

Risk of Cardiovascular Events in Patients With Diabetes Mellitus on β -Blockers

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See Editorial Commentary, pp 42–43

Abstract—Although the use of β -blockers may help in achieving maximum effects of intensive glycemic control because of a decrease in the adverse effects after severe hypoglycemia, they pose a potential risk for the occurrence of severe hypoglycemia. This study aimed to evaluate whether the use of β -blockers is effective in patients with diabetes mellitus and whether its use is associated with the occurrence of severe hypoglycemia. Using the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) data, we performed Cox proportional hazards analyses with a propensity score adjustment. The primary outcome was the first occurrence of a cardiovascular event during the study period, which included nonfatal myocardial infarction, unstable angina, nonfatal stroke, and cardiovascular death. The mean follow-up periods (\pm SD) were 4.6 ± 1.6 years in patients on β -blockers ($n=2527$) and 4.7 ± 1.6 years in those not on β -blockers ($n=2527$). The cardiovascular event rate was significantly higher in patients on β -blockers than in those not on β -blockers (hazard ratio, 1.46; 95% confidence interval, 1.24–1.72; $P<0.001$). In patients with coronary heart disease or heart failure, the cumulative event rate for cardiovascular events was also significantly higher in those on β -blockers than in those not on β -blockers (hazard ratio, 1.27; 95% confidence interval, 1.02–1.60; $P=0.03$). The incidence of severe hypoglycemia was significantly higher in patients on β -blockers than in those not on β -blockers (hazard ratio, 1.30; 95% confidence interval, 1.03–1.64; $P=0.02$). In conclusion, the use of β -blockers in patients with diabetes mellitus was associated with an increased risk for cardiovascular events. (*Hypertension*. 2017;70:103–110. DOI: 10.1161/HYPERTENSIONAHA.117.09259.) • [Online Data Supplement](#)

Key Words: ACCORD trial ■ β -blocker ■ cardiovascular disease ■ coronary heart disease ■ diabetes mellitus ■ severe hypoglycemia

Diabetes mellitus management mainly aims at preventing diabetes mellitus–related complications. Although appropriate glycemic control prevents complications,¹ the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) revealed that intensive therapy can increase all-cause and cardiovascular mortalities.² A possible explanation for the results is that a glucose-lowering therapy increases the frequency of hypoglycemic episodes, which in turn is associated with increased risks for vascular events and death.^{3,4} Patients with diabetes mellitus with severe hypoglycemia face many critical problems, such as severe hypertension, hypokalemia, and QT prolongation, resulting in cardiovascular diseases, fatal arrhythmia, and death.^{5,6}

Recent studies have suggested that β -blockers may prevent or decrease the adverse effects after the occurrence of

severe hypoglycemia, such as severe hypertension and hypokalemia, and may reduce severe hypoglycemia-associated cardiac arrhythmias and death.^{7–9} Our recent study revealed that the cardiovascular event rate in patients with diabetes mellitus on β -blockers was significantly lower in the intensive therapy group compared with the standard therapy group.⁹ Conversely, all-cause and cardiovascular mortalities in patients not on β -blockers were significantly higher in the intensive therapy group. The difference of these results between patients on and those not on β -blockers may be mainly because of the protective effects of β -blockers after the occurrence of severe hypoglycemia. However, this does not necessarily mean that the use of β -blockers is effective in patients with diabetes mellitus because the use of β -blockers poses a potential risk for the occurrence

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of severe hypoglycemia.¹⁰ Therefore, we evaluated whether the use of β -blockers was effective in patients with diabetes mellitus and whether its use was associated with the occurrence of severe hypoglycemia in recent diabetes mellitus management.

Materials and Methods

Study Design

We used ACCORD trial data to evaluate the associations between the use of β -blockers and cardiovascular events, all-cause and cardiovascular mortalities, and severe hypoglycemia in patients with diabetes mellitus. The detailed design and description of the glycemia interventions of the ACCORD trial have been previously reported.^{2,11–13}

Briefly, the ACCORD trial was sponsored by the National Heart, Lung, and Blood Institute and was conducted in 77 clinical centers across the United States and Canada. In total, 10251 men and women who were aged between 40 and 79 years with type 2 diabetes mellitus, had a glycated hemoglobin level $\geq 7.5\%$, and who either were between the ages of 40 and 79 years and had a cardiovascular disease or were between the ages of 55 and 79 years and had albuminuria, had anatomical evidence of significant atherosclerosis, had left ventricular hypertrophy, or had at least 2 additional risk factors for cardiovascular disease (current smoker, obesity, hypertension, or dyslipidemia) were included in the trial.^{2,11} Detailed eligibility criteria are presented in Table S1 in the [online-only Data Supplement](#).² All 10251 patients were randomly allocated into 1 of the 2 groups: one received a comprehensive intensive therapy that targeted a glycated hemoglobin level $<6.0\%$ and the other received a standard therapy that targeted a level of 7.0% – 7.9% . The medications used to achieve these targets were the same in the 2 groups and included metformin, short- and long-acting insulins, sulfonylureas, acarbose, meglitinides, and thiazolidinediones. Patients were followed up at least every 4 months to ensure that therapeutic goals were met and maintained and to monitor study outcomes and adverse effects. The study protocol was approved by the ethics committee of each study center and approved and monitored by an independent data safety and monitoring board. All participants provided written informed consent. Because of the increase in all-cause and cardiovascular mortalities, intensive therapy was discontinued on February 6, 2008.² Participants were switched to the standard regimen and followed up until December 31, 2010. In this study, the occurrence of outcomes was maximally followed-up for 7 years. The study was approved by the institutional review board of the National Center for Global Health and Medicine, and National Heart, Lung, and Blood Institute approved our use of the ACCORD trial data.

Outcome Measurements

In this study, the primary outcome was the first occurrence of a cardiovascular event during the study period, which included myocardial infarction, unstable angina, stroke, and cardiovascular death. The secondary outcomes were all-cause death, cardiovascular death, and severe hypoglycemia. Cardiovascular death was defined as presumed cardiovascular death, unexpected death, and death from a myocardial infarction, arrhythmia, congestive heart failure, stroke, and other cardiovascular diseases, including abdominal aortic aneurysm rupture and pulmonary emboli.¹¹ Severe hypoglycemia was defined as hypoglycemia events that required assistance from medical personnel and were confirmed by blood glucose levels <50 mg/dL. The occurrence of severe hypoglycemia was maximally followed up for 5 years.

Statistical Analysis

Study patients were first divided into 2 groups: patients on β -blockers ($n=3023$) and those not on β -blockers ($n=6988$; Table S2). To match all baseline characteristics that could be related to the indication of β -blockers, we used the propensity score and performed 1:1 nearest-neighbor matching without replacement.¹⁴ The propensity score is used to attempt to adjust for confounding, potential selection bias and differences between treatment groups.^{15,16} The propensity score estimated the probability from 0 to 1 that patients would have been assigned to the use of β -blockers given a set of known variables 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; sex; duration of diabetes mellitus; history of coronary heart disease, heart failure, and stroke; race and ethnicity; education attainment; smoking status; body mass index; use of certain medications (insulin, sulfonylurea, metformin, angiotensin II receptor blockers/angiotensin-converting enzyme inhibitors, calcium channel blockers, thiazide, statin, and aspirin); systolic blood pressure; glycated hemoglobin; low- and high-density lipoprotein cholesterol; log-transformed triglyceride; estimated glomerular filtration rate; and the assigned strategy of the ACCORD trial. All variables used for the propensity score are presented in Table 1. Standardized differences in the range of $1.96 \times (2/N)^{0.5}$ were considered inconsequential.¹⁷

Demographic data were presented as numbers with proportions (%) or means with standard deviations. Continuous variables were compared using the Student's *t* tests, and categorical variables were compared using χ^2 tests or Fisher exact tests, as appropriate. The number of events within 1 year was small, and there were concerns regarding subject identification. Therefore, follow-up times for all early events were trimmed to 1 year by National Heart, Lung, and Blood Institute before our data handling. For cardiovascular events and all-cause and cardiovascular deaths within 1 year, we compared the incidence of these events in patients on β -blockers with that in patients not on β -blockers.

We analyzed the 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 by the Cox proportional hazard models. Analyses of events before the treatment transition were also performed. The Kaplan–Meier survival curves were constructed for the cardiovascular events, all-cause and cardiovascular deaths, and severe hypoglycemia.

In addition, to minimize confounding by indication, a further adjustment was made to add self-reported health state to the variables for the propensity score matching. The self-reported health state was indicated on the scale (best state is marked by 100 and the worst state by 0). Furthermore, we similarly performed additional analyses in subgroups with intensive therapy, those with standard therapy, and those with or without heart disease based on propensity score matching within each subgroup. Heart disease included coronary heart disease and heart failure. Coronary heart disease was defined as myocardial infarction and angina pectoris. Propensity score matching minimizes confounding but may impair generalizability. Therefore, we performed a sensitivity analysis in the overall ACCORD data with adjustment for the propensity scores as a covariate.¹⁸ With the exception for this sensitivity analysis, we assessed the outcomes in propensity score-matched patients. Furthermore, we performed another sensitivity analysis using one-to-one individual matching on the basis of age, sex, history of coronary heart disease and heart failure, and randomization arm (intensive or standard glycemic therapy).

All statistical analyses were conducted using the Stata version 14.1 software (StataCorp, College Station, TX). *P* value <0.05 was considered statistically significant for all tests.

Results

Study Participants

The characteristics of propensity score-matched patients on ($n=2527$) and those not on ($n=2527$) β -blockers are shown in Table 1. All standardized differences show sufficient overlap in estimated propensity scores. Similarly, the characteristics between patients on and those not on β -blockers are well matched within each of the subgroups, such as standard therapy group, intensive therapy group, and those with and without heart diseases, including coronary heart disease and heart failure (Table S3–S6).

Cardiovascular Events and Mortalities

The incidence of cardiovascular events within 1 year was non-significantly higher in patients on β -blockers than in those

Table 1. Baseline Characteristics of Propensity Score-Matched Patients on and Not on β -Blockers*

Characteristics	β -Blockers (-)	β -Blockers (+)	Standardized Difference, %	P Value
Number	2527	2527		
Age, y	62.9 (6.9)	62.9 (7.0)	0.7	0.80
Female sex, %	36.8	36.6	0.2	0.93
Duration of diabetes mellitus, y	11.0 (7.6)	11.1 (7.9)	2.3	0.42
History of heart disease, %†	37.2	36.8	0.9	0.77
History of coronary heart disease, %	34.6	33.0	3.7	0.23
History of heart failure, %	6.4	6.3	0.2	0.95
History of stroke, %	7.7	7.3	1.6	0.59
Race and ethnicity, %				
White	63.4	63.2	0.5	0.86
Black	19.4	19.2	0.5	0.85
Hispanic	6.7	7.2	2.1	0.43
Others	10.5	10.4	0.4	0.89
Educational attainment, %				
Less than high school	15.3	15.4	0.2	0.93
High school	27.1	26.8	0.7	0.80
Some college	33.3	33.0	0.7	0.81
College degree or higher	24.3	24.8	1.3	0.64
Current smoking, %	11.3	10.9	1.1	0.68
Body mass index, kg/m ² ‡	32.5 (5.4)	32.6 (5.3)	1.2	0.66
Medications, %				
Insulin	36.8	37.5	1.4	0.62
Sulfonylurea	55.2	54.7	1.1	0.69
Metformin	65.3	64.7	1.1	0.70
ARB/ACE-I	72.5	73.0	1.0	0.70
CCB	12.7	13.0	0.8	0.76
Thiazide	31.9	31.7	0.5	0.85
Statin	72.7	73.2	1.3	0.63
Aspirin	61.5	61.9	0.7	0.79
Systolic blood pressure, mm Hg	136.6 (16.2)	136.4 (17.8)	1.6	0.73
HbA1c, %	8.3 (1.0)	8.3 (1.0)	0.4	0.89
Cholesterol, mg/dL				
Low-density lipoprotein	100.4 (32.0)	99.9 (32.4)	1.2	0.66
High-density lipoprotein	40.0 (9.8)	40.1 (10.7)	0.8	0.75

(Continued)

Table 1. Continued

Characteristics	β -Blockers (-)	β -Blockers (+)	Standardized Difference, %	P Value
Triglyceride, mg/dL	197.7 (124.8)	193.5 (121.7)	0.4	0.22
Estimated GFR, mL/min per 1.73 m ² §	88.6 (22.7)	88.3 (22.7)	1.5	0.59
Randomization arm				
Intensive glycemic therapy, %	48.9	49.1	0.4	0.88
Blood pressure trial, %	44.0	43.7	0.6	0.82
Intensive control, %	22.6	22.3	0.6	0.82
Lipid trial, %¶	56.0	56.3	0.6	0.82
Use of fibrate, %	27.9	28.6	1.6	0.57

HbA1c: 8.3%=67 mmol/mol. ACE-I indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CCB, calcium channel blockers; GFR, glomerular filtration rate; and HbA1c, glycated hemoglobin.

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

†Heart disease included coronary heart disease and heart failure.

‡The estimated GFR was calculated using the following MDRD (Modification of Diet in Renal Disease) Study equation: estimated GFR (mL/min per 1.73 m²) = 175 × (serum creatinine in mg/dL)^{-1.154} × (age in years)^{-0.203} × (0.742 for female) × (1.212 for Black).

§Body mass index was calculated as weight in kilogram divided by the square of height in meters.

||The ACCORD Blood Pressure trial (Action to Control Cardiovascular Risk in Diabetes) tested the effect of a target systolic blood pressure <120 mm Hg compared with a target systolic blood pressure <140 mm Hg on major cardiovascular events among high-risk patients with type 2 diabetes mellitus.

¶The ACCORD Lipid Therapy trial was designed to test the effect of a therapeutic strategy that uses a fibrate to increase high-density lipoprotein cholesterol and lower triglyceride levels and uses a statin for treatment of low-density lipoprotein cholesterol compared with the effect of only a statin for treatment of low-density lipoprotein cholesterol on cardiovascular outcomes in patients with type 2 diabetes mellitus.

not on β -blockers (4.1% versus 3.2%; $P=0.07$; Figure S1). In the intensive therapy group, the incidence of cardiovascular events was significantly higher in patients on β -blockers (4.8% versus 2.8%; $P=0.01$). All-cause and cardiovascular mortalities were higher in patients on β -blockers than in those not on β -blockers (1.1% versus 0.6% [$P=0.09$] and 0.7% versus 0.5% [$P=0.45$], respectively; Figure S1).

The Kaplan–Meier survival curves and cumulative event rates for the following cardiovascular events and all-cause and cardiovascular deaths in the propensity score-matched patients on and those not on β -blockers are shown in Figure 1 and Table 2, respectively. The differences in sample size across outcomes were attributed to the occurrence of events and censored cases within 1 year. The mean follow-up periods (\pm SD) were 4.4 \pm 1.5 years in patients on β -blockers and 4.6 \pm 1.5 years in those not on β -blockers (95% CI, 0.12–0.28; $P<0.001$). The rates for cardiovascular events were significantly higher in the patients on β -blockers than in those not on β -blockers (HR,

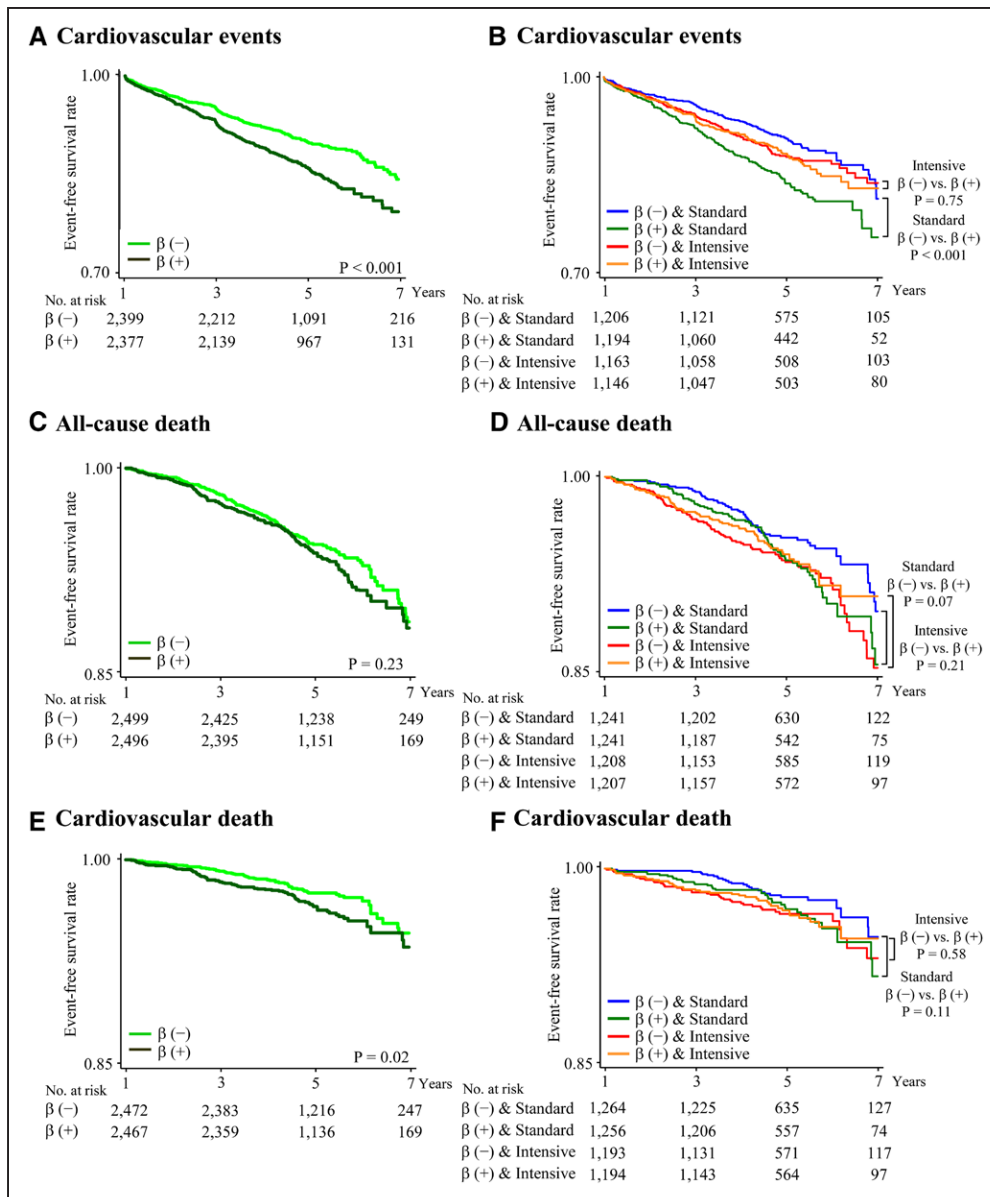


Figure 1. Kaplan–Meier survival curves for cardiovascular events and all-cause and cardiovascular deaths in patients on and not on β -blockers. Rates of freedom from cardiovascular events (**A** and **B**), all-cause death (**C** and **D**), and cardiovascular death (**E** and **F**). β indicates β -blockers; Intensive, intensive therapy; and Standard, standard therapy.

1.46; 95% CI, 1.24–1.72; $P < 0.001$; Figure 1A). In addition, the cardiovascular event rate in the standard therapy group was the highest and significantly higher in patients on β -blockers than in those not on β -blockers (HR, 1.69; 95% CI, 1.36–2.13; $P < 0.001$; Figure 1B). The cumulative event rate for all-cause death was nonsignificantly higher and that for cardiovascular death was significantly higher in patients on β -blockers. Similar results were found before treatment transition (Figure S2). Further analyses with adjustment for health state did not change the overall results in propensity score-matched patients (Table S7). Although HR slightly decreased, the cardiovascular event rate was still significantly higher in patients on β -blockers than in those not on β -blockers (HR, 1.42; 95% CI, 1.20–1.67; $P < 0.001$). Additionally, we assumed that all events trimmed to 1 year occurred at 6 months and performed additional sensitivity analyses using the continuous follow-up data (Figure

S3). The analysis for cardiovascular events showed similar results (HR, 1.42; 95% CI, 1.23–1.64; $P < 0.001$). Furthermore, the analysis using overall ACCORD data with adjustment for the propensity scores as a covariate found a significantly higher risk of cardiovascular events in patients on β -blockers than in those not on β -blockers (HR, 1.37; 95% CI, 1.19–1.58; $P < 0.001$). Another sensitivity analysis using one-to-one individual matching showed similar results (Tables S8 and S9).

Additional analyses were performed limited to diabetes mellitus patients with heart diseases (Figure 2 and Table 2). In patients with heart disease, the cumulative event rate for cardiovascular events was significantly higher in those on β -blockers than in those not on β -blockers (HR, 1.27; 95% CI, 1.02–1.60; $P = 0.03$). After additional adjustment with respect to health state (Table S10), these cardiovascular event rates were still nonsignificantly higher in patients with heart disease

Table 2. HRs for Cardiovascular Events and All-Cause and Cardiovascular Death in Propensity Score-Matched Patients on β -Blockers Compared With Those Not on β -Blockers*

Outcome	Event Rate per Year (Events no./Total no.)		HR (95% CI) for β (+) (vs β [-])	P Value
	β -Blockers (-)	β -Blockers (+)		
All patients				
Cardiovascular events	2.7% (250/2399†)	4.0% (349/2377)	1.46 (1.24–1.72)	<0.001
All-cause death	1.5% (152/2499)	1.7% (164/2496)	1.14 (0.92–1.42)	0.23
Cardiovascular death	0.6% (63/2472)	0.9% (86/2467)	1.44 (1.04–2.00)	0.02
Standard therapy group				
Cardiovascular events	2.7% (125/1206)	4.5% (192/1194)	1.69 (1.35–2.13)	<0.001
All-cause death	1.4% (70/1255)	1.8% (86/1258)	1.34 (0.97–1.83)	0.07
Cardiovascular death	0.6% (31/1241)	0.9% (41/1241)	1.45 (0.90–2.31)	0.11
Intensive therapy group				
Cardiovascular events	2.9% (137/1163)	3.5% (143/1146)	1.04 (0.82–1.31)	0.75
All-cause death	2.0% (97/1208)	1.7% (78/1207)	0.83 (0.61–1.11)	0.21
Cardiovascular death	1.0% (46/1193)	0.9% (40/1194)	.89 (0.58–1.35)	0.58
Patients with CHD/HF				
Cardiovascular events	4.4% (139/852)	5.5% (174/851)	1.27 (1.02–1.60)	0.03
All-cause death	2.4% (88/898)	2.3% (82/905)	0.96 (0.71–1.30)	0.80
Cardiovascular death	1.3% (47/890)	1.3% (45/895)	0.99 (0.67–1.49)	0.96
Patients without CHD/HF				
Cardiovascular events	2.1% (121/1516)	3.0% (168/1492)	1.45 (1.15–1.84)	0.002
All-cause death	1.4% (88/1569)	1.4% (82/1561)	0.97 (0.72–1.31)	0.85
Cardiovascular death	0.5% (35/1546)	0.6% (35/1543)	1.05 (0.66–1.68)	0.84

β indicates β -blockers; CHD, coronary heart disease; CI, confidence interval; HF, heart failure; and HR, hazard ratio.
 *Data are presented as number or HR (95% CI).
 †Because of some events and censored cases within 1 y, sample sizes were different between patients on and those not on β -blockers.

on β -blockers than in those not on β -blockers (HR, 1.18; 95% CI, 0.94–1.47; $P=0.15$). In patients without heart diseases, the cardiovascular event rate was significantly higher in those on β -blockers than in those not on β -blockers (Figure S4; Table 2). All-cause and cardiovascular death rates were not significantly different between patients on and those not on β -blockers, regardless of the presence or absence of a heart disease.

Severe Hypoglycemia

The Kaplan–Meier survival curves and HRs for severe hypoglycemia are shown in Figure 3 and Table 3, respectively. The incidence of severe hypoglycemia was significantly higher in patients on β -blockers than in those not on β -blockers (event rate per year, 1.5% versus 1.1%; HR, 1.36; 95% CI, 1.07–1.74; $P=0.01$). In addition, the incidence of severe hypoglycemia was significantly higher in patients on β -blockers limitedly to those in the intensive therapy group (event rate per year, 2.3% versus 1.7%; HR, 1.36; 95% CI, 1.03–1.81; $P=0.03$). Similar results were found before treatment transition (Figure S5).

Discussion

In the present study using the ACCORD trial data, various analyses in propensity score-matched patients revealed that the

use of β -blockers was associated with an increased risk for cardiovascular events. Furthermore, a similar relationship between the use of β -blockers and cardiovascular events was found in patients not only without heart disease but also with heart disease. The incidence of severe hypoglycemia was significantly higher in those on β -blockers than in those not on β -blockers.

Although an increased risk for hypoglycemia in patients with diabetes mellitus on β -blockers was hard to demonstrate,^{19–24} it has been well known that the use of β -blockers can be a risk factor for severe hypoglycemia and hypoglycemia unawareness presumably because of the diminished or absent early warning signs.¹⁰ Previous studies have suggested that the sympathoadrenal activation response to severe hypoglycemia is associated with cardiovascular events.^{3–5,25} Our recent study demonstrated that cardiovascular event rates in patients on β -blockers were significantly lower in the intensive therapy group compared with those in the standard therapy group.⁹ In contrast, in patients not on β -blockers, all-cause and cardiovascular mortalities were significantly higher in the intensive therapy group. The difference in the results between patients on and those not on β -blockers might suggest the protective effects of β -blockers after the occurrence of severe hypoglycemia. However, this does not imply that the use of β -blockers

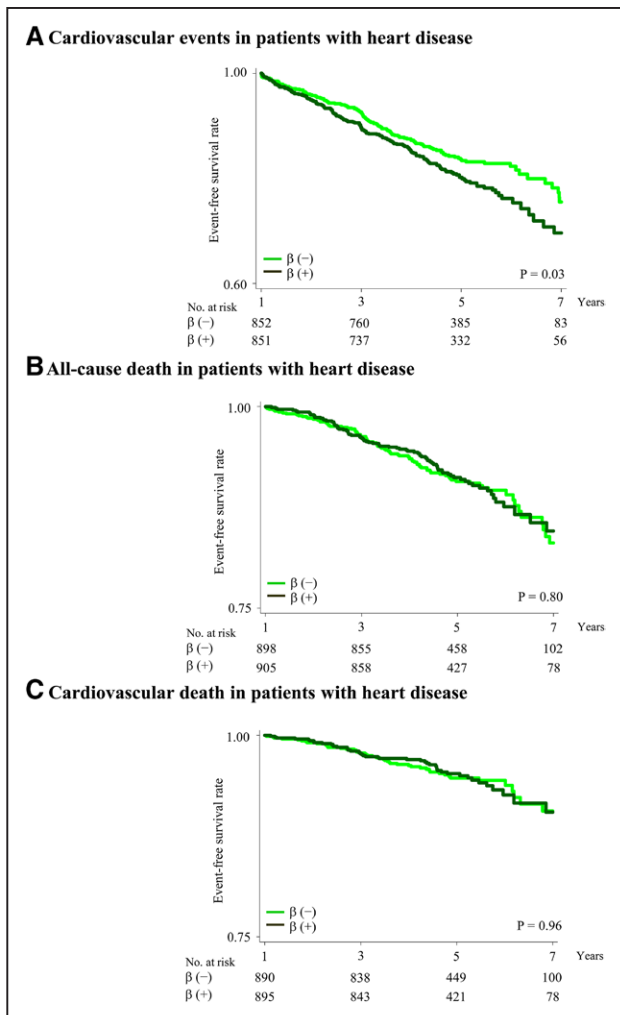


Figure 2. Kaplan–Meier survival curves for cardiovascular events and all-cause and cardiovascular deaths in patients on and not on β -blockers who had history of coronary heart disease or heart failure. Rates of freedom from cardiovascular events (A), all-cause death (B), and cardiovascular death (C). β indicates β -blockers.

is effective in diabetes mellitus patients. Thus, this study demonstrated that the use of β -blockers was associated with an increased risk for cardiovascular events, partly because of an increased occurrence of severe hypoglycemia. This risk may outweigh the benefit of decreasing adverse effects after the occurrence of severe hypoglycemia. However, several subgroup analyses could reveal the presence of other risks of β -blocker

use. In particular, in the standard therapy group, the incidence of severe hypoglycemia was not significantly different between patients on and those not on β -blockers, whereas the incidence of cardiovascular events was significantly higher in patients on β -blockers than in those not on β -blockers. Therefore, the association between β -blocker use and the increased risk for cardiovascular events might not be explained only by an increase of severe hypoglycemia. Although the exact reason remains unclear, possible explanations include increased risks for non-severe hypoglycemia, prolonged hypoglycemia, and weight gain because of β -blocker use, which can lead to increased risks of cardiovascular events.^{10,26} Further studies are needed to reveal the detailed mechanisms explaining the association between β -blocker use and the increased risk for cardiovascular events.

The present study revealed that the use of β -blockers in diabetes mellitus patients not only without heart disease but also with heart disease was associated with an increased risk for cardiovascular events. Many studies have demonstrated that β -blockers improve symptoms, reduce the risk of hospitalization, and prolong survival in patients with heart failure with reduced ejection fraction.^{27,28} In addition, β -blockers are recommended in many guidelines as the first-line therapy in patients with stable ischemic heart diseases.^{29–31} However, β -blockers have never been demonstrated to decrease mortality in patients without myocardial infarction or in those without heart failure associated with a reduction in the left ventricular systolic function. A recent study on diabetes mellitus patients with coronary heart disease suggested that the use of β -blockers was not effective in reducing all-cause mortality and cardiovascular events in those without myocardial infarction or heart failure with reduced ejection fraction.³² Several disadvantages of β -blockers may be equal to the benefits in diabetes mellitus patients with coronary heart disease.

This study has several limitations. First, although this study was large-scale, evidence-based, and with a robust subgroup representation, this was a post hoc analysis of the ACCORD trial. Patients in this study had glycated hemoglobin levels $\geq 7.5\%$ and any cardiovascular risks. Therefore, our findings may not be applicable to other diabetes mellitus patients. Second, because the number of events prior to 1 year was low enough that there were concerns regarding subject identification, we could only analyze data where early events had been trimmed to 1 year. However, our analyses revealed that the use of β -blockers was associated with an increased risk of cardiovascular events; using continuous follow-up data, we assumed that all events trimmed to 1 year occurred at 6 months. Third, using an alpha error of 5%, the powers for the

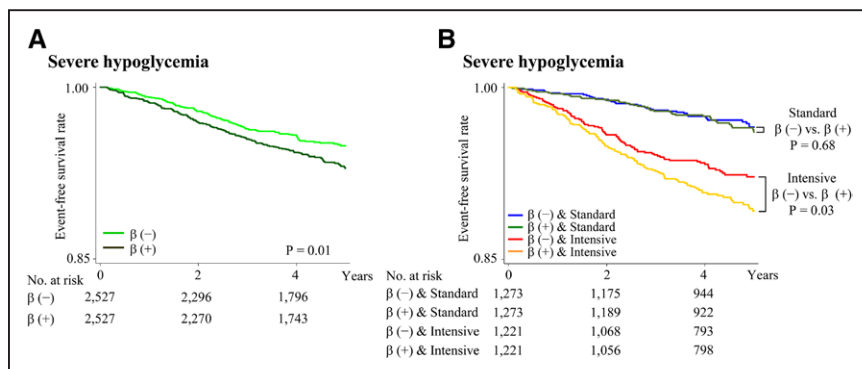


Figure 3. Kaplan–Meier survival curves for severe hypoglycemia in patients on and not on β -blockers. β indicates β -blockers; Intensive, intensive therapy; and Standard, standard therapy.

Table 3. HR for Severe Hypoglycemia in Type 2 Diabetes Mellitus Patients on β -Blockers Compared With Those Not on β -Blockers*

Event	Event Rate per Year (Events no./Total no.)		HR (95% CI) for β (+) (vs β [-])	P Value
	β -blockers (-)	β -blockers (+)		
Severe hypoglycemia				
All	1.1% (113/2527)	1.5% (152/2527)	1.36 (1.07–1.74)	0.01
Standard therapy	0.7% (37/1273)	0.7% (40/1273)	1.10 (0.70–1.71)	0.68
Intensive therapy	1.7% (83/1221)	2.3% (112/1221)	1.36 (1.03–1.81)	0.03

β indicates β -blockers; CI, confidence interval; and HR, hazard ratio.

*Data are presented as number or HR (95% CI).

analyses were calculated to be 70.5% for cardiovascular events, 8.1% for all-cause death, and 23.0% for cardiovascular death. The present study might not have sufficient subjects to avoid beta errors. Therefore, to verify our findings, more large-scale studies are needed. Fourth, this study used the propensity score to minimize the effects of the many confounders, which could be related to the indication of β -blockers. Additional adjustment with patient health status further minimized the confounding by indication. However, residual confounding such as follow-up periods and unknown variables could influence the results. The propensity score-matched analysis might not have fully alleviated these differences in the risk for cardiovascular events. Therefore, newly randomized controlled trials are required to evaluate whether the use of β -blockers in patients with diabetes mellitus shows beneficial or adverse effects.

Conclusions

Using the ACCORD trial data, this study demonstrated that the use of β -blockers was associated with an increased risk for cardiovascular events and severe hypoglycemia in the modern era. Furthermore, a similar relationship between the use of β -blockers and cardiovascular events was found in patients with heart disease. The indication of β -blockers may need to be reconsidered when this connection is elucidated through future higher-level evidence.

Perspectives

Recent studies have suggested that β -blockers may prevent or decrease the adverse effects after the occurrence of severe hypoglycemia, such as severe hypertension and hypokalemia, and may reduce severe hypoglycemia-associated cardiac arrhythmias and death. However, this does not necessarily mean that the use of β -blockers is effective in patients with diabetes mellitus because the use of β -blockers poses a potential risk for the occurrence of severe hypoglycemia. In the present study using the ACCORD trial data, various analyses in propensity score-matched patients revealed that the use of β -blockers was associated with an increased risk for cardiovascular events. Furthermore, a similar relationship between the use of β -blockers and cardiovascular events was found in patients not only without heart disease but also with heart disease. The incidence of severe hypoglycemia, which was confirmed by blood glucose levels <50 mg/dL, was significantly higher in those on β -blockers than in those not on β -blockers. Newly randomized controlled trials are required to evaluate whether the use of β -blockers in patients with diabetes mellitus shows beneficial or adverse effects.

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Novelty and Significance

What Is New?

- The use of β -blockers in diabetes mellitus patients was associated with an increased risk for cardiovascular events.
- A similar relationship between the use of β -blockers and cardiovascular events was found in diabetes mellitus patients with coronary heart disease or heart failure.
- The incidence of severe hypoglycemia, which required assistance from medical personnel and was confirmed by blood glucose levels <50 mg/dL, was significantly higher in diabetes mellitus patients on β -blockers than in those not on β -blockers.

What Is Relevant?

- The use of β -blockers in diabetes mellitus patients with hypertension may be associated with an increased risk for cardiovascular events.

Summary

This study demonstrated that the use of β -blockers was associated with an increased risk for cardiovascular events and severe hypoglycemia. Furthermore, a similar relationship between the use of β -blockers and cardiovascular events was found in patients with coronary heart disease or heart failure. The indication of β -blockers may need to be reconsidered when this connection is elucidated through future higher-level evidence.