Associations between β-blocker therapy and cardiovascular outcomes in patients with diabetes and established cardiovascular disease

Jay S. Shavadia, MD, [a,b,c] Yinggan Zheng, MA, Med, [c] Jennifer B. Green, MD, [a] Paul W. Armstrong, MD, [c] Cynthia M. Westerhout, PhD, [c] Darren K. McGuire, MD, MHSc, [d] Jan H. Cornel, MD, [e] Rury R. Holman, MB, ChB, [f] and Eric D. Peterson, MD, MPH [a]

Background The effects of β-blocker therapy in patients with type 2 diabetes (T2D) and established atherosclerotic cardiovascular disease (ASCVD) are unclear. We sought to evaluate associations between β-blocker use in T2D with ASCVD and cardiovascular (CV) outcomes.

Methods In patients with T2D and ASCVD enrolled in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), an inverse probability of treatment-weighted Cox proportional hazards model was used to examine the association between baseline β-blocker therapy (at randomization) and the primary CV composite (defined as CV death, non-fatal myocardial infarction [MI], non-fatal stroke, or hospitalization for unstable angina), including in subgroups with prior MI and heart failure (HF); other outcomes evaluated included individual components of the primary composite, hospitalization for HF, and severe hypoglycemic events.

Results Of the 14,671 patients randomized, 9322 (64%) were on a β-blocker at baseline; these patients were more likely to have prior MI or HF. Over a median 3.0 (25th, 75th percentile: 2.2, 3.6) years, the risk of the primary CV composite was significantly higher with baseline β-blocker use versus no β-blocker use (4.5 vs. 3.4 events/100-patient years, adjusted hazard ratio [HR] 1.17, 95% confidence interval [CI] 1.05–1.29); no significant interaction was noted for patients with versus without prior MI or HF. Baseline β-blocker use was not associated with risks for severe hypoglycemic events (HR 1.14, 95% CI 0.88–1.48).

Conclusions In this observational analysis of T2D and ASCVD, baseline β-blocker use was not associated with risks for severe hypoglycemia yet also was not associated with CV risk reduction over 3 years of follow-up, supporting a randomized examination of chronic β-blocker therapy in this patient population. (TECOS ClinicalTrials.gov number, NCT00790205). (Am Heart J 2019;218:92-9.)

From the [a]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, [b]Division of Cardiology, Department of Medicine, University of Saskatchewan, Saskatchewan, Canada, [c]Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada, [d]Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX, [e]Department of Cardiology, Northwest Clinics, Alkmaar, The Netherlands, and [f]Diabetes Trials Unit, University of Oxford, Oxford, UK.

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Reprint requests: Dr. Jay S. Shavadia, Royal University Hospital, University of Saskatchewan, 103 Hospital Drive, Saskatoon, SK S7N 0W8, Canada.
E-mail: jss372@usask.ca
0002-8703

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Type 2 diabetes (T2D) almost universally associates with clinical or subclinical accelerated atherosclerosis; consequently, of fundamental importance in patients with T2D is the optimization of secondary prevention pharmacotherapies. β-Blockers have historically been integral to cardiovascular (CV) risk modification, and while the evidence for their use is most robust in patients with prior myocardial infarction (MI)[1-4] and systolic heart failure (HF),[5-7] high-quality evidence also exists to support broader indications for β-blocker therapy in patients with T2D.[8]

However, with the evolution of more potent CV risk reduction therapies, equipoise has recently emerged on the role of β-blocker therapy,[9-12] especially in patients with T2D given their increased predisposition to hypoglycemia and hypoglycemia-related adverse CV events.[13,14] Moreover, novel glucose-lowering therapies have emerged and provide incremental and independent CV risk reduction benefits.[15,16] Therefore, while β-blocker therapy favorably modulated CV risk during an era with a limited array of risk reduction pharmacotherapies, its therapeutic role in present-day patients with T2D is unclear. To address this knowledge gap, we evaluated patients with T2D and established atherosclerotic cardiovascular disease (ASCVD) enrolled in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) to examine the association between β-blocker use at randomization (baseline) and within-trial CV outcomes.

Methods

Study design and patients

TECOS was a randomized, double-blind, multinational clinical trial of sitagliptin or placebo in addition to usual care in patients ≥50 years of age with T2D and established ASCVD (coronary artery disease, ischemic cerebrovascular disease, and/or atherosclerotic peripheral arterial disease) conducted between December 2008 and March 2015. Details of the TECOS trial design and its main outcomes have been previously published.[17,18] The protocol was approved by ethics committees associated with all TECOS sites, and all participants provided written informed consent for trial participation. Our study population consisted of all TECOS patients included in the intention-to-treat population, who were categorized into two groups based on β-blocker use at the time of randomization.

Study Outcome

The primary outcome was a composite of CV death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina. Secondary outcomes were individual components of the primary composite, hospitalization for HF, and severe hypoglycemia. An independent clinical events classification committee blinded to the study group assignments adjudicated all events of death, MI, stroke, and hospitalization for unstable angina or HF. The definitions for these adjudicated clinical outcomes are as outlined in the published Clinical Events Classification Committee Charter.[17] Severe hypoglycemic events were defined per protocol as episodes in which a participant was sufficiently disoriented or incapacitated by symptoms of hypoglycemia as to require third-party assistance, regardless of whether this assistance was actually provided.[19]

Statistical analysis

Baseline characteristics are reported for patients on and not on β-blocker therapy at the time of randomization. Categorical variables are reported as percentages, and continuous variables are reported as medians with 25th and 75th percentiles; chi-square and Wilcoxon rank-sum tests were used for the comparison of categorical and continuous variables, respectively.

To evaluate the unadjusted association between baseline β-blocker use and the primary composite and individual secondary outcomes of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for HF, and severe hypoglycemia, Kaplan–Meier estimates were generated and compared using the log-rank test. To account for differences in patient mix and for confounding by indication associated with baseline β-blocker use, inverse probability weighting (IPW) was used to adjust the relative association between baseline β-blocker use and the primary and secondary outcomes.[20] For these IPW analyses, the propensity model for receipt of β-blocker therapy was first developed using a multivariable logistic regression model with β-blocker therapy as the dependent variable and patient characteristics available at baseline (including prior medical history and medications at baseline [Supplemental Table I]) as the independent variables. The inverse of the predicted probabilities from the propensity model for β-blocker was then used as a weight in the Cox proportional hazards model, stratified by region, for the primary and secondary outcomes.

Since the role of β-blocker therapy has most robustly been demonstrated in patients with prior MI or systolic HF, interactions between β-blocker use and (i) prior MI and (ii) history of HF on the primary CV composite were additionally evaluated in those reporting at trial entry using similar methods described above.

The associations between β-blocker treatment and each outcome are reported as adjusted hazard ratios (HR) and their corresponding 95% confidence intervals (CIs), with *P* values; the unadjusted numbers of events are reported as events per 100-patient years of follow-up. All continuous variables with non-linear associations with respect to the primary and secondary outcomes were

modeled using linear splines. SAS PROC MI was used to impute missing baseline data, and these imputed datasets were used for all modeling procedures. All *P* values were two-sided, and a value of <.05 was considered significant for all analyses. All analyses were performed using SAS version 9.4 (SAS Institute, North Carolina).

Results

Of the 14,671 patients with T2D and established ASCVD enrolled into the trial, 9322 (64%) were on a β-blocker at baseline. Compared with patients not on a β-blocker, those on β-blocker therapy were more likely to have been enrolled from North America and Europe; they were also more likely to be male and White, and to have prior coronary heart disease (CHD), prior HF and atrial fibrillation (Table I); patients on a β-blocker were also more likely to be on other evidence-based secondary CV prevention therapies (Table II).

Baseline β-Blocker Use and Clinical Outcomes

Over a median follow-up duration of 3.0 years (25th, 75th percentiles: 2.2, 3.6), the unadjusted composite risk of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina was significantly higher with baseline β-blocker therapy compared with no β-blocker therapy (4.5 vs. 3.4 events/100-patient years, respectively; $P < .001$) (Figure 1). After adjusting for selection bias of β-blocker therapy, this adverse association remained statistically significant (adjusted HR 1.17, 95% CI 1.05–1.29, $P = .003$; Figure 2). Except for a higher adjusted hazard of non-fatal stroke associated with β-blocker use, no statistically significant differences were evident for the other secondary outcomes, including severe hypoglycemia (Figure 2).

Analyses stratified by prior MI and prior HF demonstrated no effect modification of the primary composite. In patients with and without a prior MI, the unadjusted event rates and IPW-adjusted risk for β-blocker use versus non-use were as follows: prior MI (5.1 vs. 4.6 events/100-patient years, adjusted HR 1.10, 95% CI 0.95–1.27); no prior MI (3.9 vs. 3.0 events/100-patient years, adjusted HR 1.20, 95% CI 1.04–1.37, *P*-interaction = 0.42). Similarly, in patients with and without prior HF, the unadjusted event rates and IPW-adjusted risk for β-blocker use versus non-use were as follows: prior HF (6.4 vs. 6.2 events/100-patient years, adjusted HR 1.13, 95% CI 0.94–1.37); no prior HF (0.74 vs. 0.72 events/100-patient years, adjusted HR 1.22, 95% CI 1.09–1.38, *P*-interaction = 0.50).

Discussion

The objective of this non-randomized post hoc analysis of TECOS data was to characterize the association between baseline β-blocker use and CV outcomes in patients with T2D and ASCVD. Our key findings include

Table I. Baseline characteristics categorized by baseline β-blocker use.

Variable	β-Blocker therapy at randomization: No (n = 5439)	Yes (n = 9322)	*P*
Age (years)*	65.4 (8.2)	65.5 (7.8)	.486
Female sex	1655 (30.9)	2642 (28.3)	.001
Race/Ethnicity			<.001
White	3226 (60.3)	6731 (72.2)	
Black	202 (3.8)	245 (2.6)	
Asian	1512 (28.3)	1753 (18.8)	
Other	409 (7.6)	593 (6.4)	
Hispanic or Latino	787 (14.7)	1011 (10.8)	<.001
Region			<.001
Asia Pacific and Other	2051 (38.3)	2514 (27.0)	
Eastern Europe	1117 (20.9)	2848 (30.6)	
Latin America	685 (12.8)	786 (8.4)	
North America	810 (15.1)	1784 (19.1)	
Western Europe	686 (12.8)	1390 (14.9)	
Duration of diabetes (years)†	11.7 (8.2)	11.5 (8.0)	.092
Qualifying HbA1c (%)	7.2 (0.5)	7.2 (0.5)	.699
Body mass index (kg/m^2)	29.3 (5.5)	30.7 (5.7)	<.001
Systolic blood pressure (mmHg)	135.4 (16.8)	134.8 (17.2)	.051
Diastolic blood pressure (mmHg)	77.7 (10.3)	76.9 (10.5)	<.001
eGFR (mL/min/1.73 m^2)‡	75.5 (21.2)	74.5 (21.1)	.004
eGFR category (mL/min/1.73 m^2)			.025
>60	3920 (73.3)	6639 (71.2)	
>30–60	1423 (26.6)	2674 (28.7)	
≤30	6 (0.1)	9 (0.1)	
Urinary albumin:creatinine§ (mg/g)	10.0 (3.5, 37.1)	11.3 (4.0, 35.0)	.068
Total cholesterol (mg/dL)	170.5 (46.9)	163.1 (44.2)	<.001
LDL cholesterol (mg/dL)	95.2 (56.9)	88.6 (58.2)	<.001
HDL cholesterol (mg/dL)	45.0 (13.1)	42.7 (12.1)	<.001
Triglycerides (mg/dL)	157.8 (92.9)	169.6 (103.3)	<.001
Coronary heart disease	2971 (55.5)	7892 (84.7)	<.001
Myocardial infarction	1521 (28.4)	4734 (50.8)	<.001
≥ 50% coronary stenosis	2026 (37.9)	5661 (60.7)	<.001
Prior PCI	1369 (26.0)	4345 (47.2)	<.001
CABG	962 (18.0)	2702 (29.0)	<.001
Cerebrovascular disease	1653 (30.9)	1935 (20.8)	<.001
Peripheral arterial disease	1356 (25.4)	1077 (11.6)	<.001
Congestive heart failure	584 (10.9)	2059 (22.1)	<.001
NYHA class 3 or higher	90 (15.4)	283 (13.7)	.307
Atrial fibrillation	297 (5.6%)	870 (9.3%)	<.001
Cigarette smoking			<.001
Current smoker	635 (11.9)	1043 (11.2)	
Prior smoker	1986 (37.1)	3858 (41.4)	
Never smoked	2728 (51.0)	4421 (47.4)	
Diabetic neuropathy	1388 (25.9)	1966 (21.1)	<.001

Results for continuous variables are mean (SD) or median (Q1, Q3), and categorical variables are n (%). CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.
*Age missing among patients in Lithuania as birthdate could not be provided.
†Duration = (year of randomization – year of diagnosis) + 1.
‡MDRD formula used to calculate eGFR. Site-reported values are presented.
§Urinary albumin:creatinine ratio data available for only 5148 patients.
SI conversion factors: urinary albumin:creatinine ratio (mg/g to g/mol), multiply by 0.1131; total cholesterol, LDL, and HDL (mg/dL to mmol/L), multiply by 0.0259; triglycerides (mg/dL to mmol/L), multiply by 0.0113.

Table II. Cardiovascular medications categorized by baseline β-blocker use.

Medication	β-Blocker therapy at randomization		
	No (n = 5439)	Yes (n = 9322)	*P*
Metformin	4418 (82.6)	7548 (81.0)	.015
Sulfonylurea	2481 (46.4)	4164 (44.7)	.045
Thiazolidinedione	160 (3.0)	236 (2.5)	.098
Insulin	1178 (22.0)	2230 (23.9)	.009
ACE inhibitor or ARB	4008 (74.9)	7547 (81.0)	<.001
Calcium channel blocker	1819 (34.0)	3142 (33.7)	.711
Diuretic	1891 (35.4)	4129 (44.3)	<.001
Thiazide diuretic	1205 (63.7)	2259 (54.7)	<.001
Aspirin	3896 (72.8)	7622 (81.8)	<.001
Other antiplatelet	1014 (19.0)	2173 (23.3)	<.001
Statin	3904 (73.0)	7815 (83.8)	<.001
Ezetimibe	242 (4.5)	519 (5.6)	.006
Nitrates	690 (12.9)	2123 (22.8)	<.001

Data are n (%). ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

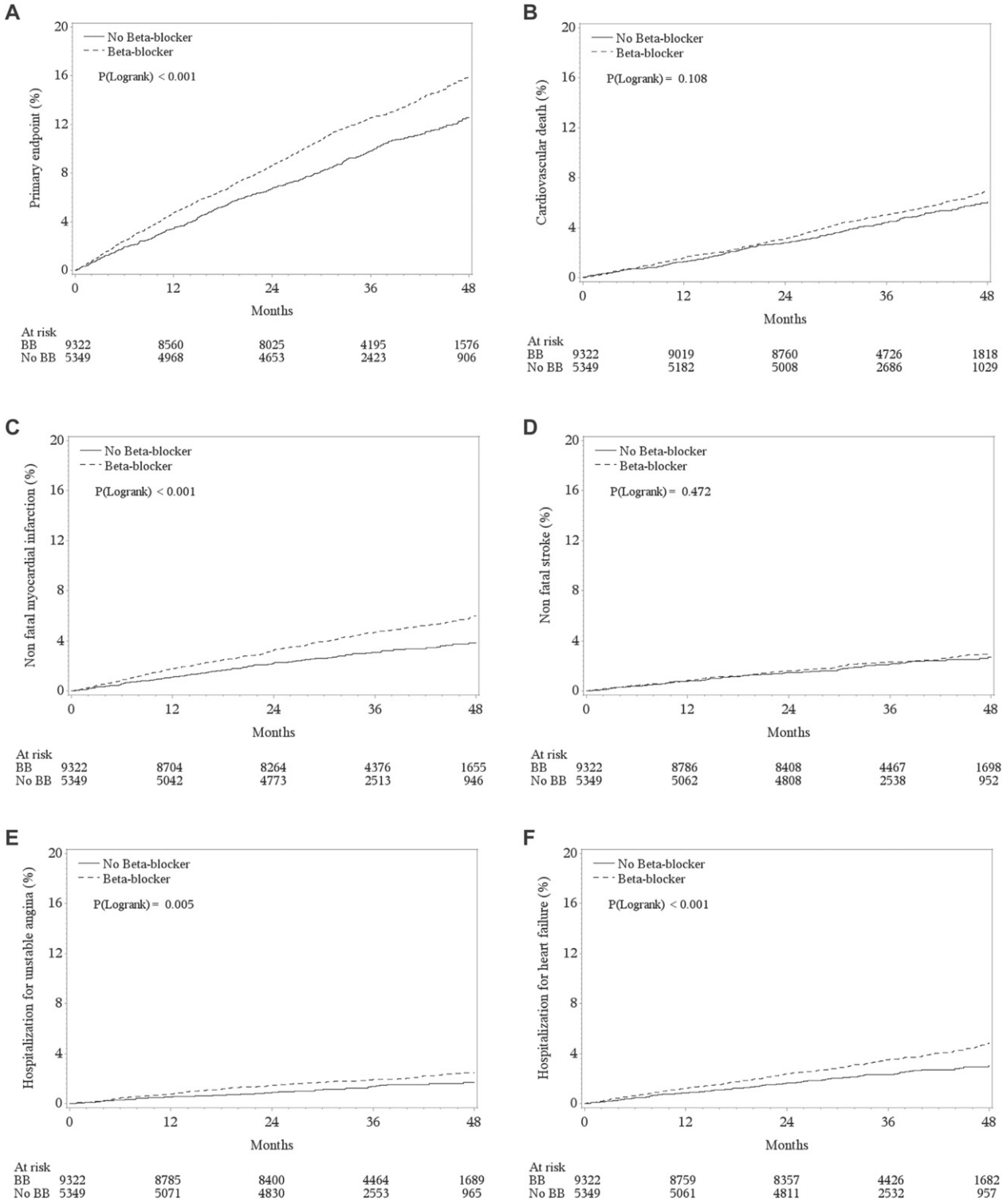
the following: First, in contemporary care, β-blockers appear to be frequently utilized (nearly 2 of every 3 patients) in patients with T2D and ASCVD; yet, compared with no β-blocker use, β-blocker therapy at baseline was associated with a similar or higher risk of CV events, individually and combined. Second, compared to patients without prior MI or HF, use of β-blockers by patients with prior MI or HF appeared to not modify the association with their use and the primary CV composite. Finally, β-blocker use was not associated with the occurrence of severe hypoglycemic events.

While β-blockers have historically been integral to long-term risk reduction, including in patients with T2D,[21] the majority of the trial evidence supporting treatment with β-blockers predated contemporary risk-reducing strategies. Therefore, the current use of β-blockers for risk reduction has increasingly come under question.[22,23] Of greater concern, however, are independent observational analyses suggesting CV harm associated with β-blocker use for secondary prevention in patients with T2D. In a post hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, a 46% (95% CI 24–72%) higher risk was noted for the composite of CV death, MI, stroke, or unstable angina associated with β-blocker use in patients with T2D, including in patient subgroups with coronary disease and HF[24]; patients with T2D on β-blocker therapy also had a significantly higher risk of CV death and severe hypoglycemia. Similarly, in another subgroup analysis from the Centers for Medicare and Medicaid Services, limited incremental benefit was associated with β-blocker use in post-MI patients ≥65 years of age adherent to angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptor blockers (ARB) and statins; in fact in this study, older post-MI patients with T2D adherent only to a β-blocker (and not using an ACE-I/ARB or statin) had markedly higher observed rates of all-cause mortality.[14] Aligned with these concerning observational associations, our results comparably demonstrate a higher adverse CV risk associated with β-blocker use for secondary prevention in patients with T2D.

The basis for these observed adverse CV risk associations with β-blocker use in patients with T2D is unclear and likely multifactorial, including confounding of analyses of non-randomized therapies, adverse treatment effects, and pathobiological underpinnings. First, patients on a β-blocker in this study had higher rates of established coronary heart disease (including prior MI) and HF at baseline; additionally, they were also more likely at randomization to be on other evidence-based secondary prevention therapies. Despite statistical adjustment to account for this bias and cofounding by indication for β-blocker use, it is possible that patients on β-blocker therapy have complex unmeasured comorbidities that not only predispose them to a higher risk of adverse long-term CV events but also represent a sicker patient phenotype at a higher risk for significant β-blocker-specific adverse events (such as high-grade conduction abnormalities, orthostasis, or hypoglycemia). Incorporating non-CV comorbidities, including indices of frailty as well as physiological and cognitive function may further help elucidate whether being on a β-blocker merely represents a marker of adverse CV risk or truly associates with β-blocker-related adverse cardiac events, particularly in subgroups most susceptible to the side effects of β-blocker therapy, such as the elderly.

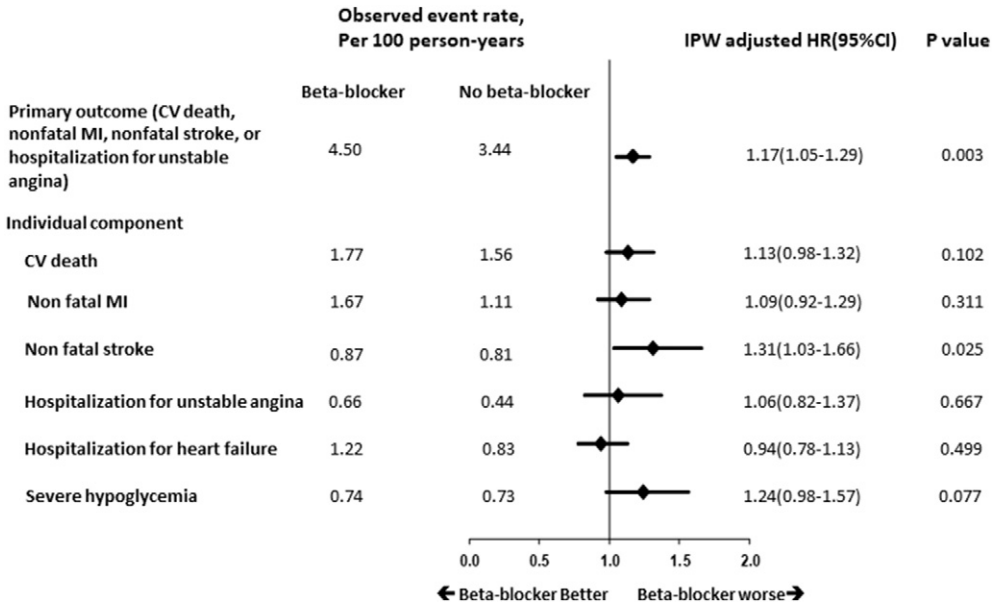
Second, some β-blockers have been well recognized to induce insulin resistance and the development of an atherogenic metabolic profile. While our analysis did not profile temporal patient-level metabolic changes, several large β-blocker hypertension trials have previously consistently demonstrated significant increases over time in serum low-density lipoproteins, triglycerides, and glucose related to β-blocker therapy[25-29]; moreover, the use of a β-blocker appeared as an independent risk factor for the development of diabetes.[30] Additionally, in patients with diabetes in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, the random assignment to atenolol compared with losartan led to significantly worse CV outcomes.[31] Furthermore, the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ACSOT-BLPA) trial also demonstrated a significantly increased risk of CV mortality over its 5.5-year follow-up with atenolol compared with amlodipine.[32] Several large well-conducted meta-analyses have also noted similar increases in the risk of all-cause mortality, CV mortality, and stroke associated with β-blocker use compared with other antihypertensive therapies.[33-35] Therefore, sufficient high-quality data

Figure 1



Association between baseline β-blocker use and primary composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (MI), non-fatal stroke or hospitalization for unstable angina (*A*), CV death (*B*), non-fatal MI (*C*), non-fatal stroke (*D*), hospitalization for unstable angina (*E*), and hospitalization for heart failure (*F*).

Figure 2



Comparative observed event rates and adjusted hazard ratios (HRs) for the primary composite and secondary outcomes.

exist to support the adverse modification of CV risk in patients on β-blocker therapy. There is no reason to believe that patients enrolled in the TECOS study on β-blocker therapy at baseline would have a different susceptibility to adverse CV outcomes from that noted in the β-blocker hypertension trials; in fact, the patients evaluated in our study had established ASCVD on a background of T2D and therefore were at even higher risk of developing adverse metabolic and clinical outcomes associated with β-blocker therapy.

Finally, the spectrum of hypoglycemia forms—severe symptomatic, severe asymptomatic, and non-severe—have all been proposed to be linked in a causal pathway between β-blockade and adverse CV outcomes.[36,37] In our analyses, while no association between β-blocker use and severe symptomatic hypoglycemia was noted, other less severe and asymptomatic hypoglycemic episodes and their duration were not captured. Therefore, in our analysis, the relationship between β-blocker therapy and hypoglycemia-related adverse CV events may still be underestimated.

Limitations

Beyond the observational nature of our analyses, we would like to acknowledge several other possible limitations. First, patients in our analyses were categorized based on their use of β-blockers at the time of randomization. We intentionally did not account for changes in β-blocker use over the study period (discontinuations, new initiation, dose adjustments), as the clinical reasons for changes during follow-up could have biased our interpretation of treatment effect. Second, differential adverse glycometabolic risk exists among β-blockers as a class; in this dataset, information on which β-blocker patients were on at randomization was unavailable, and therefore associations between the use of glycometabolic-friendly/unfriendly β-blockers and clinical outcomes could not be ascertained. Third, data on ejection fraction were also not available for the entire cohort, and therefore not included in our subgroup analysis. Additionally, we lack data related to the timing since last MI, which would have provided an interesting perspective on the relationship between β-blocker use and CV outcomes in post-MI survivors with longer-term T2D, as the greatest benefit of β-blocker therapy in patients with coronary artery disease has traditionally been greatest within the first 3 years. Finally, as in all clinical trials, patients with T2D enrolled in the TECOS study may not be completely representative of the patient population seen in day-to-day clinical practice, thereby limiting the generalizability of our results.

Conclusions

β-Blockers appear to be utilized frequently in patients with T2D and ASCVD. Our comparative safety and effectiveness analysis of chronic β-blocker use in this high-risk population demonstrated no association between use of β-blockers and increased risk of severe hypoglycemic events, nor a decrease in risk of major

adverse CV events, including in patients with prior MI or HF. These results are consistent with other observational analyses and, with several novel drug classes now demonstrating incremental CV benefit in patients with T2D, support the need for a randomized evaluation of β-blockers' benefits and safety in patients with T2D and ASCVD.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.09.013.

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