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ORIGINAL INVESTIGATIONS

Association of Beta-Blocker Therapy With Cardiovascular Outcomes in Patients With Stable Ischemic Heart Disease

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ABSTRACT

BACKGROUND Previous studies have failed to show a cardioprotective benefit of beta-blockers in patients with stable coronary artery disease (CAD).

OBJECTIVES This study sought to determine the association between beta-blockers and cardiovascular events in patients with stable CAD using a new user design.

METHODS All patients aged >66 years undergoing elective coronary angiography in Ontario, Canada, from 2009 to 2019 with diagnosed obstructive CAD were included. Exclusion criteria included heart failure or a recent myocardial infarction, as well as having a beta-blocker prescription claim in the previous year. Beta-blocker use was defined as having at least 1 beta-blocker prescription claim in the 90 days preceding or after the index coronary angiography. The main outcome was a composite of all-cause mortality and hospitalization for heart failure or myocardial infarction. Inverse probability of treatment weighting using the propensity score was used to account for confounding.

RESULTS This study included 28,039 patients (mean age: 73.0 ± 5.6 years; 66.2% male), and 12,695 of those (45.3%) were newly prescribed beta-blockers. The 5-year risks of the primary outcome were 14.3% in the beta-blocker group and 16.1% in the no beta-blocker group (absolute risk reduction: −1.8%; 95% CI: −2.8 to −0.8; HR: 0.92; 95% CI: 0.86-0.98; $P = 0.006$). This result was driven by reductions in myocardial infarction hospitalization (cause-specific HR: 0.87; 95% CI: 0.77-0.99; $P = 0.031$), whereas no differences were observed in all-cause death or heart failure hospitalization.

CONCLUSIONS In patients with angiographically documented stable CAD without heart failure or a recent myocardial infarction, beta-blockers were associated with a small but significant reduction in cardiovascular events at 5 years.
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ABBREVIATIONS AND ACRONYMS

csHR = cause-specific HR

NNT = number needed to treat

Beta-blockers have been incorporated in the management of coronary artery disease since early clinical trials showed substantial reductions in all-cause and cardiovascular mortality compared with placebo in patients with an acute myocardial infarction.[1,2] For those with stable coronary artery disease, however, there is a paucity of randomized trial data to show whether beta-blockers are associated with any cardiovascular prognostic benefits apart from angina relief.[3] The REACH (Reduction of Atherothrombosis for Continued Health) study was an international registry including 7,198 matched patients with stable coronary artery disease without prior myocardial infarction and showed no significant reductions in cardiovascular events associated with the use of beta-blockers.[4] Some other registry studies or post hoc analyses of clinical trials have also failed to demonstrate a benefit of beta-blockers in patients with stable coronary artery disease.[5-7] Importantly, these studies included patients with prevalent instead of incident new use of beta-blockers, which prevented estimation of the beta-blocker benefits from the time of initial prescription and might have biased the results.[8,9] Most studies also included participants more than a decade ago, using various definitions of coronary artery disease not necessarily supported by imaging tests, and were frequently underpowered for the subgroup of patients without prior myocardial infarction or heart failure.[4-7]

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Despite the lack of good evidence, beta-blockers are currently used in >70% of the patients with stable coronary artery disease, which perhaps is a reflection of the uncertainty of the existing data and persistence of treatment habits.[10,11] In this contemporary population-based cohort study from Ontario, Canada, we studied the association between recently initiated beta-blocker therapy and long-term cardiovascular events in patients with angiographically confirmed stable coronary artery disease without heart failure or recent myocardial infarction.

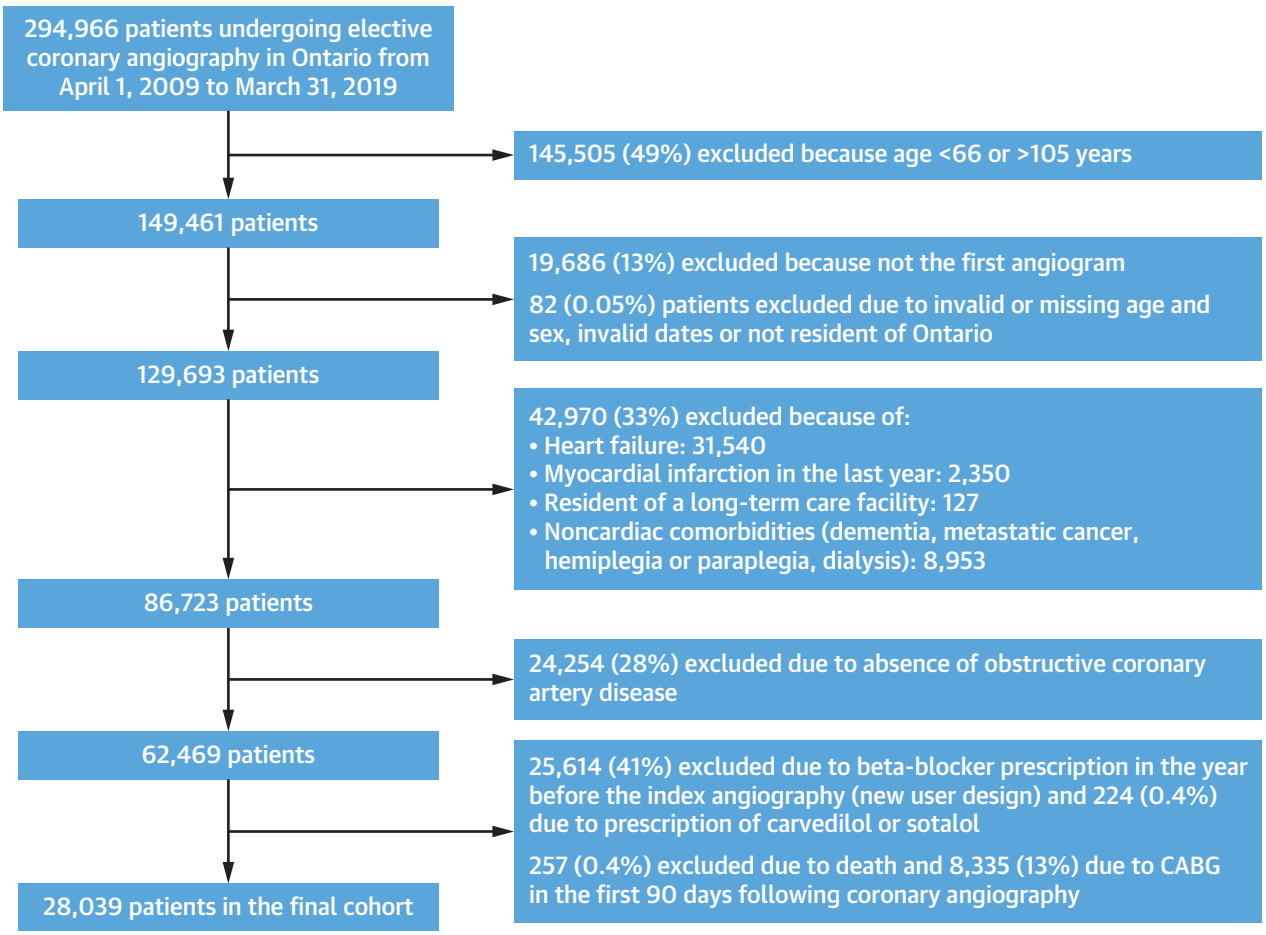
METHODS

A population-based retrospective cohort study was conducted using linked clinical, administrative, and laboratory data from Ontario, Canada.

DATA SOURCES. Demographics, clinical, and cardiac test data, including identification of the index coronary angiography, were extracted from the CorHealth Ontario Cardiac Registry. This clinical registry prospectively collects information on all patients undergoing an invasive cardiac procedure in Ontario since 2008 and currently comprises >1.3 million records collected by trained abstractors.[12,13] To obtain information on the use of beta-blockers and other drugs, we linked the CorHealth Ontario Registry to the Ontario Drug Benefit database, which includes claims (dispensed prescription) for medications received under the Ontario Drug Benefit program since 1990 for those 65 years of age and older.[14] Additionally, we linked registry records to the following administrative databases: the Ontario Health Insurance Plan Physician Claims Database, the Canadian Institute for Health Information—Discharge Abstract Database, and the National Ambulatory Care Reporting System to capture additional comorbidities and cardiovascular outcomes; the Registered Persons Database and the Office of the Registrar General's Vital Statistics—Death database to ascertain additional demographics, vital status, and cause of death; the Ontario Laboratories Information System to identify laboratory test results; the Immigration, Refugees, and Citizenship Canada's Permanent Resident Database to identify immigrant status; the Toronto Community Health Profiles and Statistics Canada Census to ascertain neighborhood income and to create a geographically based marginalization index (the Ontario Marginalization Index).[15,16] All data sets were linked using unique encoded identifiers and analyzed at ICES (formerly known as the Institute for Clinical Evaluative Sciences). The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act and did not require review by a Research Ethics Board.

STUDY POPULATION. The study cohort was composed of adults between 66 and 105 years of age with obstructive coronary artery disease defined as >50% in the left main coronary artery or >70% in any major epicardial arteries, diagnosed during an elective coronary angiogram in Ontario between April 1, 2009, and March 31, 2019. If a patient had multiple coronary angiograms during the study period, only the first was considered. We excluded patients with heart failure or left ventricular ejection fraction <35% and myocardial infarction in the year prior to the index angiogram because current guidelines recommend that these patients should be treated with beta-blockers for cardiovascular risk reduction.[17,18] Patients who underwent coronary artery bypass graft during the 90 days following the coronary angiography were also excluded (**Figure 1**), as were patients with severe noncardiac comorbidities (dementia, metastatic cancer, hemi- or paraplegia, or

FIGURE 1 Flow Diagram Illustrating the Cohort Formation



A total of 294,966 patients underwent an elective coronary angiography in Ontario from April 1, 2009, to March 31, 2019, for coronary artery disease evaluation. Sequential exclusion criteria are shown on the right and further discussed in the text. The final study population was composed of 28,039 patients, from which 12,695 (45.3%) were in the beta-blocker treatment group and 15,344 (54.7%) were in the no beta-blocker group. CABG = coronary artery bypass graft.

renal replacement therapy) or those in a long-term care facility because they may have limited life expectancy and might not benefit from beta-blocker therapy.

EXPOSURE ASSESSMENT. We conducted a new user design study by defining beta-blocker use as having at least 1 beta-blocker prescription claim in the 90 days preceding or after the index coronary angiography and by excluding those who had beta-blocker use in the year before the coronary angiography (Supplemental Figure 1). The following orally administered beta-blockers were included: acebutolol, atenolol, bisoprolol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, pindolol, propranolol, timolol. Patients receiving carvedilol or sotalol were excluded, because in Ontario these beta-blockers are primarily used in the treatment of heart failure or atrial fibrillation, respectively.

OUTCOMES. The outcome assessment window started 90 days after the index coronary angiography. The main outcome was the first occurrence of the composite of all-cause mortality and hospitalization for heart failure or myocardial infarction. Secondary outcomes included the individual components of the primary outcome, as well as cardiovascular death, subsequent coronary revascularization, hospitalization for stroke, emergency department visit or hospitalization for unstable angina, and hospitalization for hypoglycemic events (safety outcome). Patients were followed until March 31, 2020, for all the main

TABLE 1 Baseline Characteristics Before and After Propensity Score Weighting, Comparing Patients Treated With and Without Beta-Blockers

	Original Cohort (N = 28,039)			IPTW Cohort		
	Beta-Blockers (n = 12,695)	No Beta-Blockers (n = 15,344)	*P* Value	Beta-Blockers	No Beta-Blockers	Standardized Difference
Age, y	72.8 ± 5.5	73.3 ± 5.7	<0.001	73.0 ± 8.3	73.0 ± 7.6	0.001
Male	8,456 (66.6)	10,106 (65.9)	<0.001	66.4	66.3	0.002
Immigrant status			<0.001			
Recent immigrant (≤5 y)	363 (2.9)	269 (1.8)		2.3	2.3	0.001
Nonrecent immigrant	1,185 (9.3)	1,250 (8.1)		8.9	8.9	0.003
Canadian born or long-term resident	11,147 (87.8)	13,825 (90.1)		88.8	88.9	0.002
Income quintile			0.672			
1	2,151 (16.9)	2,618 (17.1)		16.9	16.8	0.002
2	2,507 (19.7)	2,958 (19.3)		19.6	19.6	0.001
3	2,625 (20.7)	3,174 (20.7)		20.8	20.8	0.001
4	2,593 (20.4)	3,094 (20.2)		20.4	20.4	0.001
5	2,786 (21.9)	3,449 (22.5)		22.3	22.4	0.003
Ontario Marginalization Index	3.1 ± 0.8	3.1 ± 0.8	0.105	3.1 ± 1.1	3.1 ± 1.0	0.002
Rural dwelling	1,627 (12.8)	1,886 (12.3)	0.411	11.9	11.9	0.001
Diabetes	4,370 (34.4)	5,492 (35.8)	0.017	35.2	35.2	0.000
Hypertension	9,404 (74.1)	11,969 (78.0)	<0.001	76.7	76.5	0.005
COPD	2,460 (19.4)	4,010 (26.1)	<0.001	22.9	23.0	0.004
Asthma	1,607 (12.7)	2,871 (18.7)	<0.001	16.1	16.1	0.001
Dyslipidemia	5,932 (46.7)	7,816 (50.9)	<0.001	49.4	49.3	0.001
Atrial fibrillation	713 (5.6)	1,235 (8.0)	<0.001	7.3	7.0	0.009
Previous stroke	180 (1.4)	245 (1.6)	0.230	1.6	1.6	0.002
Peripheral artery disease	717 (5.6)	1,052 (6.9)	<0.001	6.4	6.4	0.002
Chronic kidney disease	640 (5.0)	922 (6.0)	<0.001	5.7	5.6	0.002
Cancer	623 (4.9)	768 (5.0)	0.707	5.0	5.0	0.002
LVEF			<0.001			
35%-49%	1,444 (11.4)	1,388 (9.0)		10.2	10.1	0.003
≥50%	10,246 (80.7)	12,867 (83.9)		82.3	82.4	0.003
Unknown	1,005 (7.9)	1,089 (7.1)		7.5	7.5	0.001
Smoking			0.007			
Never	6,869 (54.1)	8,034 (52.4)		53.1	53.2	0.001
Current	1,294 (10.2)	1,613 (10.5)		10.4	10.4	0.001
Former	4,177 (32.9)	5,192 (33.8)		33.5	33.5	0.001
Unknown	355 (2.8%)	505 (3.3%)		3.0%	3.0	0.003
CCS class			<0.001			
No chest pain	2,239 (17.6)	3,981 (25.9)		22.5	22.3	0.005
1	2,017 (15.9)	2,731 (17.8)		17.0	17.0	0.002
2	5,025 (39.6)	5,694 (37.1)		38.5	38.5	0.001
3	2,898 (22.8)	2,504 (16.3)		19.3	19.3	0.001
4	430 (3.4)	342 (2.2)		2.8	2.8	0.003
Ischemic stress test			<0.001			
High risk	6,441 (50.7)	6,299 (41.1)		45.3	45.6	0.006
Low risk	3,564 (28.1)	4,851 (31.6)		30.0	30.0	0.001
Unknown	2,690 (21.2)	4,194 (27.3)		24.7	24.4	0.008
Previous coronary revascularization	818 (6.4)	1,963 (12.8)	<0.001	10.1	9.9	0.006
PCI in the first 90 days of follow-up	6,585 (51.9)	6,257 (40.8)	<0.001	45.6	45.9	0.006
Previous myocardial infarction (>1 y ago)	111 (0.9)	384 (2.5)	<0.001	1.9	1.8	0.013
Multivessel disease[a]	2,833 (22.3)	2,668 (17.4)	<0.001	19.6	19.3	0.009
Left main disease	653 (5.1)	716 (4.7)	0.065	4.8	4.8	0.000
Glomerular filtration rate, mL/min/1.73 m^2	72.4 ± 15.7	72.1 ± 16.0	0.122	71.9 ± 23.7	72.3 ± 21.6	0.026
HbA_{1c}, %	6.3 ± 1.0	6.3 ± 1.0	0.759	6.3 ± 1.5	6.3 ± 1.4	0.005
Total cholesterol, mg/dL	173.4 ± 44.6	166.4 ± 42.8	<0.001	169.8 ± 65.0	169.0 ± 58.8	0.019
LDL-C, mg/dL	95.7 ± 38.1	88.8 ± 36.4	<0.001	92.1 ± 55.5	91.5 ± 50.3	0.018
HDL-C, mg/dL	50.1 ± 14.0	51.4 ± 14.6	<0.001	50.5 ± 21.1	51.0 ± 19.7	0.032

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TABLE 1 Continued

	Original Cohort (N = 28,039)			IPTW Cohort		
	Beta-Blockers (n = 12,695)	No Beta-Blockers (n = 15,344)	*P* Value	Beta-Blockers	No Beta-Blockers	Standardized Difference
Triglycerides, mg/dL	139.1 ± 73.9	132.2 ± 70.1	<0.001	136.8 ± 107.8	133.9 ± 96.1	0.040
Insulin	847 (6.7)	1,117 (7.3)	0.047	7.0	7.0	0.001
ACE inhibitor	5,958 (46.9)	6,432 (41.9)	<0.001	44.3	44.2	0.002
ARBs	3,619 (28.5)	4,664 (30.4)	0.001	29.8	29.8	0.001
Statins	11,563 (91.1)	12,912 (84.2)	<0.001	86.9	87.3	0.010
Other antilipemic drugs	1,295 (10.2)	1,823 (11.9)	<0.001	11.3	11.3	0.000

Values are mean ± standard deviation, n (%), or %. Percentage of missing observations: income quintile (0.3%); Ontario Marginalization Index (0.9%); rural dwelling (0.2%); CCS class (0.6%), glomerular filtration rate (11.1%); HbA_{1c} (34.9%); total cholesterol (22.9%); LDL-C (23.6%); HDL-C (23.1%), triglycerides (23.0%). [a]Defined as 3-vessel coronary disease or 2-vessel disease with involvement of the proximal left anterior descending coronary artery.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; IPTW = inverse probability of treatment weighting; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

study outcomes. For the analysis of cardiovascular death, patients were followed until December 31, 2018, because cause of death was not ascertained beyond this point.

STATISTICAL ANALYSIS. Baseline demographic and clinical characteristics were compared between treatment groups using chi-square and Student's *t*-tests for categorical and continuous variables, respectively. A propensity score for the receipt of beta-blockers (vs not receiving beta-blockers) was estimated using logistic regression. Demographics, comorbidities, medications, and cardiovascular and laboratory test results were included in the propensity score model (Supplemental Figure 2). The inverse probability of treatment weighting method was then used to create a weighted cohort, using average treatment effect weights generated from the propensity score. Weighted standardized differences of <0.1 were taken to indicate an adequate balance between the baseline variables of the beta-blocker and no beta-blocker groups in the weighted cohort.[19] The association between beta-blockers and outcomes was estimated using cause-specific HRs, derived from Cox proportional hazards regression with a robust variance estimator.[20] Death was considered a competing risk for the nonfatal outcomes and graphical depictions of the cumulative incidence functions of the main outcomes were created from the inverse probability of treatment-weighted cohort. The Aalen-Johansen estimator of the cumulative incidence function allows one to estimate the incidence of an event over time, while taking competing risks into account.[21] The proportional hazards assumption was tested and satisfied for all outcomes, using product terms between beta-blocker treatment and a logarithmic function of time. Absolute risk reductions and number needed to treat (NNT) were calculated from the cumulative incidence estimates, with 95% CIs generated in 1,000 bootstrap resamples. Treatment-interaction terms were used to perform subgroup analyses in the weighted cohort.

ADDITIONAL AND SENSITIVITY ANALYSES. Additional analyses were performed to further evaluate the association between beta-blockers and the primary outcome. First, we used a bootstrap variance estimator with 1,000 bootstrap resamples as an alternative way to calculate the CI of the HR of the primary outcome.[22] Second, we used alternative time windows to ascertain beta-blocker use: 30 days before and after the coronary angiography and 180 days before and after the coronary angiography. We also modeled beta-blocker treatment as a time-varying exposure during the first year of follow-up, starting either at the time of the index coronary angiography or 90 days before the coronary angiography (in accordance with the starting time of our main exposure window). A multivariable Cox regression with the same predictors as in the propensity score was used in the time-varying analyses. Third, to assess possible residual confounders, we studied the association between beta-blockers and 2 negative control outcomes: hospitalization for urinary tract infection and hospitalization for external injuries. Fourth, we repeated the main analyses using stabilized weights in the same analytical population and stabilized weights after removing subjects with propensity scores <0.10 or >0.90.[23] We also repeated the main analyses using 1:1 greedy matching without replacement on the logit of the propensity score (caliper width of 0.2 standard deviations). Fifth, to assess the impact of the definition of heart failure in our results, we repeated the main analyses excluding: 1) patients with left ventricular ejection fraction <50%; 2) patients with a diagnosis of heart failure (regardless of

their left ventricular ejection fraction); and 3) patients with either a diagnosis of heart failure or left ventricular ejection fraction <50%. A 2-sided *P* value of <0.05 was considered statistically significant in all comparisons. *P* values and 95% CIs have not been adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible. SAS EG version 7.15 (SAS Institute) was used to perform all statistical analyses.

RESULTS

STUDY COHORT. A total of 294,966 patients underwent an elective coronary angiography in Ontario from April 1, 2009, to March 31, 2019, for coronary artery disease evaluation (**Figure 1**). From this sample, 145,505 patients (49%) were excluded because they were younger than 66 years or older than 105 years, and 19,686 (13%) were excluded for having a previous coronary angiography. Approximately one-third of the remaining cohort was excluded because of prior heart failure (n = 31,540), myocardial infarction in the previous year (n = 2,350), or clinical comorbidities (n = 8,953). Additionally, 24,254 (28%) were excluded for not having obstructive coronary artery disease, and 25,614 (41%) were excluded for having a previous beta-blocker prescription. The final study population was composed of 28,039 patients.

BASELINE CHARACTERISTICS BEFORE AND AFTER INVERSE PROBABILITY OF TREATMENT WEIGHTING. Before inverse probability of treatment weighting, there were 12,695 patients (45.3%) in the beta-blocker treatment group and 15,344 patients (54.7%) in the no beta-blocker group (**Table 1**). The most prescribed beta-blocker was bisoprolol (in 66% of the patients), followed by metoprolol (28.7%) and atenolol (4.6%). Compared with the no beta-blocker group, patients treated with beta-blockers were slightly younger (mean age: 72.8 ± 5.5 vs 73.3 ± 5.7 years) and predominantly male (66.6% vs 65.9%). Patients in the beta-blocker group were less likely to have chronic obstructive pulmonary disease and peripheral artery disease and more likely to have a high-risk ischemic test and multivessel coronary artery disease. After inverse probability of treatment weighting by the propensity score, patients in the beta-blocker and no beta-blocker groups were well balanced for demographics, comorbidities, medications, and cardiac and laboratory tests, with standardized differences consistently <0.1 (**Table 1**, Supplemental Table 1).

CARDIOVASCULAR OUTCOMES ASSOCIATED WITH BETA-BLOCKERS. The cumulative incidence of the primary composite outcome at 5 years in the inverse probability of treatment weighting cohort was 14.3% in the beta-blocker group and 16.1% in the no beta-blocker group (**Table 2**). Beta-blockers were associated with an absolute risk reduction of −1.8% (95% CI: −2.8 to −0.8), resulting in an NNT to prevent 1 major cardiovascular event at 5 years of 56 (95% CI: 36-120). In the relative scale, beta-blockers were associated with an 8% reduction in the hazards of the primary outcome as compared with the no beta-blocker group over a median follow-up of 5.2 years (HR: 0.92; 95% CI: 0.86-0.98; *P* = 0.006).

Beta-blockers were associated with a 13% relative reduction in the hazards of hospitalization for myocardial infarction (cause-specific HR [csHR]: 0.87; 95% CI: 0.77-0.99; *P* = 0.031; cumulative incidence at 5 years in the beta-blocker group of 3.4% vs 4.0% in the no beta-blocker group). No statistically significant differences were observed regarding all-cause mortality (HR: 0.95; 95% CI: 0.88-1.02) and hospitalizations for heart failure (csHR: 0.93; 95% CI: 0.82-1.06) (**Figure 2**). No differences were observed between the beta-blocker and no beta-blocker groups for cardiovascular death (csHR: 0.90; 95% CI: 0.77-1.05), unstable angina, stroke, and subsequent revascularization. The benefits associated with beta-blockers regarding the primary outcome were consistent across all subgroups, which included sex, age, diabetes, hypertension, coronary revascularization status, left ventricular ejection fraction range, and different patterns of myocardial ischemia and coronary anatomy (**Figure 3**).

ADDITIONAL AND SENSITIVITY ANALYSES. The same results as in the primary analysis of the main outcome were obtained when using a bootstrap variance estimator (HR between beta-blocker and no beta-blocker groups: 0.92; 95% CI: 0.86-0.98; *P* = 0.006). Sensitivity analyses of the primary outcome changing the duration of the beta-blocker exposure window or allowing for time-varying beta-blocker exposure assessment showed similar trends as for the primary analysis, albeit with varying statistical significance (Supplemental Table 2). No association was observed between beta-blocker use and the negative outcomes of hospitalization for urinary tract infection (csHR: 0.97; 95% CI: 0.92-1.03) and hospitalization for external injuries (csHR: 0.97; 95% CI: 0.88-1.06), whereas a 13% nonsignificant increase in the safety outcome of hospitalizations for hypoglycemia was noted among those treated with vs without beta-blockers (csHR: 1.13; 95% CI: 0.84-1.53). Results did not change significantly when using stabilized weights (Supplemental Table 3), excluding subjects with very low or very high propensity scores (Supplemental Table 4), using propensity score

TABLE 2 Primary and Secondary Outcomes After Propensity Score Weighting

	Beta-Blockers[a]	No Beta-Blockers[a]	Absolute Risk Reduction, % (95% CI)[b]	HR (95% CI)[c]	*P* Value[d]
Primary composite outcome[e]	14.3	16.1	−1.8 (−2.8 to −0.8)	0.92 (0.86 to 0.98)	0.006
All-cause death	10.2	11.4	−1.2 (−2.0 to −0.3)	0.95 (0.88 to 1.02)	0.141
Hospitalization for heart failure	2.9	3.2	−0.3 (−0.8 to 0.2)	0.93 (0.82 to 1.06)	0.300
Hospitalization for myocardial infarction	3.4	4.0	−0.6 (−1.1 to 0.0)	0.87 (0.77 to 0.99)	0.031
Cardiovascular death[f]	2.9	3.3	−0.4 (−0.9 to 0.2)	0.90 (0.77 to 1.05)	0.169
Unstable angina (ED visits or hospitalizations)	6.3	6.4	−0.1 (−0.7 to 0.6)	1.00 (0.91 to 1.11)	0.942
Hospitalization for stroke	2.6	2.4	0.2 (−0.2 to 0.7)	1.06 (0.92 to 1.23)	0.421
Subsequent coronary revascularization	17.1	16.5	0.6 (−0.4 to 1.5)	1.02 (0.96 to 1.08)	0.564

Values are % unless otherwise indicated. [a]Cumulative incidence function estimates in the weighted cohort at 5 years. The cumulative incidence function allows one to estimate the incidence of an event over time, while taking competing risks into account. [b]Absolute risk reductions were calculated from the weighted cumulative incidence estimates, with 95% CI generated in 1,000 bootstrap resamples. [c]HRs were estimated from weighted cause-specific proportional hazards models (HR for nonfatal outcomes are cause-specific HRs). [d]*P* values refer to the null hypothesis that the HR = 1. No corrections for multiple testing were applied. [e]The primary composite outcome was defined as the first occurrence of the composite of all-cause death and hospitalization for heart failure or myocardial infarction. [f]Patients were followed only through December 31, 2018, because cause of death was not ascertained beyond this point (n = 23,678).

ED = emergency department.

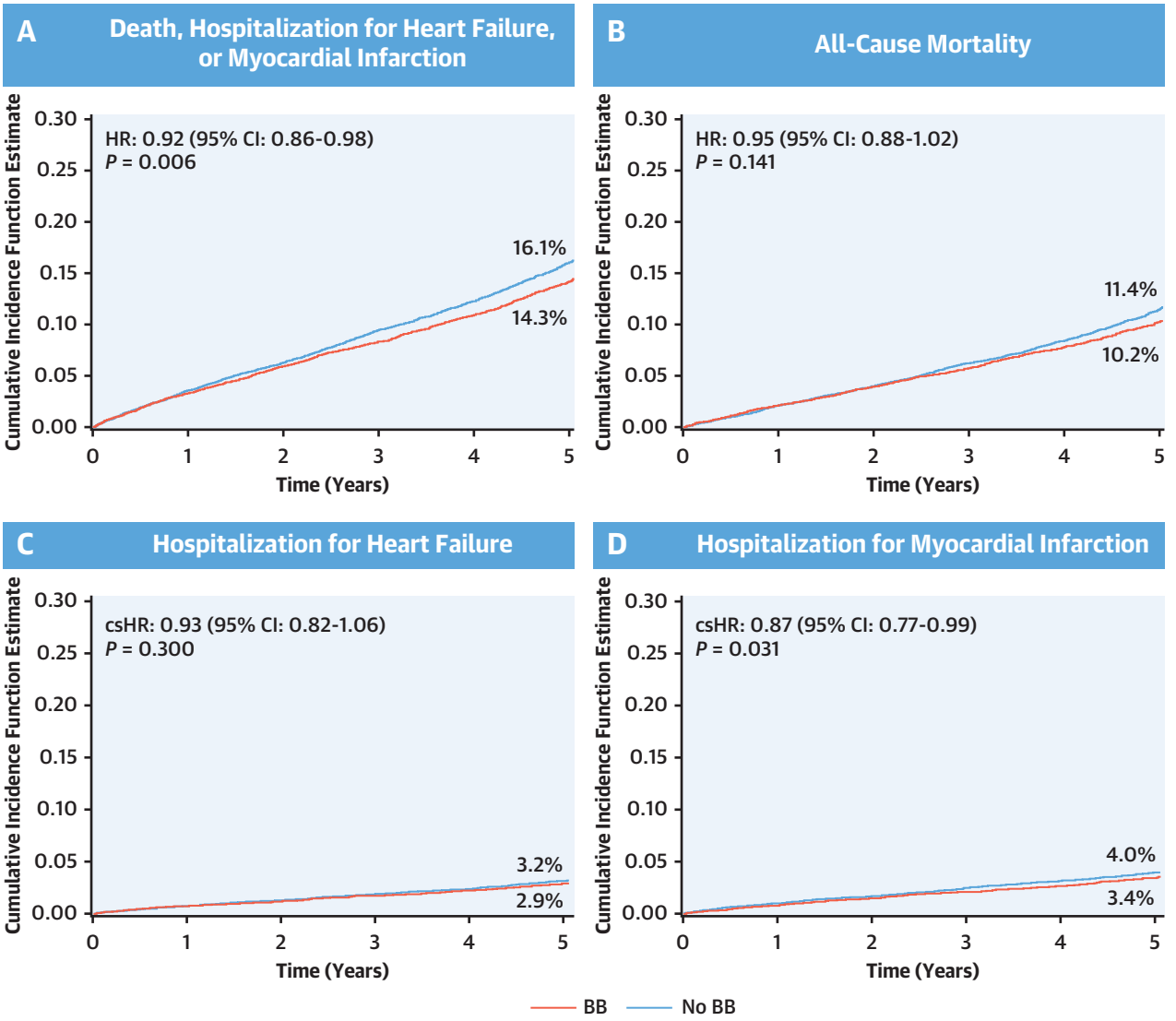
matching (Supplemental Table 5), or modifying the definitions of the exclusion criteria based on heart failure and left ventricular ejection fraction (Supplemental Tables 6 to 8).

DISCUSSION

In this population cohort study of patients with angiographically documented stable coronary artery disease without heart failure or a recent myocardial infarction, beta-blocker therapy was associated with an 8% relative and 1.8% absolute risk reduction in the composite of all-cause mortality and hospitalization for heart failure or myocardial infarction at 5 years, when compared with patients not prescribed with beta-blockers. This result was driven primarily by reductions in hospitalization for myocardial infarction and was consistent across subgroups, including those with hypertension and diabetes, and in most sensitivity analyses (**Central Illustration**).

The American clinical practice guidelines provide a weak recommendation (Class IIb, Level of Evidence: C) regarding the prescription of beta-blockers for cardiovascular protection in patients with stable coronary artery disease without heart failure or a recent myocardial infarction, while the European and Canadian guidelines provide no recommendation, highlighting the lack of robust clinical evidence.[17,18,24] Whereas the findings from our study of a significant association between beta-blockers and cardiovascular protection might seem at odds with prior studies, the 8% relative risk reduction in major events that we observed was identical to that reported in the REACH international registry.[4] The differences in statistical significance between both studies might be caused by a larger sample in our study compared with REACH and differences in the components of the primary outcome.[4] In the U.S. NCDR (National Cardiovascular Data Registry) Cath-PCI registry, beta-blockers were also not associated with improved cardiovascular outcomes in patients without prior myocardial infarction undergoing an elective percutaneous coronary intervention.[5] In fact, beta-blockers were associated with a small but significant 4% increase in the composite of all-cause death, myocardial infarction, stroke, and heart failure at 3 years, driven by increases in heart failure hospitalization.[5] There were more patients with heart failure at baseline prescribed with beta-blockers in this study, which might explain the higher rates of heart failure hospitalization.[5] A smaller study conducted in Japan also suggested that beta-blockers could be associated with an increased risk of cardiac death and myocardial infarction at 3 years among 5,288 patients without heart failure undergoing an elective percutaneous coronary intervention.[25] Besides differences in ethnic composition and patterns of clinical practice (this study was conducted more than a decade ago), the use of a prevalent user design in a setting where only ∼20% of the patients were prescribed beta-blockers might explain these divergent results.[25,26] In the current study, we included patients with angiographically proven stable coronary artery disease, regardless of the need for a coronary intervention, and excluded patients with heart failure. Additionally, we restricted our cohort to new users of beta-blockers. As a result, we avoided patients who had recently stopped beta-blockers to be included in the no beta-blocker group and avoided patient with long-standing beta-blocker use to be grouped together with those who had recently started the

FIGURE 2 **Cumulative Incidence Function Curves of the Primary Outcome and Its Components**



Plots represent the cumulative incidence function estimates in the weighted cohort, taking into account the competing risk of death for the outcomes hospitalization for heart failure and hospitalization for myocardial infarction. **(A)** The primary composite outcome is presented. **(B to D)** The components of the primary outcome are presented. No corrections for multiple testing were applied. BB = beta-blockers; csHR = cause-specific HR.

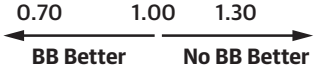
medication, a deviation from what would be done in a clinical trial studying the same question.[27]

The mechanisms behind the benefits of beta-blockers in patients with stable coronary artery disease are unclear. It has been suggested that long-term beta-blocker therapy may slow the progression of coronary atherosclerosis,[28] prevent plaque rupture,[29,30] and reduce platelet aggregation,[31] although all these mechanisms remain to be proven. Conversely, reductions in heart rate alone are probably not enough to elicit cardioprotective responses, as demonstrated in a randomized trial with ivabradine in patients with stable coronary artery disease.[32] Given the mixed results and intrinsic limitations of observational studies, randomized trials are still needed to address the use of beta-blockers in patients with stable coronary artery disease.[33,34]

In our study, beta-blockers were associated with an 8% relative and 1.8% absolute cardiovascular risk reductions, with an estimated NNT of 56 at 5 years.

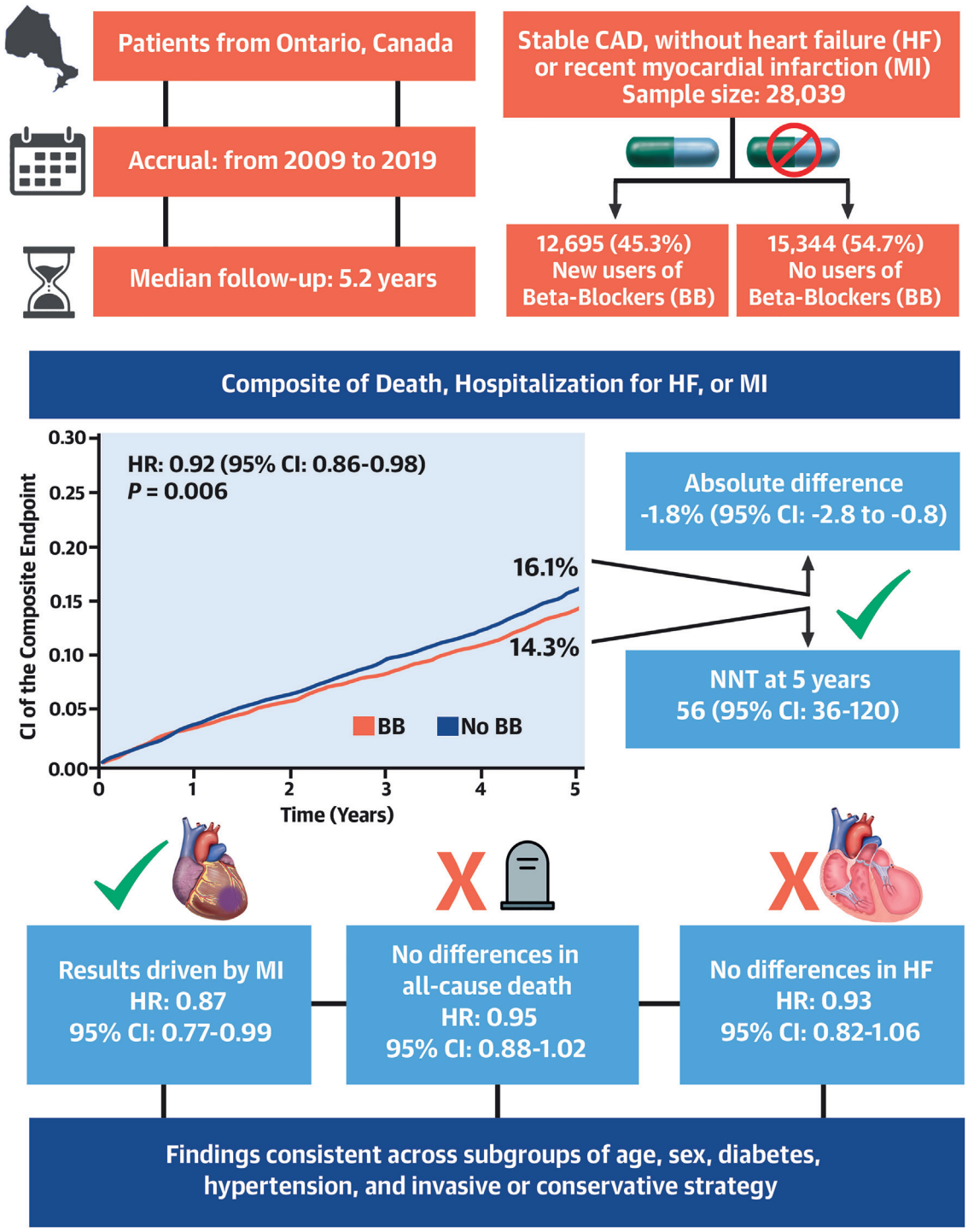
FIGURE 3 Subgroup Analysis of the Primary Outcome

Subgroup	BB 5-Year Event Rates, %	No BB 5-Year Event Rates, %	HR (95% CI)	*P* Interaction
All patients	14.3	16.1	0.92 (0.86-0.98)	
Sex				0.363
Female	12.9	14.7	0.96 (0.86-1.06)	
Male	15.0	16.9	0.90 (0.84-0.97)	
Age				0.729
<75 y	10.8	12.0	0.91 (0.83-0.99)	
≥75 y	21.0	24.0	0.93 (0.85-1.01)	
Diabetes				0.934
No	12.7	14.4	0.92 (0.85-0.99)	
Yes	17.3	19.4	0.92 (0.84-1.01)	
Previous revascularization				0.598
No	13.8	15.8	0.91 (0.85-0.97)	
Yes	18.6	19.1	0.96 (0.80-1.16)	
Ischemic risk*				0.149
Low risk	12.8	14.6	0.90 (0.80-1.02)	
High risk	13.8	14.2	1.01 (0.92-1.10)	
Multivessel disease†				0.270
No	12.9	15.0	0.90 (0.84-0.97)	
Yes	20.0	20.9	0.98 (0.86-1.10)	
Left main disease				0.361
No	13.8	15.6	0.91 (0.86-0.97)	
Yes	23.0	26.8	1.02 (0.81-1.27)	
PCI within 90 days postindex				0.492
No	14.9	17.6	0.90 (0.83-0.98)	
Yes	13.5	14.3	0.94 (0.86-1.03)	
Hypertension				0.375
No	10.8	13.3	0.87 (0.76-1.00)	
Yes	15.3	17.0	0.93 (0.87-1.00)	
Left ventricular ejection fraction*				0.212
≥50%	13.4	14.9	0.94 (0.88-1.01)	
35%-49%	20.0	24.0	0.85 (0.72-0.99)	



The association between beta-blocker treatment and the composite of all-cause mortality, hospitalization for heart failure, or hospitalization for myocardial infarction is presented in prespecified subgroups from the weighted cohort. Risk estimates are presented at 5 years. The reference group for the HR calculations is treatment without a beta-blocker (BB). No significant interactions were observed in any subgroups. No corrections for multiple testing were applied. *Due to missingness, the subgroup analysis according to ischemic risk was based on the data of 21,155 patients (75% of the population) and the subgroup analysis according to left ventricular ejection fraction was based on data of 25,945 patients (93% of the population). †Defined as 3-vessel coronary disease or 2-vessel disease with involvement of the proximal left anterior descending coronary artery. PCI = percutaneous coronary intervention.

CENTRAL ILLUSTRATION **Summary of the Main Study Results**



Godoy LC, et al. J Am Coll Cardiol. 2023;81(24):2299-2311.

In this cohort study, beta-blockers (BB) were associated with a significant 1.8% absolute and 8.0% relative reduction in the composite of all-cause death and hospitalization for heart failure (HF) or myocardial infarction (MI) at 5 years, compared to patients not prescribed with beta-blockers. These results were primarily driven by reductions in hospitalizations for myocardial infarction. CAD = coronary artery disease; NNT = number needed to treat.

Although the NNT might seem small in magnitude, it is somewhat similar to many approved therapies for coronary artery disease. Examples are perindopril in EUROPA (European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease) (NNT of 50 over 4.2 years)[35]; ezetimibe in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) (NNT of 50 over 6 years)[36]; and empagliflozin in EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) (NNT of 63 over 3.1 years).[37] Given the low cost and known safety profile, even small risk reductions might be enough to justify a more generalized use of beta-blockers in patients with stable coronary artery disease, especially considering that most antianginal medications are not associated with cardioprotective benefits.[38,39] Additionally, our results were consistent across all subgroups. These subgroups included patients who underwent percutaneous coronary intervention, in whom beta-blockers were previously reported not to be beneficial[5,25,40]; patients with diabetes, in whom the unfavorable metabolic effects of beta-blockers might be particularly concerning[41,42]; patients with and without hypertension; and patients in the entire spectrum of left ventricular ejection fraction included in this study (>35%).

STUDY LIMITATIONS. First, as is frequently the case when attempting to infer causality in nonrandomized settings, it is not possible to completely disregard the potential influence of unmeasured confounders on our results, especially given the small observed treatment effect size. Still, we accounted for multiple possible confounders when estimating the propensity score and achieved an adequate balance in all measured baseline characteristics. Second, given the eligibility criteria for cohort entry, our findings might not be generalizable to the entire population of patients with stable coronary artery disease. Data regarding medication use in Ontario are only available for patients older than 65 years, and approximately one-half of the patients in the initial cohort were excluded because of their younger age. Also because of data availability, we excluded patients with left ventricular dysfunction based on a left ventricular ejection fraction <35%, whereas clinical practice guidelines often endorse a threshold of 40%.[43] We also excluded patients with a diagnosis of heart failure regardless of their ventricular function and, therefore, results might not be applicable to patients with heart failure with preserved ejection fraction. Finally, as would be expected in a real-world setting, adherence to the beta-blocker or no beta-blocker strategies may have declined during the follow-up, which may reduce the observed treatment effect.

CONCLUSIONS

In patients with stable coronary artery disease without a recent myocardial infarction or heart failure, beta-blockers were associated with a small but significant reduction in the composite of all-cause mortality and hospitalization for heart failure or myocardial infarction, a result that was primarily driven by reductions in myocardial infarction. Randomized trials are needed to confirm the cardiovascular benefits of beta-blockers in the contemporary era.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: For patients with SIHD who do not exhibit heart failure, extended beta-blocker therapy is associated with a small but significant reduction in major cardiovascular events.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to determine the optimum type, intensity, and duration of beta-blocker treatment in patients with SIHD.

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KEY WORDS beta-blocker, cardiovascular outcomes, stable coronary artery disease

APPENDIX For supplemental figures and tables, please see the online version of this paper.