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Outcomes of "Diabetes-Friendly" versus "Diabetes-Unfriendly" Beta-blockers in Older Nursing Home Residents with Diabetes after Acute Myocardial Infarction

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STRUCTURED ABSTRACT

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Aims—Some beta-blockers may worsen glycemic control, which could be important for frail older nursing home (NH) residents with type 2 diabetes mellitus (T2D). There is little evidence that prescribers consider the glycometabolic properties of beta-blockers or that such properties affect clinical outcomes. We assessed whether NH residents with T2D preferentially received "T2D-friendly" (versus "T2D-unfriendly") beta-blockers after acute myocardial infarction (AMI), and evaluated their comparative effects.

Materials and Methods—This new-user retrospective cohort study of NH residents with AMI from May 2007 to March 2010 used national data from the Minimum Data Set and Medicare. T2D-friendly beta-blockers were those hypothesized to increase peripheral glucose uptake through vasodilation: carvedilol, nebivolol, and labetalol. Primary outcomes were hypoglycemia and hyperglycemia hospitalizations in the 90 days after AMI. Secondary outcomes were functional decline, death, all-cause rehospitalization and fracture hospitalization. We compared outcomes using binomial and multinomial logistic regression models after propensity score matching.

Results—Twenty-nine percent of 2,855 NH residents with T2D initiated a T2D-friendly beta-blocker versus 24% of 6,098 without T2D (p-value<0.001). For primary outcomes among residents with T2D, T2D-friendly versus T2D-unfriendly beta-blockers were associated with a reduction in hospitalized hyperglycemia (OR=0.45, 95% confidence interval [CI] 0.21–0.97), but unassociated with hypoglycemia (OR=2.05, CI 0.82–5.10). For secondary outcomes, T2D-friendly beta-blockers were associated with increased rehospitalization (OR=1.26, CI 1.01–1.57), but not death (OR=1.06, CI, 0.85–1.32), functional decline (OR=0.91, CI, 0.70–1.19), or fracture (OR=1.69, CI 0.40–7.08).

Conclusions—In older NH residents with T2D, T2D-friendly beta-blocker use was associated with decreased hospitalization for hyperglycemia, but increased all-cause rehospitalization.

Keywords

Beta-blockers; myocardial infarction; diabetes; aging; nursing home

INTRODUCTION

Clinicians must consider co-morbidities such as type 2 diabetes mellitus (T2D) when prescribing guideline-recommended medications for secondary prevention like beta-blockers after acute myocardial infarction (AMI).[1,2] Previous studies have demonstrated that non-vasodilating beta-blockers, such as metoprolol and atenolol, are associated with increases in hemoglobin A1c (HbA1c), mean plasma glucose, body weight, and triglycerides.[3,4] In contrast, vasodilating beta-blockers such as carvedilol, nebivolol, and labetalol, have been associated with reduced HbA1c levels.[3,4] These vasodilating beta-blockers, so-called "T2D-friendly" beta-blockers, may be a more optimal choice for patients with T2D, though little data are available on actual clinical outcomes.[5,6] Previous studies in younger populations have demonstrated that utilization of T2D-friendly beta-blockers among patients with T2D is low.[7]

No evidence currently exists on whether clinicians preferentially prescribe T2D-friendly beta-blockers to frail, older adults with T2D after AMI, or whether the choice of beta-blocker affects clinically relevant outcomes for these individuals. The evidence gap is

especially pronounced for the oldest and frailest individuals in the U.S. population: nursing home (NH) residents. These questions are important because NH residents have a high burden of AMI and T2D[8,9], and are particularly sensitive to the adverse effects of medications.[8–10] Age-related changes in pharmacokinetics, such as decreased hepatic and renal drug clearance, could lead to prolonged medication half-lives and increased plasma concentrations.[11,12] The increased availability of drug in the body could potentiate both the desired and unintentional effects of beta-blockers.[8] Moreover, the complex effects of beta-blockers may yield different outcomes in vulnerable older adults compared with younger, healthier adults in which these and most other drugs are typically studied. On one hand, T2D-friendly beta-blockers may reduce plasma glucose levels and could therefore reduce the risk of hyperglycemia. On the other hand, their effects on peripheral vasodilation may increase the risk of orthostatic hypotension and subsequently increase the risk of falls and fractures.[13] Each of these consequences could be detrimental to older adults, specifically frail NH residents. Yet, clinical trials have excluded frail older adults, creating a gap in the evidence base.[15] This gap, as well as the vulnerability of older NH residents, warrants a comparison of T2D-friendly beta-blockers to T2D-unfriendly beta-blockers.[2]

Therefore, the objectives of this study were (1) to determine if older NH residents with T2D preferentially receive T2D-friendly beta-blockers after AMI, and (2) to evaluate the potential benefits and harms of T2D-friendly beta-blockers in older NH residents after AMI. We hypothesized that NH residents with T2D would be preferentially prescribed T2D-friendly beta-blockers. We also hypothesized that although T2D-friendly beta-blockers would result in fewer hospitalizations for hyperglycemia, they would increase the risk of fractures and declines in physical functioning.

MATERIALS AND METHODS

Data Sources and Study Population

The data sources and study population for our study have been previously described.[8,9,16] Using national Medicare data from 2007–2010, we linked denominator (eligibility) information, Part A inpatient hospital claims, Part D prescription drug claims, and Minimum Data Set (MDS) 2.0 data for all fee-for-service beneficiaries who were eligible for inclusion. The MDS is a comprehensive, federally-mandated clinical assessment instrument that captures information on cognitive, physical, and psychosocial functioning; active clinical diagnoses and health conditions; and treatments and services.[17,18] NHs must evaluate each resident at least quarterly as a requirement of the Centers for Medicare and Medicaid Services (CMS).[17,18] We utilized the Online Survey Certification and Reporting (OSCAR) data for NH facility-level information, including NH characteristics, staffing level information, quality of care deficiencies, and aggregate resident characteristics..[19,20] We employed a previously validated residential history file algorithm to track the timing and location of health service use.[21]

The study cohort and measures of covariates have also been previously described.[8,9,16] In brief, we conducted a retrospective inception cohort study of a national cohort of long-stay nursing home residents without a history of AMI who were hospitalized for AMI, had not previously taken beta-blockers for at least four months prior to AMI, and were re-admitted

to U.S. nursing homes directly following hospital discharge between May 1, 2007 and March 31, 2010 (Supplementary Figure S1).[9] Our final sample consisted of 15,720 NH residents admitted to 8,349 NHs.

Measures

For our first objective, our outcome was new use of a T2D-friendly beta-blocker versus a T2D-unfriendly beta-blocker in the immediate post-hospital period. As in prior studies using the cohort, we identified oral beta-blockers in Medicare Part D prescription drug claims, which contain a complete history of drug dispensings for this population, including date dispensed, dose, route, and days' supply.[8,9] T2D-friendly beta-blockers theoretically have neutral or beneficial effects on blood glucose levels and other metabolic parameters by increasing peripheral uptake of glucose through peripheral vasodilation.[4] As defined in prior work[7], T2D-friendly beta-blockers included all beta-blockers with vasodilating properties from any mechanism, including alpha-1 blockade, calcium channel blockade, or nitric oxide pathways (carvedilol, nebivolol, and labetalol).[3,22,23] We defined beta-blockers without vasodilating properties as T2D-unfriendly (atenolol, bisoprolol, and metoprolol). These T2D-unfriendly beta-blockers may cause more compensatory peripheral vasoconstriction by reducing cardiac output.[7] Many of them have been associated with increased insulin resistance and more atherogenic lipid profiles.[3,7,23,24] The primary predictor for our first objective was the presence of a diagnosis of T2D prior to or on the day of the AMI, which we ascertained from Part A hospital claims.

For our second objective, we examined the use of T2D-friendly versus T2D-unfriendly beta-blockers in the immediate post-hospital period as the exposure, and we examined outcomes within 90 days of the index hospital discharge. Primary outcomes were hypoglycemia and hyperglycemia hospitalizations. Secondary outcomes were significant functional decline, all-cause rehospitalization, all-cause death, and fracture hospitalizations. The definitions for significant functional decline, all-cause rehospitalization, and all-cause death in this cohort have been previously described.[8] Briefly, we defined functional decline as a gain of 3 points on a validated 28-point MDS scale of independence in activities of daily living (ADLs) between the pre-hospital baseline and the first available assessment following hospitalization.[25] A 3 point increase corresponds to a major loss of independence in 1 ADL or incremental losses in 2 or more ADLs. Consistent with prior studies, we used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes in the principal or secondary position on a Part A inpatient hospital claim to identify hypoglycemia (ICD-9-CM codes 251.0X, 251.1X, or 251.2X; algorithm positive predictive value [PPV], 89%)[26], hyperglycemia (ICD-9-CM codes 250.02, 250.03, 250.1, 250.2, 250.3; PPV unavailable), and fractures [hip fracture (ICD-9-CM 820), radius/ulna fracture (ICD-9-CM 813), humerus fracture (ICD-9-CM 812), hand (ICD-9-CM 814–817), tibia/fibula (ICD-9-CM 823), ankle (ICD-9-CM 824), or skull/face (ICD-9-CM 800, 804); PPV ranges from ~30% to 98% depending on fracture site].[27–31] We measured all outcomes within 90 days of the nursing home readmission after the index AMI hospital discharge.[8]

Analytic Approach

We used the chi-square test to initially test whether overall and T2D-friendly beta-blocker use differed for individuals with T2D versus without T2D. Among NH residents who received a beta-blocker, we then evaluated univariable associations between potential predictors and T2D-friendly versus unfriendly beta-blocker initiation using logistic regression models to estimate odds ratios (OR) with 95% confidence intervals (CIs). To test our hypothesis that certain individual and facility factors were independently associated with T2D-friendly versus T2D-unfriendly beta-blocker prescribing for residents after AMI, we used a multivariable logistic regression model.[32] Because residents are clustered within NH facilities, we used multilevel modeling and included random intercepts for facilities in the models to ensure more accurate standard errors.[33] We modeled patient and facility characteristics as fixed effects.[33]

Among patients with T2D who were treated with a beta-blocker upon returning to the NH after AMI, we used propensity score-based methods to evaluate the relationship between type of beta-blocker exposure and outcomes. Following the observational study analogue of an intention-to-treat exposure definition, we defined subjects as T2D-friendly beta-blocker users or T2D-unfriendly beta-blocker users throughout the follow-up period based on their exposure in the immediate post-AMI period. We estimated the propensity score (here, the probability of receiving a T2D-friendly versus T2D-unfriendly beta-blocker) via a flexible logistic regression model with 103 covariates. Covariates included sociodemographic characteristics, chronic medical conditions, baseline medication use, hospitalization history, baseline functional and cognitive status, geriatric syndromes, symptoms, characteristics of the AMI hospitalization, and nursing home characteristics. We then trimmed the areas of non-overlap in the propensity score distribution between the treatment groups and applied a 1:1 greedy 5-to-1 digit matching algorithm without replacement, such that each user of a T2D-friendly beta-blocker was matched with a user of a T2D-unfriendly beta-blocker and the distribution of characteristics in the T2D-unfriendly group mimicked that of the T2D-friendly group.[34] We evaluated the quality of resulting matches by comparing standardized differences between groups for each covariate in our model, and by using t-tests to assess differences in the distribution of propensity scores.[34–36]

Within the propensity-score matched cohort, the associations between T2D-friendly versus T2D-unfriendly beta-blockers and all-cause mortality or functional decline were estimated using binomial logistic regression models. To estimate the association between T2D-friendly vs T2D-unfriendly beta-blockers and all-cause rehospitalization while accounting for the competing risk of death, we used multinomial logistic regression. We also used multinomial logistic regression that accounted for the competing risk of death to examine significant declines in physical functioning, as well as hospitalizations for hypoglycemia, hyperglycemia, and fractures. At the end of the 90-day follow-up, participants were classified as alive without an outcome event, having had an outcome event, or having died without evidence of an outcome event. Finally, to better convey the effect of T2D-friendly versus T2D-unfriendly beta-blockers on the absolute measurement scale, we calculated the absolute risk difference and numbers needed to treat or harm. Confidence intervals for the numbers needed to treat or harm are presented in the format recommended by Altman.[37]

Data were analyzed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC) and Stata, version 14.0 (Stata Corp., College Station, TX), software. The study protocol was approved by the Institutional Review Board of Brown University, the University of California San Francisco, and the San Francisco VA Health Care System, who waived the need for informed consent.

RESULTS

Study Population

Among 15,720 residents readmitted to the NH after AMI, 4,797 (30.5%) had T2D. The overall population had a mean (standard deviation, SD) age of 83 (8) years and 4,580 (29%) were male. Residents with T2D (vs. without T2D) were younger, more likely to be male, and more likely to have heart failure (HF), asthma, and unstable angina (Table 1). Those with T2D were taking more medications overall, and were more likely to receive antiplatelet agents, warfarin, and statin medications.

Beta-blocker Use

Overall, 56.9% of residents (n=8,953/15,720) initiated a beta-blocker after AMI upon NH readmission, including 59.5% of those with T2D and 55.8% of those without T2D (chi-square p<0.001). Among residents with T2D, the most commonly used beta-blockers were metoprolol (66%), carvedilol (27%), and atenolol (5%). Similarly, among residents without T2D, the most commonly used beta-blockers were also metoprolol (71%), carvedilol (23%), and atenolol (4%). Carvedilol accounted for 97.1% of T2D-friendly beta-blocker use, labetalol for 1.7%, and nebivolol for 1.1%. Metoprolol accounted for 92% of T2D-unfriendly beta-blocker use, atenolol for 7%, and bisoprolol for 1%.

Among residents who initiated a beta-blocker (n=8,953), 29% (n=815/2855) of residents with T2D initiated a T2D-friendly beta-blocker versus 24% (n=1460/6098) of those without T2D (chi-square p<0.001; Supplementary Tables S1 and S2). After covariate adjustment, use of T2D-friendly beta-blockers was greater in residents with T2D (adjusted OR (adjOR) 1.14, 95% CI 1.00–1.29). By far the strongest predictor of T2D-friendly beta-blocker use was a diagnosis of HF at baseline (adjOR=2.84, 95%CI 2.50–3.22). Use of T2D-friendly beta-blockers was less likely among older patients (adjOR=0.73 for age ≥95 compared to age 65 to <75, 95%CI 0.56–0.97), patients with diagnosis of atrial fibrillation at baseline (adjOR=0.87, 95% CI 0.76–1.00) and females (adjOR=0.86, 95%CI 0.76–0.98) (Supplementary Tables S1 and S2). T2D-friendly beta-blocker use also varied geographically, with greater use in the Midwest, South, and West (Supplementary Table S1).

Outcomes

Propensity score matching yielded a cohort of 1,530 patients with T2D, with 765 new T2D-friendly beta-blocker users and 765 new T2D-unfriendly beta-blocker users (Table 2). The mean age was 80 years. The distribution of propensity scores was nearly identical between the matched groups (mean [SD], 0.34 [0.13] in both T2D-friendly beta-blocker users and T2D-unfriendly users, P=0.97)(Supplementary Figure S2). All 103 covariates, including NH

characteristics, were well-balanced between treatment groups and had standardized mean differences of 0.09 or less (Supplementary Tables S3 and S4).[35]

Within 90 days after hospital discharge, 21 (1.4%) of 1,530 subjects were hospitalized for hypoglycemia, 32 (2.1%) were hospitalized for hyperglycemia, 271 (17.7%) experienced functional decline, 158 (10.3%) died, 476 (31.1%) were rehospitalized for any cause, and less than 11 were hospitalized for fracture

T2D-friendly versus T2D-unfriendly beta-blocker use was not observed to impact hospitalizations for hypoglycemia (OR 2.05, 95% CI 0.82–5.10)(Table 3). T2D-friendly beta-blocker users did have a significantly lower likelihood of hospitalization for hyperglycemia compared to T2D-unfriendly beta-blocker users (OR 0.45, 95% CI 0.21–0.97). The number needed to treat to prevent one hyperglycemia hospitalization was 64 (95% CI 34–715).

T2D-friendly beta-blocker users did not have a significantly different likelihood of functional decline than T2D-unfriendly beta-blocker users (OR 0.91, 95% CI 0.70–1.19). T2D-friendly versus T2D-unfriendly beta-blocker use was not associated with death (OR 1.11, 95% CI, 0.81–1.56) or fracture hospitalization (OR 1.69, 95% CI 0.40–7.08) within 90 days after AMI, but was associated with an increase in all-cause rehospitalization (OR 1.26, 95% CI 1.01–1.57), with a number needed to harm of 21 (95% CI 11–477) to cause one additional rehospitalization.

DISCUSSION

In our large national cohort of older NH residents who recently had an AMI, we found that having T2D was associated with a modest increase in the use of T2D-friendly beta-blockers, even after adjustment for HF and other potential determinants of prescribing. Use of T2D-friendly versus T2D-unfriendly beta-blockers (effectively carvedilol versus metoprolol due to the overwhelming use of these two medications) was associated with a decrease in hospitalized hyperglycemia and an increase in all-cause rehospitalization, but no marked differences in death, functional decline, hypoglycemia, or fracture. The observed association with all-cause rehospitalization may be attributable to residual confounding by missing information on ejection fraction, but this suspicion is not empirically testable in the data. Therefore, the potential trade-off between a reduction in hospitalized hyperglycemia (number needed to *treat* 64, 95%CI 34–715) and a larger magnitude increase in all-cause rehospitalization (number needed to *harm* 21, 95% CI 11–5,000) suggests that while T2D-friendly beta-blockers might optimize glycemic outcomes, this benefit may come at the cost of more all-cause hospitalizations. Given the remaining uncertainty about confounding of the rehospitalization effect, and since few NH residents or caregivers would accept a higher risk of worse overall outcomes to reduce the risk of a single cause of hospitalization, T2D-friendly beta-blockers should not yet be widely recommended over T2D-unfriendly beta-blockers after AMI until additional corroborative evidence is available for vulnerable older adults.

Basic science studies have examined the glycometabolic effects of individual beta-blockers. Those studies suggest that vasodilating beta-blockers may be "T2D-friendly" by increasing peripheral glucose uptake via peripheral vasodilation.[38] A more limited number of studies have examined the glycometabolic effects of individual beta-blockers in clinical practice. Most notably, Arnold et al. used data from the TRIUMPH study to examine the use of T2D-friendly beta-blockers in a general adult population after AMI.[7] While the use of T2D-friendly beta-blockers was low overall, their study found that T2D-friendly beta-blockers were more likely to be prescribed to patients with T2D. The primary outcome in Arnold and colleagues' study was worsening glycemic control, defined as an increase in HbA1c, among those with T2D at 6 months after AMI. They observed that T2D-friendly beta-blockers were associated with a lower risk of worsened glycemic control, though this association was not statistically significant.[7] Although our study did not use HbA1c as a measure, the reduction in hospitalizations for hyperglycemia suggests that those taking T2D-friendly beta-blockers had better glycemic control than those taking T2D-unfriendly beta-blockers. This should be weighed against the potential harms of T2D-friendly beta-blockers (i.e., carvedilol), such as orthostatic hypotension and subsequent falls among older adults, which have been demonstrated in small prior studies.[39,40]

We cannot be certain why there was differential prescribing of T2D-friendly versus T2D-unfriendly beta-blockers for certain patient groups. One factor that could account for differences in prescribing is more involvement of cardiologists in the care of certain patient subgroups (e.g., younger patients and those with more intensive care unit use) since cardiologists are more likely to be aware of the differences between T2D-friendly and T2D-unfriendly beta-blockers than non-cardiologists, and thus, may be more likely to prescribe T2D-friendly beta-blockers. Another important factor could be that certain patient subgroups are more likely to have HF with preserved ejection fraction (HFpEF) than HF with reduced ejection fraction (HFrEF), which could decrease the likelihood of receiving a T2D-friendly beta-blocker since carvedilol is especially prescribed to individuals with HFrEF. To the extent that the distinction between HFrEF and HFpEF is not captured by our data, the distribution of HFpEF across the subgroups could partly explain the observed patterns. Geographic variability in T2D-friendly beta-blocker prescribing is most likely due to local clinical practices, providers' attitudes, preferences of patients, and the differential density of geriatric and cardiology medical expertise by region.

Pharmacotherapy for older adults in the NH setting requires special consideration, as this population is typically excluded from clinical trials and can be especially sensitive to medications and their adverse effects.[2] Our study adds to the existing literature by demonstrating that although T2D-friendly beta-blockers may help optimize glycemic outcomes after AMI among older NH residents with T2D, who represent nearly a third of the NH population with AMI, this benefit may come at the cost of a higher risk of all-cause rehospitalization. On the relative effect scale, the estimate for all-cause rehospitalization appears modest (OR, 1.26) while the estimate for hyperglycemia appears to be relatively large (OR, 0.45). On the absolute effect scale, the estimate for rehospitalization (risk difference, 4.84%; NNH, 21) is actually three times larger in magnitude than the estimate for hyperglycemia (risk difference, −1.57%; NNT 64). In other words, on average, for every 1 hyperglycemia hospitalization prevented, there will be 3 additional all-cause

rehospitalizations incurred. It is therefore important to note that at the population level, the data suggest that systematically recommending T2D-friendly beta-blockers would lead to a net *increase* in harm among frail, older adults, even before accounting for other potential detrimental effects that were unmeasured in the current study.

This study has several limitations. As with any observational study, we cannot rule out the possibility of confounding.[41,42] In particular, carvedilol—the most common T2D-friendly beta-blocker—is prescribed more often for individuals with HF and reduced ejection fraction. Although we adjusted for measures of HF, residual confounding may still remain. However, the measured baseline covariates, including HF, were well-balanced between T2D-friendly and T2D-unfriendly beta-blocker users after matching. The balance achieved for HF may be attributable to the fact that metoprolol, a T2D-unfriendly beta-blocker, and carvedilol, a T2D-friendly beta-blocker, are both effective options for AMI and HF treatment.[43] Nonetheless, we do not have information on ejection fraction or HF severity, which impact the choice of beta-blocker and the risk of adverse health outcomes. If such confounding exists, one might expect an elevated risk of adverse health outcomes (e.g., rehospitalizations) among T2D-friendly beta-blocker users since those drugs (e.g., carvedilol) are more likely to be used in individuals with HF. However, while ejection and HF severity might confound the relationship between T2D-friendly versus T2D-unfriendly beta-blocker use and all-cause hospitalization, these covariates are unlikely to significantly confound the relationship with hyperglycemia and hypoglycemia hospitalizations.

Another limitation is that we were unable to differentiate ST-elevation myocardial infarction (STEMI) from non-STI-elevation myocardial infarction (NSTEMI) during the index AMI hospitalization, which may have influenced prescribing and induced residual confounding. Although current AMI guidelines for STEMI[1] and NSTEMI[44] are quite similar regarding beta-blocker therapy recommendations, this was not the case with earlier guidelines in place during the study period.[45,46] The 2007 STEMI guidelines provide detailed guidance for the use of metoprolol, without specific recommendations for other beta-blockers.[46] The 2007 guidelines for NSTEMI emphasize the use of metoprolol, atenolol, and carvedilol.[45] Another notable limitation of our study cohort was the lack of information on HbA1c to help diagnose T2D or adjust for confounding by glycemic control, which future studies using Veterans Affairs or other data should aim to address. However, we did adjust for proxies for glycemic control, including pre-AMI history of hypoglycemia hospitalization, hyperglycemia hospitalization, and diabetes medication use. Information about T2D was obtained from Part A hospital claims, which may be a less sensitive measure than HbA1c. Our study had limited statistical power to detect small differences for rare outcomes, though larger studies are unlikely to be conducted. Due to the nature of our data, we were unable to conduct as-treated analyses to account for beta-blocker discontinuation, to conduct analyses of beta-blocker dose to assess dose-response relationships with outcomes, or to examine whether T2D-friendly and T2D-unfriendly beta-blockers were prescribed at equipotent doses. However, prior work in this study population suggests that NH residents who started beta-blockers after AMI typically continued them until 90 days of follow-up and as long as discontinuations were non-differential by treatment group, estimates are likely attenuated toward the null. Finally, our study focused on the immediate post-AMI period, which may affect the generalizability of our results to other periods in residents' stay in the NH if

unique characteristics of the post-AMI period modify the relationship between beta-blocker use and outcomes. Other limitations of the study cohort have been previously described.[8,9,16]

In conclusion, in a large national cohort of older NH residents with recent hospitalization for AMI, initiation of T2D-friendly beta-blockers was unassociated with death, functional decline, hypoglycemic events, or fracture events compared to initiation of T2D-unfriendly beta-blockers. Although residual confounding remains a plausible explanation and more corroborative data would be helpful, especially on other outcomes like orthostatic hypotension and falls, T2D-friendly beta-blockers were associated with a reduction in hospitalization for hyperglycemia and an increase in all-cause rehospitalization. Given that in addition to all-cause rehospitalization, T2D-friendly beta-blockers may also be associated with other detrimental effects that were unmeasured in the current study, they should not be preferentially prescribed despite their potential advantage for glycemic control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Selected Characteristics[†] of Study Nursing Home Residents by Type 2 Diabetes Status (N=15,720)

Characteristic	T2D n=4,797	No T2D n= 10,923
Age in years, mean (SD)	81 (8)	84 (8)
Male, n (%)	1,472 (31)	3,108 (29)
Race/ethnicity		
White, non-Hispanic, n (%)	3,664 (76)	9,165 (84)
Black, non-Hispanic, n (%)	721 (15)	1,193 (11)
Hispanic, n (%)	305 (6)	372 (3)
Other, n (%)	107 (2)	193 (2)
Nursing home length of stay in days, median (IQR)	534 (130–1218)	591 (174–1303)
Primary or secondary diagnoses (prior year)		
Atrial fibrillation, n (%)	1,132 (24)	2,675 (25)
Heart failure, n (%)	2,472 (52)	5,113 (47)
Angina pectoris, n (%)	628 (13)	1,400 (13)
Unstable angina, n (%)	599 (13)	1,035 (10)
Asthma, n (%)	91 (2)	147 (1)
Chronic obstructive pulmonary disease, n (%)	1,280 (27)	2,880 (26)
CHESS score (overall health stability)[‡]		
No instability, n (%)	2,595 (54)	6,241 (57)
Minimal instability, n (%)	1,393 (29)	3,131 (29)
Low instability, n (%)	681 (14)	1,260 (12)
Moderate to very high instability, n (%)	128 (3)	291 (3)
Cognitive performance		
Cognitively intact, n (%)	992 (21)	1,749 (16)
Mild dementia, n (%)	1,622 (34)	3,469 (32)
Moderate to severe dementia, n (%)	2,183 (46)	5,705 (52)
Activities of daily living status		
Independent to limited supervision, n (%)	1,252 (26)	3,052 (28)
Extensive assistance required, n (%)	2,203 (46)	4,993 (46)
Dependent or totally dependent, n (%)	1,342 (28)	2,878 (26)
Statin medications, n (%)	1,794 (37)	2,734 (25)
Antiplatelet medications, n (%)	947 (20)	1,671 (15)
Warfarin, n (%)	643 (13)	1,287 (12)
Number of Medications (last MDS assessment), mean (SD)	13 (5)	12 (5)
AMI index hospitalization characteristics		
Length of stay in days, median (IQR)	6 (4–9)	6 (4–9)
One or more days in CCU or ICU, n (%)	2,795 (58)	6,263 (57)
Initial Post-AMI Type of Care		
Skilled Nursing Facility, n (%)	3,406 (71)	7,877 (72)
Long-Term Care, n (%)	1,391 (29)	3,046 (28)

T2D, type 2 diabetes; SD, standard deviation; IQR, interquartile range; MDS, minimum data set; AMI, acute myocardial infarction; CCU, coronary care unit; ICU, intensive care unit.

[†]All characteristics measured before the acute myocardial infarction unless otherwise noted.

[‡]The Changes in Health, End-Stage Disease, Signs, and Symptoms Scale was designed to identify individuals at risk of serious decline. It creates a 6- point scale from 0 = not at all unstable to 5 = highly unstable, with higher levels predictive of adverse outcomes such as mortality, hospitalization, pain, caregiver stress, and poor self-rated health.

Table 2

Characteristics of “T2D-Friendly” and “T2D-unfriendly” Beta-blocker Users in Older Nursing Home Residents with Type 2 Diabetes after Acute Myocardial Infarction, Before and After Propensity Score Matching

Characteristics	n (%)[†]			
	Before Matching		After Matching	
	T2D- Friendly (n=815)	T2D-Unfriendly (n=2,040)	T2D-Friendly (n=765)	T2D-Unfriendly (n=765)
Age, mean (SD), y	80.0 (7.8)	81.0 (7.9)	80.2 (7.7)	79.9 (8.1)
Female sex	543 (66.6)	1,424 (69.8)	518 (67.7)	522 (68.2)
Race				
White, non-Hispanic	611 (75.0)	1,553 (76.1)	577 (75.4)	578 (75.6)
Black, non-Hispanic	127 (15.6)	317 (15.5)	123 (16.1)	119 (15.6)
Hispanic	61 (7.5)	119 (5.8)	49 (6.4)	50 (6.5)
AI/AN/API	16 (2.0)	51 (2.5)	16 (2.1)	18 (2.4)
Chronic conditions				
HF	582 (71.4)	963 (47.2)	533 (69.7)	532 (69.5)
COPD	205 (25.2)	508 (24.9)	188 (24.6)	208 (27.2)
Depression	98 (12.0)	279 (13.7)	95 (12.4)	90 (11.8)
Dyslipidemia	226 (27.7)	501 (24.6)	202 (26.4)	217 (28.4)
Hypertension	591 (72.5)	1,420 (69.6)	550 (71.9)	552 (72.2)
Atrial fibrillation	187 (22.9)	461 (22.6)	172 (22.5)	181 (23.7)
Tachyarrhythmias	50 (6.1)	106 (5.2)	44 (5.8)	48 (6.3)
T2D-related hospitalizations				
Hypoglycemia	65 (8.0)	179 (8.8)	60 (7.8)	58 (7.6)
Hyperglycemia	96 (11.8)	253 (12.4)	92 (12.0)	80 (10.5)
Elixhauser comorbidity score, median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	4 (3–5)
ADL status before hospitalization[‡]				
Independent to limited assistance required	235 (28.8)	519 (25.4)	219 (28.6)	223 (29.2)
Extensive assistance required	352 (43.2)	950 (46.6)	329 (43.0)	360 (47.1)
Extensive dependency	228 (28.0)	571 (28.0)	217 (28.4)	182 (23.8)
Cognitive status before hospitalization[§]				
Intact or borderline intact	187 (22.9)	415 (20.3)	172 (22.5)	184 (24.1)
Mild to moderate dementia	308 (37.8)	672 (32.9)	286 (37.4)	280 (36.6)
Moderately severe to very severe dementia	320 (39.3)	953 (46.7)	307 (40.1)	301 (39.4)
CHESS score before hospitalization, mean (SD)[¶]	0.7 (0.8)	0.6 (0.8)	0.7 (0.8)	0.7 (0.8)
Geriatric symptoms before hospitalization				
Dizziness, vertigo, or syncope	<11	30 (1.5)	<11	<11

Characteristics	n (%)†			
	Before Matching		After Matching	
	T2D- Friendly (n=815)	T2D-Unfriendly (n=2,040)	T2D-Friendly (n=765)	T2D-Unfriendly (n=765)
Falls	148 (18.2)	421 (20.6)	142 (18.6)	167 (21.8)
Dyspnea	70 (8.6)	143 (7.0)	60 (7.8)	67 (8.8)
No. of medications before hospitalization, median (IQR)	13 (10–17)	13 (10–16)	13 (10–16)	13 (10–16)
Medication use before hospitalization				
Statins	300 (36.8)	760 (37.3)	279 (36.5)	283 (37.0)
Antiplatelets	153 (18.8)	385 (18.9)	145 (19.0)	142 (18.6)
Warfarin	97 (11.9)	232 (11.4)	88 (11.5)	98 (12.8)
Atypical antipsychotics	84 (10.3)	250 (12.3)	82 (10.7)	82 (10.7)
Hypnotics	86 (10.6)	205 (9.9)	79 (10.3)	87 (11.4)
Metformin	118 (14.5)	359 (17.6)	111 (14.5)	107 (14.0)
Sulfonylureas	181 (22.2)	498 (24.4)	171 (22.4)	167 (21.8)
Rapid-acting insulin	119 (14.6)	295 (14.5)	109 (14.3)	114 (14.9)
Short-acting insulin	190 (23.3)	515 (25.3)	186 (24.3)	182 (23.8)
Long-acting insulin	158 (19.4)	417 (20.4)	151 (19.7)	149 (19.5)
Any T2D medication	467 (57.3)	1,256 (61.6)	445 (58.2)	448 (58.6)
Length of hospital stay for AMI, median (IQR), d	6 (4–9)	6 (4–9)	6 (4–9)	6 (4–9)
No. of days in ICU or CCU				
None	263 (32.3)	787 (38.6)	254 (33.2)	271 (35.4)
1–2	223 (27.4)	580 (28.4)	213 (27.8)	214 (28.0)
≥3	329 (40.4)	673 (33.0)	298 (39.0)	280 (36.6)
Nursing home care pathway after hospitalization				
Skilled nursing facility benefit	634 (77.8)	1,501 (73.6)	593 (77.5)	584 (76.3)
Long-term care	181 (22.2)	539 (26.4)	172 (22.5)	181 (23.7)

Abbreviations: ADL, activities of daily living; AMI, acute myocardial infarction; CCU, cardiac care unit; CHESS, Changes in Health, End-Stage Disease, Signs, and Symptoms; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; T2D, type 2 diabetes; AI/AN/API, American Indian/Alaskan Native/Asian Pacific Islander; HF, heart failure.

† Percentages have been rounded and may not total 100.

‡ Measured using the Morris 28-point scale of Independence in ADLs and categorized as 0 to 14 (independent to limited assistance required), 15 to 19 (extensive assistance required), and 20 or higher (extensive dependency).

§ Measured by the Cognitive Performance Scale and trichotomized as 0 to 1 (Intact to borderline intact), 2 to 3 (mild to moderate dementia), and 4 to 6 (moderately severe to very severe dementia).

¶ Scores range from 0 to 5, with higher scores indicating greater health instability.

Cells containing a value of less than 11 and any risk (percentage) that could be used in combination with other reported information to obtain a cell of less than 11 have been suppressed to comply with the Centers for Medicare and Medicaid Services Cell Size Suppression Policy.

Table 3

Effect of “T2D-friendly” versus “T2D-unfriendly” Beta-blockers on Outcomes in Older Nursing Home Residents with Type 2 Diabetes after Acute Myocardial Infarction

	Risk (%)			
Outcome	**T2D-friendly Beta-blocker Users (n=765)**	**T2D-unfriendly Beta-blocker Users (n=765)**	**OR (95%CI)**	**Absolute Risk Difference, % (95% CLs)[†]**
Hypoglycemia	>1.44	<1.44	2.05 (0.82–5.10)	0.92 (−0.25, 2.08)
Hyperglycemia	<1.44	>1.44	0.45 (0.21–0.97)	−1.57 (−3.00, −0.14)
Functional decline	16.99	18.43	0.91 (0.70–1.19)	−1.44 (−5.26, 2.39)
Death	10.85	9.80	1.11 (0.81–1.56)	1.05 (−2.00, 4.09)
Rehospitalization	33.33	28.50	1.26 (1.01–1.57)	4.84 (0.21, 9.46)
Fracture	<1.44	<1.44	1.69 (0.40–7.08)	0.26 (−0.46, 0.98)

Abbreviations: T2D, type 2 diabetes; CI, confidence interval; OR, odds ratio; CLs, confidence limits.

[†]Positive values of the absolute risk difference indicate that individuals who received T2D-friendly beta-blockers had higher risks of the outcome than taking T2D-unfriendly beta-blockers; negative numbers indicate T2D-friendly beta-blocker users had a lower risk than T2D-unfriendly beta-blocker users.

[‡]Calculated as 1/(risk among beta-blockers nonusers – risk among beta-blocker users).

Cells containing a value of less than 11 and any risk (percentage) that could be used in combination with other reported information to obtain a cell of less than 11 have been suppressed to comply with the Centers for Medicare and Medicaid Services Cell Size Suppression Policy.