 1.08, 95% CI 0.59-1.95, P = .79). Unadjusted and adjusted HRs for MI and stroke were not significantly different between patients on and not on β-blockers, regardless of whether there was a history of MI/HFrEF.

The Kaplan–Meier survival curves for severe hypoglycaemia in patients with and without MI/HFrEF are shown in Figure S1. The incidence of severe hypoglycaemia was not significantly different between patients on and not on β-blockers. Similar results were found after multivariable adjustment.

4 | DISCUSSION

In the present study using BARI 2D trial data, various analyses of patients with type 2 diabetes and CHD showed that the use of β-blockers in those with MI/HFrEF was associated with a decreased risk of all-cause, cardiovascular and cardiac mortality, whereas the use of β-blockers in those without MI/HFrEF was not associated with these mortalities. Among patients with MI/HFrEF, all-cause mortality in patients who received intensive medical therapy alone for CHD was significantly lower in those on β-blockers than in those not on β-blockers. This was not, however, the case in patients who had undergone coronary revascularization. In addition, the incidence of major cardiovascular events in patients without MI/HFrEF was not significantly different in those on and not on β-blockers. The
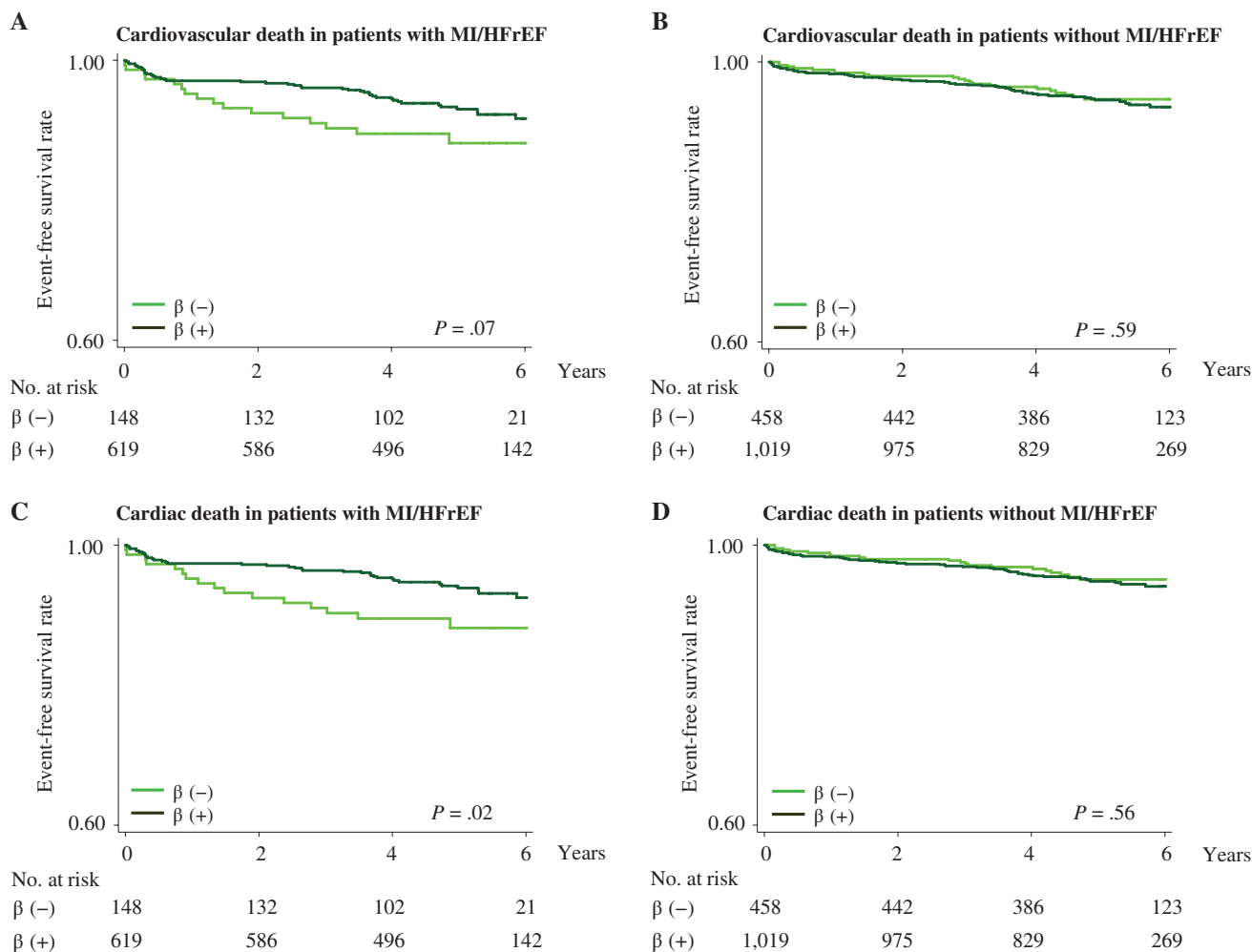
FIGURE 3 Kaplan–Meier survival curves for cardiovascular and cardiac deaths in patients on and not on β-blockers. Rates of freedom from cardiovascular deaths in patients (A) with and (B) without MI/HFrEF and from cardiac death in patients (C) with and (D) without MI/HFrEF. β (+), on β-blockers; β (−), not on β-blockers.

incidence of severe hypoglycaemia did not differ significantly regardless of the whether or not patients were on β-blockers in the glycaemic control strategy of the BARI 2D study.

Current guidelines recommend the use of β-blockers in patients with CHD.[7–10] Indeed, previous studies have shown the effectiveness of β-blockers in patients with MI.[22] In addition, several studies have reported the beneficial effects of β-blockers in patients with diabetes with MI and those with left ventricular systolic dysfunction.[23,24] However, evidence regarding the efficacy of β-blockers has never been demonstrated in all patients with stable CHD. Moreover, there are few studies reporting the efficacy of β-blockers in patients with diabetes and CHD who had undergone coronary revascularization or intensive medical therapy alone. In the present study, all-cause mortality in patients with diabetes and CHD who had a history of MI/HFrEF, particularly in those who received intensive medical therapy alone for CHD, was significantly lower in patients on β-blockers than in those not on β-blockers; however, among patients without MI/HFrEF, all-cause mortality did not differ significantly between those on and not on β-blockers. Although β-blockers might have the cardioprotective effects in patients with diabetes and CHD, the disadvantages of β-blockers, such as metabolic adverse effects and weight gain,[12,25]

might be equal to the positive effects of β-blockers. In addition, based on the results of the present study, a target HbA1c level of <7.0% might be safe in patients on β-blockers; however, because the incidence of hypoglycaemia may be higher in real-world settings compared with clinical trial settings with careful patient selection and close monitoring,[26] the disadvantages of β-blockers may become more evident in normal clinical practice. Further studies are needed to show the association between β-blocker use and hypoglycaemia risk.

The present study has several limitations. First, it was a *post hoc* analysis of the BARI 2D trial, and our findings may not be applicable to other patients with diabetes and CHD. Second, the relatively small number of events might influence the results. In addition, residual confounding might still be present. The study was large-scale, evidence-based, and had robust subgroup representation. In addition, we performed various analyses to minimize the effects of confounders, and additional adjustments including patient health status further decreased confounding; however, uncontrolled confounding still influenced the results of mortality and cardiovascular events. Further randomized controlled trials are therefore required to evaluate whether the use of β-blockers is beneficial and safe in patients with

diabetes and CHD. Third, because the number of patients with HFrEF was small, we could not perform the analysis for the patients with HFrEF only. Additional large-scale studies are needed to assess the effects of β-blockers in patients with HFrEF. Fourth, we could not classify the types of β-blockers, such as cardioselective or non-selective. An important issue is whether there were different effects between the use of β-1-selective β-blockers and combined α- and β-blockers in patients with diabetes and CHD. Although β-blockers exert their effects by competitively inhibiting catecholamine binding to β receptors, each β-blocker has different characteristics with respect to cardioselectivity, pharmacokinetics, intrinsic sympathomimetic activity, and α-adrenergic blocking activity. Thus, further studies are needed to clarify the types of β-blockers that are more beneficial or have a different safety profile.

In conclusion, the present study on type 2 diabetes and CHD showed that the use of β-blockers in patients with MI/HFrEF was associated with a decreased risk of all-cause mortality; however, this association was not found in patients with MI/HFrEF who underwent early coronary revascularization. In addition, among patients without MI/HFrEF, all-cause mortality did not differ between those on and not on β-blockers. To clarify the indications for β-blockers in patients with diabetes and CHD, randomized controlled trials are needed.

Conflict of interest

The authors have no conflict of interest to declare.

Author contributions

T. T. was responsible for study concept and design. T. T. and T. S. contributed to data acquisition, analysis and interpretation, and statistical analysis. T. T., T. S. and H. K. were responsible for drafting the manuscript. T. T. had full access to all data in the study and takes responsibility for the integrity and accuracy of data analysis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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