

# Risk of All-Cause Mortality in Diabetic Patients Taking $\beta$ -Blockers

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## Abstract

**Objective:** To assess the relationship between use of  $\beta$ -blockers and all-cause mortality in patients with and without diabetes.

**Patients and Methods:** Using data from the US National Health and Nutrition Examination Survey 1999-2010, we conducted a prospective cohort study. The study participants were followed-up from the survey participation date until December 31, 2011. We used a Cox proportional hazards model for all-cause mortality analysis. The multivariate-adjusted hazard ratios (HRs) of the participants taking  $\beta$ -blockers were compared with those of the participants not taking  $\beta$ -blockers.

**Results:** This study included 2840 diabetic participants and 14,684 nondiabetic participants. Compared with diabetic participants not taking a  $\beta$ -blocker, all-cause mortality was significantly higher in diabetic participants taking any  $\beta$ -blocker (HR, 1.49; 95% CI, 1.09-2.04;  $P=.01$ ), taking a  $\beta_1$ -selective  $\beta$ -blocker (HR, 1.60; 95% CI, 1.13-2.24;  $P=.007$ ), or taking a specific  $\beta$ -blocker (bisoprolol, metoprolol, and carvedilol) (HR, 1.55; 95% CI, 1.09-2.21;  $P=.01$ ). In addition, all-cause mortality in diabetic participants with coronary heart disease (CHD) was significantly higher in those taking beta-blockers, compared with those not taking beta-blockers (HR, 1.64; 95% CI, 1.08-2.48;  $P=.02$ ), whereas that in non-diabetic participants with CHD was significantly lower in those taking beta-blockers (HR, 0.68; 95% CI, 0.50-0.94;  $P=.02$ ). A propensity score-matched Cox proportional hazards model yielded similar results.

**Conclusion:** Use of  $\beta$ -blockers may be associated with an increased risk of mortality for patients with diabetes and among the subset who have CHD.

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Diabetes is associated with higher risks of heart diseases such as coronary heart disease (CHD) and congestive heart failure (CHF).<sup>1,2</sup> The incidence of diabetes is increasing worldwide, and its management in patients with CHD and/or CHF is important to improving survival of patients with those conditions. Previous studies have suggested that  $\beta$ -blockers improve survival in patients who have had a myocardial infarction or in those with CHF due to left ventricular systolic dysfunction.<sup>3-7</sup> However,  $\beta$ -blockers have never been found to improve survival in all other patients with stable CHD in the absence of myocardial infarction or CHF without systolic dysfunction. Moreover, the efficacy of  $\beta$ -blockers in diabetic patients with CHD/CHF remains unknown. Recent studies have

suggested that  $\beta$ -blockers may prevent or decrease the adverse effects after the occurrence of severe hypoglycemia.<sup>8-11</sup> However, these results do not necessarily mean that use of  $\beta$ -blockers is effective in diabetic patients<sup>11</sup> because the major adverse effects of  $\beta$ -blockers include the potential risk of the occurrence of severe hypoglycemia and weight gain,<sup>11-14</sup> both of which can lead to increased risks of cardiovascular disease and death.<sup>15,16</sup> Hospital admissions for hypoglycemia are increasing in diabetic patients.<sup>17,18</sup> Therefore, use of  $\beta$ -blockers for diabetic patients may become associated with additional mortality risk. We analyzed the relationship between use of  $\beta$ -blockers and all-cause mortality in a nationally representative sample of the adult US population with and without diabetes.



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## PATIENTS AND METHODS

### Data Source and Study Population

We conducted a prospective cohort study using data from the US National Health and Nutrition Examination Survey (NHANES).<sup>19,20</sup> The NHANES was conducted by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention.<sup>19,20</sup> It uses a stratified, multistage probability sampling design that enabled representation of the noninstitutionalized US civilian population.<sup>19,20</sup> Data were collected at home and at mobile examination centers (MECs), and blood samples were collected during an MEC examination.<sup>19,20</sup>

Among those participating in the NHANES during 1999–2010, the unweighted response rate of household interviews was 80.6% and that of the MEC examination was 77.1%.<sup>20,21</sup> We focused on 17,524 participants aged 20 to 79 years on the date of home interview (survey participation). The study participants in the NHANES 1999–2010 were prospectively followed up from the date of survey participation until December 31, 2011. The occurrence of study outcomes was maximally followed up for 10 years. Written informed consent was obtained from all participants. The NCHS Research Ethics Review Board approved the NHANES protocols.<sup>22</sup>

### Definition of Diabetes, Heart Disease, and Use of $\beta$ -Blockers

We defined as diabetic those participants who met any of the following 3 criteria: previous diagnosis of diabetes, current use of antidiabetic medications or insulin, or a hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) level of 6.5% or higher, which was measured at the time of the MEC examination.<sup>23</sup> Participants who did not fulfill any of these 3 criteria were defined as without diabetes.<sup>20</sup> Coronary heart disease was defined as a previous diagnosis of CHD, myocardial infarction, or angina pectoris. Congestive heart failure was defined as a previous diagnosis of CHF. Well-trained interviewers confirmed these diagnoses by asking the participants whether they had ever been informed of having these diseases by a doctor or other health care professional.

Use of  $\beta$ -blockers was defined as currently taking a  $\beta$ -blocker, either as a separate pill or in a fixed-dose combination. We excluded

$\beta$ -blockers contained in ophthalmic preparations. Reported use of a  $\beta$ -blocker was confirmed by the interviewer through examination of medication containers, then matched to a comprehensive prescription drug database.<sup>19</sup> In contrast to unselective  $\beta$ -blockers,  $\beta_1$ -selective  $\beta$ -blockers may not have adverse effects on glucose metabolism and recovery from hypoglycemia.<sup>24</sup> In addition, there is sufficient evidence that bisoprolol, carvedilol, and metoprolol reduce mortality in patients with heart disease, particularly CHF with systolic dysfunction. Therefore, we performed various analyses for each type of  $\beta$ -blocker. We identified 14 types of  $\beta$ -blocker ingredients prescribed for NHANES participants, of which 6 were  $\beta_1$ -selective  $\beta$ -blockers (acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, and nebivolol), 3 were specific  $\beta$ -blockers (bisoprolol, carvedilol, and metoprolol), which have been reported to reduce the risk of death in patients with CHF with reduced ejection fraction,<sup>5–7</sup> and 7 had neither of these characteristics (labetalol, nadolol, penbutolol, pindolol, propranolol, sotalol, and timolol). Although a meta-analysis of randomized trials reported beneficial effects of  $\beta$ -blockers,<sup>3,25</sup> there is insufficient data identifying specific  $\beta$ -blockers with benefits of improved survival after myocardial infarction. We divided participants into  $\beta$ -blocker users and nonusers.  $\beta$ -Blocker nonusers included those without hypertension and those with hypertension but not receiving  $\beta$ -blockers.

### Outcome Measures

The main outcome measure was all-cause mortality. We used the mortality follow-up data that were provided in the public-use versions of the NCHS Linked Mortality Files.<sup>20,26</sup> To identify causes of death occurring in participants in or after 1999, the NHANES used the *International Classification of Diseases, Tenth Revision* codes.<sup>20</sup>

### Potential Confounders

We extracted data on potential confounders, including age, sex, body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), race and ethnicity, educational attainment, smoking status, hyperlipidemia, hypertension, HbA<sub>1c</sub> levels, duration of diabetes, use of insulin and oral antidiabetic medications, and history of CHD, CHF, cancer, asthma, and

chronic obstructive pulmonary disease (COPD). Race and ethnicity were classified into 4 categories: non-Hispanic white; non-Hispanic black; Mexican American; and others, including other Hispanics, Asian, and multiracial participants.<sup>20</sup> We classified educational attainment as less than high school, high school graduation or General Educational Development certificate, and more than high school.<sup>20</sup> Dyslipidemia was defined as a previous diagnosis of hyperlipidemia or intake of lipid-lowering medications. Hypertension was defined as either a previous diagnosis of hypertension or intake of antihypertensive medications.<sup>20</sup> Hemoglobin A<sub>1c</sub> levels were measured at MEC examination in this survey.<sup>20</sup> Duration of diabetes was divided according to a cutoff of 10 years, which was the approximate overall mean value in diabetic participants in this study. Cancer, asthma, and COPD were defined as a previous diagnosis of cancer/malignancy, asthma, and emphysema/chronic bronchitis, respectively.

### Statistical Analyses

Demographic data are presented as numbers with proportions (percentage) or mean  $\pm$  SD.<sup>20</sup> Both diabetic and nondiabetic participants were further divided into groups taking  $\beta$ -blockers and not taking  $\beta$ -blockers. Study participants taking  $\beta$ -blockers were compared with those not taking  $\beta$ -blockers using the *t* test for continuous variables and the  $\chi^2$  test for categorical variables. For all-cause mortality, we used a Cox proportional hazards model to analyze the unadjusted and multivariate-adjusted hazard ratios (HRs) in study participants taking  $\beta$ -blockers compared with those not taking  $\beta$ -blockers. We included age, sex, BMI, race and ethnicity, educational attainment, smoking status, hyperlipidemia, hypertension, and history of CHD, CHF, cancer, asthma, and COPD for adjustment. When we compared all-cause mortality in diabetic participants taking  $\beta$ -blockers with those not taking  $\beta$ -blockers, additional adjustment was made for HbA<sub>1c</sub> levels, duration of diabetes, and use of insulin and oral antidiabetic medications. We performed similar analyses limited to the participants with CHD or CHF. In addition, we conducted additional analyses limited to the participants taking  $\beta_1$ -selective  $\beta$ -blockers or specific  $\beta$ -blockers (bisoprolol, metoprolol, and carvedilol) and participants not taking  $\beta$ -blockers. To explore effect

modification, we tested for interaction between the use of  $\beta$ -blockers and a history of CHD in multivariate models in diabetic patients.

Furthermore, we performed sensitivity analyses to evaluate the HRs for all-cause mortality in the study participants taking  $\beta$ -blockers compared with those not taking  $\beta$ -blockers using propensity score—matched Cox proportional analyses. The propensity score estimates the proportion of those assigned to use  $\beta$ -blockers and was derived using a logistic regression model that included the following predictors: age, sex, BMI, race and ethnicity, educational attainment, smoking status, hyperlipidemia, hypertension, HbA<sub>1c</sub> levels, duration of diabetes, use of insulin and oral antidiabetic medications (these 4 variables were included if a participant had diabetes), and history of CHD, CHF, cancer, asthma, and COPD. To achieve well-matched baseline characteristics, we added the squared age and 2 interaction terms (if a participant had diabetes) for the history of CHD and CHF and for the history of asthma and COPD to the calculation of the propensity score.<sup>27</sup> Kaplan-Meier survival curves were constructed for all-cause mortality in diabetic and nondiabetic participants taking and not taking  $\beta$ -blockers. In addition, we constructed Kaplan-Meier survival curves limited to participants taking  $\beta_1$ -selective  $\beta$ -blockers or specific  $\beta$ -blockers (bisoprolol, metoprolol, and carvedilol), as well as those not taking  $\beta$ -blockers.

All statistical analyses were conducted using Stata statistical software, version 14.1 (Stata-Corp), accounting for the complex survey design.<sup>28</sup> Following Centers for Disease Control and Prevention's recommendations for the analysis of NHANES data, we used an appropriate weight for each analysis on the basis of variables selected. The weights were provided by the NCHS and accounted for unequal probabilities of selection and nonresponses to make unbiased national estimates.<sup>29</sup> Therefore, the findings including the event rates and the percentages are different from those simply calculated using the number of events and study participants.  $P < .05$  was considered statistically significant for all tests.

### RESULTS

The characteristics of the participants with and without diabetes are presented in Table 1. The

TABLE 1. Baseline Characteristics of Study Participants Taking and Not Taking  $\beta$ -Blockers<sup>a,b</sup>

Variable	DM (N=2840)			Non-DM (N=14,684)		
	No $\beta$ -blocker (n=2143)	$\beta$ -blocker (n=697)	P value	No $\beta$ -blocker (n=13,100)	$\beta$ -blocker (n=1584)	P value
Age (y)	56.4±11.8	62.4±10.0	<.001	46.8±10.7	59.4±9.8	<.001
Female sex	49.8	45.2	.15	54.2	53.5	.64
Race/ethnicity						
Non-Hispanic white	61.7	70.3	.001	76.4	83.8	<.001
Non-Hispanic black	16.0	15.8	.88	9.1	7.6	.02
Mexican American	8.5	4.1	<.001	5.2	2.4	<.001
Others <sup>c</sup>	13.8	9.9	.05	9.3	6.1	<.001
Education attainment						
<High school	27.1	30.5	.14	13.1	16.8	<.001
High school or GED	24.5	27.3	.25	22.4	28.4	<.001
>High school	48.4	42.2	.05	64.5	54.8	<.001
Current smoking	18.3	14.8	.02	20.1	16.5	.003
Body mass index (kg/m <sup>2</sup> ) <sup>d</sup>	32.8±7.0	34.0±7.3	.002	28.3±4.8	30.1±5.2	<.001
Dyslipidemia	58.9	65.9	.02	34.7	57.4	<.001
Hypertension	57.6	89.1	<.001	24.8	80.7	<.001
HbA <sub>1c</sub> (%) <sup>e</sup>	7.4±1.7	7.1±1.4	.001	5.3±0.3	5.5±0.3	<.001
Duration of diabetes (y)	8.4±10.3	10.6±11.7	.005	NA	NA	NA
≥10	32.5	39.9	.02	NA	NA	NA
Antidiabetic medications						
Insulin	20.7	25.9	.04	NA	NA	NA
Oral antidiabetic medications	59.0	61.3	.40	NA	NA	NA
Coronary heart disease	9.6	43.3	<.001	3.3	24.9	<.001
Congestive heart failure	4.4	21.3	<.001	0.9	7.1	<.001
Cancer	12.6	15.5	.11	8.3	16.5	<.001
Asthma	16.4	16.8	.85	13.5	10.9	.02
COPD	10.7	16.1	.003	7.2	9.3	.01

<sup>a</sup>COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; GED = General Educational Development certificate; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; NA = not applicable.

<sup>b</sup>Data are presented as percentage of participants or mean ± SD.

<sup>c</sup>Category includes other Hispanics and other races, including multiracial participants.

<sup>d</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>e</sup>HbA<sub>1c</sub>: 7.4% = 57 mmol/mol; 7.1% = 54 mmol/mol; 5.3% = 34 mmol/mol; 5.5% = 37 mmol/mol.

study included 2840 diabetic participants (697 diabetic participants taking  $\beta$ -blockers and 2143 not taking  $\beta$ -blockers) and 14,684 nondiabetic participants (1584 nondiabetic participants taking  $\beta$ -blockers and 13,100 not taking  $\beta$ -blockers). Coronary heart disease and CHF were significantly more prevalent in participants taking  $\beta$ -blockers than in participants not taking  $\beta$ -blockers ( $P<.001$ ).

### Mortality in Diabetic and Nondiabetic Participants

Event rates for all-cause death among diabetic and nondiabetic participants are presented in Table 2. Mean ± SD follow-up periods in diabetic participants were 4.8±2.6 years in those taking  $\beta$ -blockers and 5.9±2.9 years in those

not taking  $\beta$ -blockers; 695 of the 697 diabetic participants taking  $\beta$ -blockers (99.7%) and 2141 of the 2143 not taking  $\beta$ -blockers (99.9%) completed follow-up. The event rates for all-cause death in diabetic participants taking and not taking  $\beta$ -blockers were 40.6 and 17.1 per 1000 person-years, respectively, whereas those in nondiabetic participants taking and not taking  $\beta$ -blockers were 13.8 and 5.9 per 1000 person-years, respectively. Among diabetic participants, the unadjusted HR (95% CI) for all-cause death was 2.51 (1.90-3.34) for those taking  $\beta$ -blockers compared with those not taking  $\beta$ -blockers ( $P<.001$ ). Using multivariate Cox proportional hazards models, all-cause mortality in diabetic participants was significantly higher in those taking  $\beta$ -blockers than in those not

TABLE 2. Risks for All-Cause Mortality in Diabetic and Nondiabetic Participants Taking and Not Taking  $\beta$ -Blockers<sup>a</sup>

Variable	DM			Non-DM		
	No $\beta$ -blocker	$\beta$ -blocker	P value	No $\beta$ -blocker	$\beta$ -blocker	P value
All participants						
No. of events/total participants	248/2143	141/697	NA	658/13,100	156/1584	NA
Event rate (per 1000 person-years)	17.1	40.6	NA	5.9	13.8	NA
Unadjusted HR (95% CI)	1.00 [ref]	2.51 (1.90-3.34)	<.001	1.00 [ref]	2.41 (1.95-3.00)	<.001
Adjusted HR (95% CI) <sup>b</sup>	1.00 [ref]	1.49 (1.09-2.04)	.01	1.00 [ref]	0.99 (0.79-1.25)	.96
Participants with CHD						
No. of events/total participants	45/242	75/292	NA	109/523	59/440	NA
Event rate (per 1000 person-years)	32.7	56.6	NA	26.3	20.5	NA
Unadjusted HR (95% CI)	1.00 [ref]	1.86 (1.18-2.92)	.008	1.00 [ref]	0.80 (0.58-1.09)	.16
Adjusted HR (95% CI)	1.00 [ref]	1.64 (1.08-2.48)	.02	1.00 [ref]	0.68 (0.50-0.94)	.02
Participants with CHF						
No. of events/total participants	37/120	54/149	NA	46/158	25/146	NA
Event rate (per 1000 person-years)	65.8	98.7	NA	43.4	29.0	NA
Unadjusted HR (95% CI)	1.00 [ref]	1.54 (0.96-2.44)	.06	1.00 [ref]	0.68 (0.37-1.23)	.20
Adjusted HR (95% CI)	1.00 [ref]	1.66 (0.93-2.96)	.08	1.00 [ref]	0.76 (0.39-1.48)	.42

<sup>a</sup>CHD = coronary heart disease; CHF = congestive heart failure; DM = diabetes mellitus; HR = hazard ratio; NA = not applicable; ref = reference.

<sup>b</sup>Multivariate model was made by adjusting for age, sex, body mass index, race and ethnicity, educational attainment, smoking status, hyperlipidemia, hypertension, and history of CHD, CHF, cancer, asthma, and chronic obstructive pulmonary disease. If a participant had diabetes, additional adjustment was made for hemoglobin A<sub>1c</sub> levels, duration of diabetes (<10 y and  $\geq$ 10 y), and use of insulin and oral antidiabetic medications.

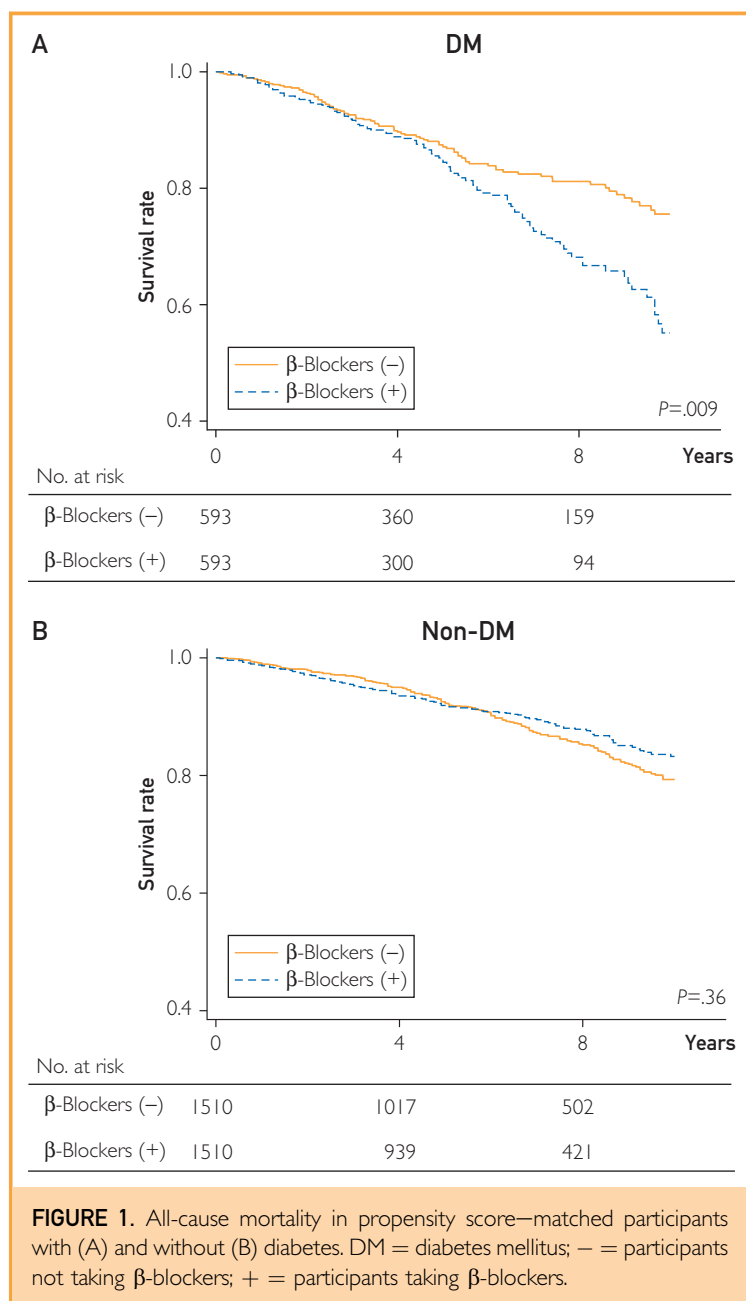
taking  $\beta$ -blockers (adjusted HR, 1.49; 95% CI, 1.09-2.04;  $P=.01$ ). Similar results were found among those taking  $\beta_1$ -selective  $\beta$ -blockers (adjusted HR, 1.60; 95% CI, 1.13-2.24;  $P=.007$ ) and those taking specific  $\beta$ -blockers (adjusted HR, 1.55; 95% CI, 1.09-2.21;  $P=.01$ ) compared with those not taking  $\beta$ -blockers. The analysis limited to diabetic patients taking insulin yielded a similar hazard ratio (adjusted HR, 1.51; 95% CI, 0.89-2.55;  $P=.12$ ). Among nondiabetic participants, the adjusted HR was not significantly different between those taking and not taking  $\beta$ -blockers (adjusted HR, 0.99; 95% CI, 0.79-1.25;  $P=.96$ ).

All-cause mortality in diabetic participants with CHD taking and not taking  $\beta$ -blockers was 56.6 and 32.7 per 1000 person-years, respectively; whereas, that in nondiabetic individuals taking and not taking  $\beta$ -blockers was 20.5 and 26.3 per 1000 person-years, respectively. All-cause mortality in diabetic participants with CHD was significantly higher in those taking  $\beta$ -blockers compared with those not taking  $\beta$ -blockers (adjusted HR, 1.64; 95% CI, 1.08-2.48;  $P=.02$ ), whereas that in nondiabetic participants with CHD was significantly lower in those taking  $\beta$ -blockers (adjusted HR, 0.68; 95% CI, 0.50-0.94;  $P=.02$ ). No significant interaction was observed between the use of  $\beta$ -blockers and a history of CHD in a multivariate

model in diabetic participants ( $P=.47$  for the interaction term). Furthermore, all-cause mortality in diabetic participants with a history of myocardial infarction was significantly higher in those taking  $\beta$ -blockers than in those not taking  $\beta$ -blockers (adjusted HR, 2.24; 95% CI, 1.24-4.07;  $P=.008$ ), whereas mortality in nondiabetic participants with myocardial infarction was significantly lower in those taking  $\beta$ -blockers (adjusted HR, 0.59; 95% CI, 0.38-0.93;  $P=.02$ ). A similar pattern (lower mortality among nondiabetic participants and higher mortality among diabetic participants taking  $\beta$ -blockers) was found for participants with CHF.

#### Mortality in Propensity Score—Matched Diabetic and Nondiabetic Participants

There was no difference in the baseline characteristics of diabetic ( $N=1186$ ) and nondiabetic ( $N=3020$ ) participants taking and not taking  $\beta$ -blockers (Supplemental Table, available online at <http://www.mayoclinicproceedings.org>). All-cause mortality in diabetic participants was higher in those taking  $\beta$ -blockers than in those not taking  $\beta$ -blockers (propensity score—adjusted HR, 1.65; 95% CI, 1.13-2.40;  $P=.009$ ; Figure 1). In nondiabetic participants, all-cause mortality was not significantly different between those taking and not taking  $\beta$ -blockers ( $P=.36$ ). Similarly, all-cause mortality was significantly higher



in diabetic participants taking  $\beta_1$ -selective  $\beta$ -blockers ( $P=.02$ ) or taking specific  $\beta$ -blockers ( $P=.002$ ) compared with those not taking  $\beta$ -blockers (Figures 2 and 3, respectively).

## DISCUSSION

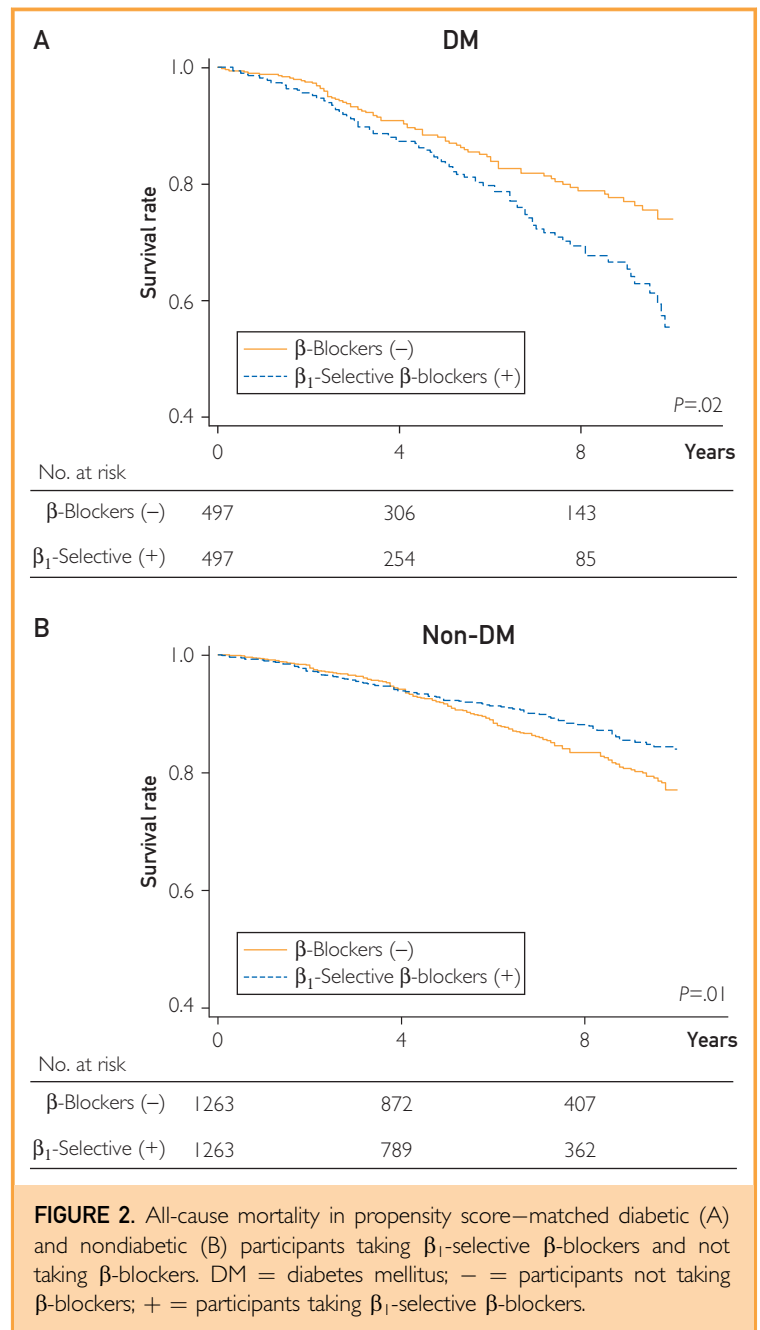
In the present study using nationally representative data, all-cause mortality in diabetic participants was higher in those taking  $\beta$ -blockers than in those not taking  $\beta$ -blockers. Similar

results were observed in those taking  $\beta_1$ -selective  $\beta$ -blockers and in those taking specific  $\beta$ -blockers. These results were observed in analyses limited to the propensity score–matched diabetic participants. Furthermore, adjusted HRs were higher in diabetic participants with CHD taking  $\beta$ -blockers than in those not taking  $\beta$ -blockers. In contrast, consistent with previous studies, all-cause mortality was lower in nondiabetic participants with CHD taking  $\beta$ -blockers than in those not taking  $\beta$ -blockers. In addition, all-cause mortality was lower in those taking  $\beta_1$ -selective  $\beta$ -blockers or specific  $\beta$ -blockers and in the propensity score–matched nondiabetic participants.

$\beta$ -Blockers act directly on the heart to reduce heart rate and contractility, leading to a decrease in myocardial oxygen demand, a reduction in angina onset, and an improvement in the ischemic threshold. Previous studies have revealed that  $\beta$ -blockers significantly reduced death and recurrent myocardial infarction in patients with recent acute myocardial infarction.<sup>3,4</sup> In addition,  $\beta$ -blockers achieved a reduction in mortality in patients with current or previous symptoms of CHF with systolic dysfunction.<sup>5-7</sup> Therefore,  $\beta$ -blockers are recommended in many guidelines as a first-line therapy in patients with CHD and CHF.<sup>30-33</sup> However, there is no supportive evidence of improved survival in patients with stable CHD without myocardial infarction or CHF without systolic dysfunction.<sup>34</sup> Although some retrospective studies reported benefits for  $\beta$ -blockers about 2 or 3 decades ago,<sup>35,36</sup> there have been no recent reports that  $\beta$ -blockers are effective in diabetic patients. Moreover, despite myocardial infarction, improved survival with  $\beta$ -blockers was found in the previous preperfusion era but not in the recent reperfusion era.<sup>25</sup> In this prospective study, use of  $\beta$ -blockers in diabetic participants was associated with a reversal of the pattern of mortality observed in nondiabetic participants. All-cause mortality was significantly higher in diabetic participants taking  $\beta$ -blockers than in those not taking  $\beta$ -blockers, regardless of the different types of  $\beta$ -blockers. Similar results were also observed in diabetic patients with CHD, even after various adjustments were made. Because recent management of patients with CHD often includes the implementation of other

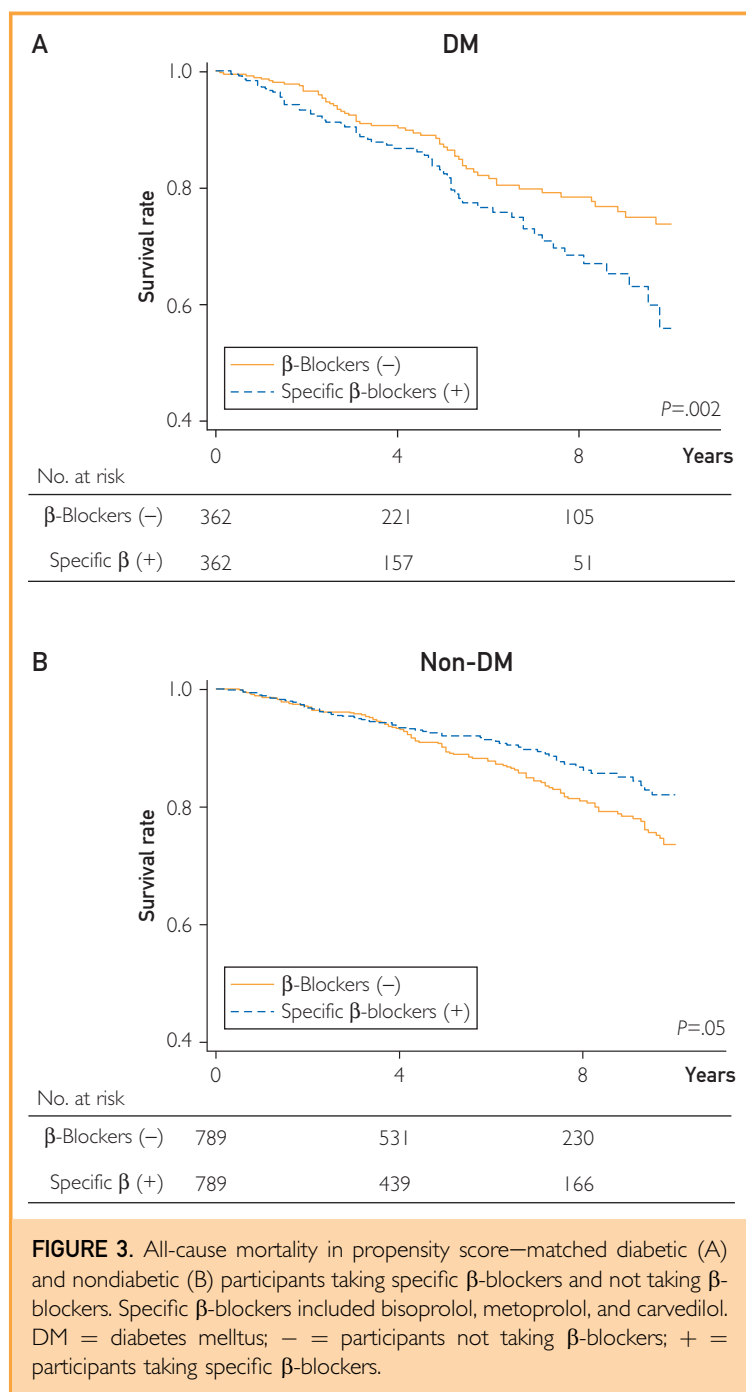
strong therapies such as statins and new revascularization procedures, the benefits of  $\beta$ -blocker therapy may be smaller than previously thought because of concomitant standard treatment such as statins and revascularization. In fact, some recent studies have found that the use of  $\beta$ -blockers is not associated with a lower risk of cardiovascular events or death.<sup>37,38</sup>

Recent studies have suggested that  $\beta$ -blockers may prevent or decrease the adverse effects after the occurrence of severe hypoglycemia.<sup>8-11</sup> However, these results do not necessarily mean that use of  $\beta$ -blockers is effective in diabetic patients,<sup>11</sup> because the use of  $\beta$ -blockers poses a potential risk for the occurrence of severe hypoglycemia, which has been a concern for decades.<sup>11-13</sup> Catecholamines induced by hypoglycemia have important effects on glucose metabolism, and the use of  $\beta$ -blockers can facilitate hypoglycemia and hypoglycemia unawareness due to diminished or absent early warning signs.<sup>39</sup> Previous studies have found that hypoglycemia, particularly severe hypoglycemia, is associated with increased risks of cardiovascular events and death.<sup>15,40</sup> As the prevalence of severe hypoglycemia is increasing in diabetic patients,<sup>17,18</sup> the adverse effects of  $\beta$ -blockers may outweigh their benefits even in diabetic patients with CHD. The major adverse effects of  $\beta$ -blockers, such as the potential risk of the occurrence of hypoglycemia and weight gain, may have more adverse impact on mortality in patients with diabetes than in those without diabetes. Most differences in mortality between participants taking and not taking  $\beta$ -blockers emerged after several years. Although the exact reasons for these differences remain unclear, these findings may support the hypothesis that adverse effects on glucose metabolism and weight gain induced by  $\beta$ -blockers may lead to an increased risk of mortality. In addition, a recent study reported that  $\beta$ -blockers may increase central blood pressure.<sup>41</sup> This prohypertensive effect can be expected to be more pronounced in stiff arteries such as those seen in diabetic patients. This mechanism might have contributed to the increased mortality. Moreover, further studies are warranted to reveal whether the use of  $\beta$ -blockers influences the outcomes in diabetic patients taking the newer classes of diabetes medication, such



as the sodium-dependent glucose cotransporter 2 inhibitor and the glucagon-like peptide 1 receptor agonist, which are less likely to cause hypoglycemia and decrease body weight.<sup>42,43</sup>

The present study has several limitations. First, this was an observational study using data from the NHANES 1999-2010, and the missing data and underpowering may have influenced the results. In addition, because the



baseline data were collected between 1999 and 2010, the findings of the present study may not be fully applicable to current management using newer therapies. There has not been a randomized controlled trial to assess the effectiveness of  $\beta$ -blockers in diabetic patients; therefore, a randomized controlled trial is required to confirm the results of the present

study. Second, bias due to unknown and unmeasured confounders, notably by atrial fibrillation and severity of CHD and CHF, could not be excluded. Third, the follow-up period did not start at the initiation of  $\beta$ -blocker treatment. Because recent trials have suggested that long-term  $\beta$ -blocker therapy may not be needed for patients without heart failure,<sup>44</sup> the duration of the follow-up period might influence the results. Fourth, because we did not have sufficient data, we could not perform analyses using more detailed classifications of  $\beta$ -blockers. A previous study reported that carvedilol resulted in improved cardiovascular risk factors and the stabilization of glycemic control compared with metoprolol in diabetic patients.<sup>45</sup> Further studies are required to evaluate the association between  $\beta$ -blockers without worsening glucose metabolism and cardiovascular outcomes in diabetic patients. Fifth, adherence to medication could not be clarified in the present study. Adherence to medications is a worldwide issue even in patients with type 2 diabetes following myocardial infarction.<sup>46</sup> In the present study, some patients taking  $\beta$ -blockers at baseline may have discontinued their use of  $\beta$ -blockers during the follow-up period.

## CONCLUSION

This study found that the use of  $\beta$ -blockers is associated with an increased risk of all-cause mortality in diabetic patients and among the subset who have CHD. Further studies are needed to assess whether  $\beta$ -blockers are effective in reducing mortality and coronary events in diabetic patients receiving optimal medical treatment.

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## SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.



**Abbreviations and Acronyms:** BMI = body mass index; CHD = coronary heart disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; HR = hazard ratio; MEC = mobile examination center; NCHS = National Center for Health Statistics; NHANES = National Health and Nutrition Examination Survey

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