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Clinical Research

Clinical Outcomes With Beta-Blocker Use in Patients With Recent History of Myocardial Infarction

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ABSTRACT

Background: It is uncertain whether beta-blockers (BBs) are beneficial in contemporary stable patients with prior myocardial infarction (MI). Therefore, we sought to examine the effectiveness of BB use in this population.

Methods: We conducted a cohort study with the use of administrative databases of patients ≥ 65 years of age, alive on April 1, 2012 (index date) with a hospital discharge diagnosis of MI within the previous 3 years.

RÉSUMÉ

Contexte : On ne sait pas avec certitude si les bêtabloquants (BB) sont bénéfiques chez les patients contemporains qui présentent des antécédents d'infarctus du myocarde (IM) et dont l'état est stable. Nous avons donc cherché à examiner l'efficacité des BB au sein de cette population.

Méthodologie : Nous avons utilisé des bases de données administratives afin de mener une étude de cohorte portant sur des patients de 65

The benefit of oral beta-blockers (BBs) in patients with heart failure with reduced ejection fraction (HFrEF) and acute myocardial infarction (MI) is well established. However, recent observational studies, with highly heterogeneous results on meta-analysis, have raised uncertainty about the use of BB therapy in stable patients after MI.[1-4] The vast majority of the clinical trial evidence demonstrating morbidity and mortality reduction with the use of BBs originates from older randomized trials that preceded the current reperfusion era, the current statin era, and the introduction of troponin assays to diagnose acute MI.[5] The most recent BB trial, the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), which studied the early use of BBs in a largely ST-segment-elevation myocardial infarction (STEMI) patient population, does not help to answer the question regarding the utility of BB therapy in contemporary stable patients chronically with prior MI because it was conducted from 1999 to 2005 in a setting with minimal reperfusion, primarily with the use of the fibrinolytic streptokinase, and focused on early outcomes with intravenous BB therapy at 1 month.[6]

The American College of Cardiology/American Heart Association guidelines for acute coronary syndromes and for chronic secondary prevention treatment of ischemic heart disease began questioning use of BBs in stable post-MI patients owing to concerns about long-term patient tolerability.[1,7,8] Their 2011 secondary prevention guidelines were the first to make a change in recommending the

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The primary outcome was time to death or hospitalization for MI or angina 1 year after the index date, with inverse probability of treatment weighting.

Results: We included 33,811 patients with prior MI, of whom 21,440 (63.4%) were dispensed a BB. The median age was 78 years, and 56% were male. There was no difference in the 1-year hazard of death/hospitalization for MI or angina (14.8% vs 14.7%, hazard ratio 1.00, 95% confidence interval 0.94-1.07; $P = 0.90$) in those receiving vs not receiving BB. Similarly, there was no difference in the individual end points in composite nor in 3-year outcomes. Subgroup analysis by age, sex, MI timing, MI type, heart failure, and atrial fibrillation found no benefit. Patients with a history of revascularisation treated with BBs had a lower rate of the composite outcome compared with those without such history ($P = 0.006$ for interaction) at 1 year but not at 3 years.

Conclusions: In this large contemporary population-based observational study of older stable patients with prior MI, BBs were not associated with a reduction in major cardiovascular events or mortality in those with MI within the previous 3 years. This study supports the need to conduct contemporary clinical trials evaluating the use of BBs after MI.

ans et plus qui étaient vivants en date du 1er avril 2012 (date de référence) et qui avaient reçu un diagnostic d'IM à leur sortie de l'hôpital au cours des trois années précédentes. Le paramètre d'évaluation principal était le temps écoulé avant le décès ou l'hospitalisation pour cause d'IM ou d'angine un an après la date de référence, avec pondération par probabilité inverse de traitement.

Résultats : Nous avons inclus 33 811 patients présentant des antécédents d'IM, dont 21 440 (63,4 %) avaient reçu des BB. L'âge médian était de 78 ans, et 56 % des patients étaient de sexe masculin. Aucune différence n'a été notée quant au risque de décès ou d'hospitalisation pour cause d'IM ou d'angine sur un an (14,8 % vs 14,7 %, rapport des risques instantanés : 1,00, intervalle de confiance à 95 % : 0,94-1,07; $p = 0,90$) chez les patients traités par des BB par rapport à ceux qui ne l'étaient pas. De même, aucune différence n'a été observée au regard de chaque paramètre d'évaluation dans les résultats composites ni dans les résultats à trois ans. Une analyse de sous-groupes en fonction de l'âge, du sexe, du moment de survenue de l'IM, du type d'IM, de l'insuffisance cardiaque et de la fibrillation auriculaire n'a mis en évidence aucun bienfait. Les patients présentant des antécédents de revascularisation traités par des BB, comparativement à ceux qui ne présentaient pas de tels antécédents, avaient un taux de résultats composites moins élevé ($p = 0,006$ pour l'interaction) à un an, mais pas à trois ans.

Conclusions : Dans le cadre de cette vaste étude d'observation de population contemporaine portant sur des patients âgés présentant des antécédents d'IM et dont l'état est stable, les BB n'étaient pas associés à une réduction des événements cardiovasculaires majeurs ou de la mortalité chez les patients qui avaient subi un IM au cours des trois années précédentes. Cette étude confirme qu'il est nécessaire de mener des essais cliniques contemporains visant à évaluer l'utilisation de BB après un IM.

continuation of BBs for only 3 years after MI rather than indefinitely as in previous guidelines, unless patients have other compelling reasons for ongoing BB therapy.[8] Subsequent stable ischemic heart disease and STEMI guidelines followed suit in 2012 and 2013, limiting the duration of BB therapy while maintaining the class IA recommendation, respectively.[1,7] The European Society of Cardiology STEMI and non−ST-segment-elevation acute coronary syndrome guidelines in 2015 further questioned the utility of chronic BB use after MI by recommending chronic use only in those patients with heart failure or left ventricular dysfunction, generating further uncertainty given the discrepancies in professional society recommendations surrounding BB use.[9,10] Their justification was that BBs have been investigated in contemporary randomized trials only in MI patients with heart failure or without normal left ventricular function.

The observational studies that have questioned the usefulness of BBs in patients with prior MI have been limited in size, resulting in confidence intervals that cannot exclude a potentially clinically meaningful benefit.[3,11-16] Furthermore, prior studies were conducted using selected populations from registries, limiting the generalizability of the findings.[3,11-13] In order to improve generalizability, certainty, and precision regarding the estimate of treatment effect for this important clinical decision, we used multiple linked health care databases to evaluate the effectiveness of BBs in a large, contemporary population-based cohort of stable patients with prior MI.

Methods

Study design and data sources

We conducted a population-based observational cohort study linking multiple health care databases and used inverse probability of treatment weighting (IPTW) with the use of the propensity score to account for confounding. The data sources have been widely used for health services and outcomes research.

To identify patients for eligibility for cohort entry and to document cardiac risk factors and comorbidities, we used the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, which contains primary and secondary discharge diagnoses for all hospital admissions in Ontario, including cardiac procedures, such as percutaneous coronary intervention and coronary catheterization. To ascertain medication use, we used the Ontario Drug Benefit prescription claims database, which contains outpatient prescriptions dispensed for all elderly patients ($\geq$ 65 years of age) in Ontario, as well as those on social assistance. The Ontario Health Insurance Plan database contains data on physician services. The Ontario Registered Persons database contains information on vital status of all Ontario residents and was used to ascertain death. The Statistics Canada census database contains demographic and socioeconomic data, and was used to determine geographic location and median neighbourhood income of patients according to their location of residence. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences, Toronto.

Study population

Our study included patients ≥ 65 years of age who were alive on April 1, 2012. We created a cohort of stable patients who had been discharged with an acute MI within the 3 years before April 1, 2012, the cohort index date, as identified with the use of the codes I21 and I22 from the International Classification of Disease, 10th Revision, in the CIHI Discharge Abstract Database. We excluded patients with a presumed history of HFrEF, which was defined by those prescribed carvedilol (which in Ontario is reserved for the treatment of HFrEF). We also excluded patients older than 105 years and those with an invalid Ontario health insurance number.

Exposure

BB exposure was defined as dispensation of a BB prescription within 100 days before the index date of April 1, 2012. All BBs qualified for exposure with the exceptions of sotalol and carvedilol. Sotalol is generally used as an antiarrhythmic rather than for purposes of atherosclerotic cardiovascular risk reduction, and in Ontario, carvedilol is recommended exclusively for patients with HFrEF. Because our intention was to examine a post-MI cohort that did not already have a compelling indication for a BB, we excluded patients prescribed carvedilol.

Outcomes

The primary outcome was death or hospitalization for MI or angina within 1 year after April 1, 2012. Secondary outcomes included death alone and death or hospitalization for MI. Primary and secondary hospitalization outcomes were ascertained from CIHI discharge abstract data. Death was determined from the Ontario Registered Persons Database. Follow-up for ascertainment of outcomes began on April 1, 2012, the time of cohort entry, and patients were followed for events up to 1 year after cohort entry for the primary outcome. A secondary analysis also followed patients for 3 years after cohort entry.

Statistical analysis

In the overall cohort, baseline demographic and clinical variables were compared between those using BBs and those not using BBs by means of the chi-square test for proportions, 1-way analysis of variance for means, and Kruskal-Wallis test for medians of continuous variables. Potential confounders measured at baseline were adjusted for IPTW with the use of the propensity score. The propensity score (the probability of receiving BB therapy conditional on relevant baseline and clinical characteristics) was estimated with the use of a multivariable logistic regression model based on the baseline demographic and clinical characteristics listed in Table 1. Patients were weighted by the inverse of the probability of receiving the treatments that they actually received. To determine whether the treatment groups were balanced after weighting, we estimated the weighted standardised differences for each baseline covariate.[17] Differences < 0.1 were taken to represent good balance between groups.

Weighted Kaplan-Meier curves were estimated in each group to compare outcomes between groups. Cox proportional hazard models were constructed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the estimates of treatment effect between the BB and no-BB groups for the primary and secondary outcomes. IPTW was incorporated into the models. A robust variance estimator was used to account for the weighted nature of the sample.[18]

We also conducted subgroup analyses to compare the BB treatment effect according to age (< 75 years, ≥ 75 years), sex (male, female), timing of prior MI, history of coronary revascularisation (percutaneous coronary intervention or coronary artery bypass surgery), heart failure, and history of atrial fibrillation and tested for interactions. As a further analysis, we restricted the sample to those patients treated with BBs and compared outcomes in patients who received high- or standard-dose with those who received low-dose BBs, thereby allowing us to explore a dose-response effect. This analysis used a new IPTW analysis with a new propensity score estimated for use of high- or standard-dose BB vs low-dose BB. (Dose thresholds are presented in Supplemental Table S1.) All analyses were conducted with the use of SAS version 9.3 (SAS Institute, Cary, NC, USA). A P value of < 0.05 was considered to be statistically significant. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Results

We included 33,811 patients in the present cohort, and of these, 21,440 (63.4%) had been dispensed BBs (Fig. 1). The baseline characteristics were well balanced after IPTW, with all standardized differences < 0.1. (Table 1; Supplemental Table S2) In the weighted cohort, the median age was 78 years, 56% were male, ~ 70% had NSTEMI, and the median time to the most recent MI was 16.1 months (interquartile range 7.3–25.8 months). Patients had many common cardiovascular risk factors, including hypertension (89.3%), diabetes (43.5%), and dyslipidemia (52.9%). Approximately 74% of patients had undergone coronary catheterization, and 43% had undergone percutaneous coronary intervention. Within the 100 days before the cohort index date, 68% of patients had filled a prescription for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 76% had filled a prescription for statins. The most common BB dispensed was metoprolol (61.5%), followed by bisoprolol (30.0%) and atenolol (6.3%). Of those receiving BBs, 60.9% received a high or standard dose of BB. Mean proportion of days covered for all those in the BB group was 87.2% at 1 year, 85.4% at 2 years, and 84.0% at 3 years after the index date of cohort entry.

Primary and secondary outcomes

There were a total of 3,748 deaths and 1,591 admissions due to MI or angina. There was no difference in the rate of occurrence of the primary composite outcome of death or hospitalization for MI or angina between the BB group and the no-BB group at 1 year (14.8% vs 14.7%, IPTW-adjusted hazard ratio [aHR] 1.00, 95% CI 0.94-1.07; $P = 0.90$). (Table 2) There was also no difference in the 1-year hazard of death (11.1% vs 11.1%, HR 1.00, 95% CI 0.93-1.08; $P = 1.00$) or of death or hospitalization for MI (13.7% vs

Table 1. Baseline characteristics after IPTW

Characteristic	β-Blocker	No β-blocker	Standardised difference
n	21,440	12,371	
Demographics			
Age, y*, mean ± SD	77.8 ± 10.2	77.8 ± 13.8	0.004
Male sex*	55.8	55.8	0.001
Income quintile*			
1 (lowest)	21.5	21.4	0.002
2	20.8	20.9	0.002
3	19.9	19.8	0.001
4	19.5	19.7	0.005
5 (highest)	18.2	18.1	0.003
Rural setting*	15.9	16.0	0.004
Last MI to Apr 1, 2012, mo,* mean ± SD	16.8 ± 13.3	16.8 ± 17.8	0.001
Last MI of type STEMI	25.3	23.3	0.047
Coronary procedures and revascularisation history			
Coronary catheterization*	74.4	74.2	0.002
Percutaneous coronary intervention*	43.4	43.3	0.002
Coronary artery bypass grafting*	17.0	17.1	0.001
Cardiovascular comorbidities			
Chronic ischemic heart disease	78.4	77.1	0.030
Atrial fibrillation/flutter*	26.1	26.5	0.009
Cerebrovascular disease*	10.6	10.6	< 0.001
Diabetes*	43.5	43.5	0.001
Dyslipidemia*	52.9	52.6	0.006
Heart failure*	29.5	29.6	0.004
Hypertension*	89.3	89.3	0.000
Peripheral vascular disease*	7.7	7.8	0.004
Shock*	6.7	6.7	0.001
Other comorbidities			
Anemia/blood disease*	25.7	26.1	0.008
Cancer*	13.1	13.1	0.002
Chronic obstructive pulmonary disease*	16.6	16.7	0.001
Liver disease*	1.4	1.4	0.001
Peptic ulcer disease*	4.7	4.8	0.003
Renal disease*	12.5	12.8	0.009
Medication use within 100 days before index admission			
Antiarrhythmics*	4.1	4.1	0.004
Antiplatelet agents (P2Y12 inhibitor)*	43.8	44.3	0.010
ACEI/ARB*	68.0	68.1	0.003
Calcium channel blockers*	28.8	29.2	0.010
Digoxin*	5.1	5.3	0.009
Direct oral anticoagulants*	0.1	0.1	0.002
Diuretics*	42.2	42.9	0.014
Nitrates*	23.4	24.4	0.023
Nonstatin lipid-lowering agents*	6.9	7.1	0.006
Statin*	76.7	76.4	0.007
Vitamin K antagonists*	12.5	12.9	0.012

Data are presented as % unless otherwise specified.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; STEMI, ST-segment-elevation myocardial infarction.

*Used in the IPTW model.

13.9%, HR 0.98, 95% CI 0.92-1.05; $P = 0.64$) between the groups. When outcomes were examined at 3 years after the study index date, there were also no differences found between groups in the primary or the secondary outcomes. There was no difference in the composite outcome of death or hospitalization for MI or angina in the BB group compared with the no-BB group at 3 years (33.5% vs 33.4%, aHR 1.00, 95% CI 0.96-1.05; $P = 0.92$). There was also no difference in the hazard of death (27.8% vs 28.0%, HR 0.99, 95% CI 0.95-1.04; $P = 0.80$) or of death or hospitalization (31.9% vs 31.9%, HR 1.00, 95% CI 0.96-1.05; $P = 1.00$) for MI between the BB and no-BB groups at 3 years. (Table 2) We also found no difference in outcomes between high-dose and low-dose BBs.

Subgroup analyses

Subgroup analyses that were conducted according to age, sex, timing of MI, type of MI, heart failure, and atrial fibrillation found no interactions to identify a specific subgroup that benefited from BB use. (Fig. 2) A significant interaction was found in treatment effect for the composite outcome at 1 year for the subgroup of those with vs without a history of coronary revascularisation with percutaneous coronary intervention or coronary artery bypass graft surgery (revascularisation history HR 0.90, 95% CI 0.80-1.00, vs no revascularisation history HR 1.09, 95% CI 1.00-1.18; $P = 0.006$ for interaction). However, at 3 years, this effect did not persist.

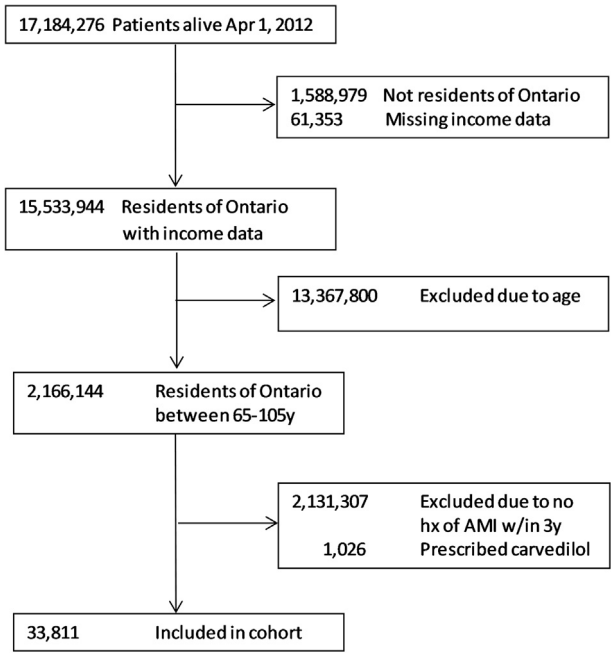

Figure 1. Flowchart of cohort creation according to inclusion and exclusion criteria. AMI, acute myocardial infarction.

Discussion

In this study, in a contemporary population-based cohort, BBs were not associated with a reduction in major cardiovascular events, namely, death or hospitalization for MI or angina in a stable population with prior MI. A large impact on cardiovascular events was not expected in our contemporary cohort, because patients were already well treated with other evidence-based risk reduction medications, with more than 70% of patients receiving statins and nearly 70% receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and many had undergone coronary revascularisation. The results were consistent across multiple subgroups, although in one subgroup, those with prior coronary revascularisation, BBs were associated with a modest reduction in major cardiovascular events at 1 year, though not at 3 years. Although it is possible that those who were revascularised may represent a higher-risk population, this subgroup finding should be considered as hypothesis generating because it could be a chance finding given the multiple subgroups that we analyzed in our comprehensive evaluation.

Whereas most previous research included patients immediately after MI enrolled in MI registries, we focused on examining a stabilized cohort with MI within the previous 3 years, with the majority of patients having their most recent MI ~ 1.5 years before cohort entry.[3,11-16] Thus, our study examined the association of BB use with clinical outcomes beyond the acute MI period. In a subgroup analysis, we compared patients with a more recent AMI (< 1 year before) vs those with a more remote AMI (≥ 1 year before) and found no statistical interaction to suggest a beneficial association between BB use and clinical outcomes in either group. The current American College of Cardiology/American Heart Association secondary prevention guidelines recommend limiting BB therapy to a duration of 3 years because the original prospective BB randomized controlled trials that demonstrated morbidity and mortality benefits were of 3 years' duration.[8] Ongoing clinical trials, such as REDUCE-SWEDEHEART, are examining the benefit of BBs in a contemporary well treated population 1-7 days after MI, but the question of longer-term optimal chronic BB use (beyond 1-3 years) remains unanswered.[19] Until further clinical trials address this issue, our findings add to the growing observational literature questioning the utility of BB use chronically after MI.

We summarize the results of our current study for death and acute coronary syndrome events along with the results of previous studies of BB use from cohort studies of populations with prior MI in Figure 3. Two other cohort studies examined a composite end point of major cardiovascular events and death. Andersson et al.,[14] using a time-varying Cox model, found a significant 8% reduction in composite events primarily in the recent MI subgroup of a mixed cohort from 2000-2008 of post—acute MI patients and those undergoing revascularisation. In contrast, Bangalore et al.,[3] in a propensity score-matched analysis with the use of a smaller cohort of 6,758 post—acute MI patients from the REACH (**Re**duction of **A**therothrombosis for **C**ontinued **H**ealth) registry, found a modest, but nonsignificant, 10% reduction in composite events, with CIs that did not preclude a possible treatment

Table 2. One- and 3-year cardiovascular and death outcomes

	Unadjusted, n (%)		Model with IPTW using robust variance				
Outcome	β-Blocker	No β-blocker	β-Blocker KM rate, %	No β-blocker KM rate, %	Absolute risk difference, %	HR (95% CI)	*P* value
n	21,440	12,371					
1 year after Apr 1, 2012							
Death	2355 (11.0)	1393 (11.3)	11.1	11.1	0	1.00 (0.93-1.08)	1.00
Death/hospitalization for MI	2948 (13.8)	1679 (13.6)	13.7	13.9	0.2	0.98 (0.92-1.05)	0.64
Death/hospitalization for MI or angina	3195 (14.9)	1758 (14.2)	14.8	14.7	0.1	1.00 (0.94-1.07)	0.90
3 years after Apr 1, 2012							
Death	5928 (27.6)	3373 (27.3)	27.8	28.0	0.2	0.99 (0.95-1.04)	0.80
Death/hospitalization for MI	6847 (31.9)	3825 (30.9)	31.9	31.9	0	1.00 (0.96-1.05)	1.00
Death/hospitalization for MI or angina	7198 (33.6)	3979 (32.2)	33.5	33.4	0.1	1.00 (0.96-1.05)	0.92

Data are expressed as n (%) unless otherwise noted.
IPTW, inverse probability of treatment weighting; KM, Kaplan-Meier; MI, myocardial infarction.

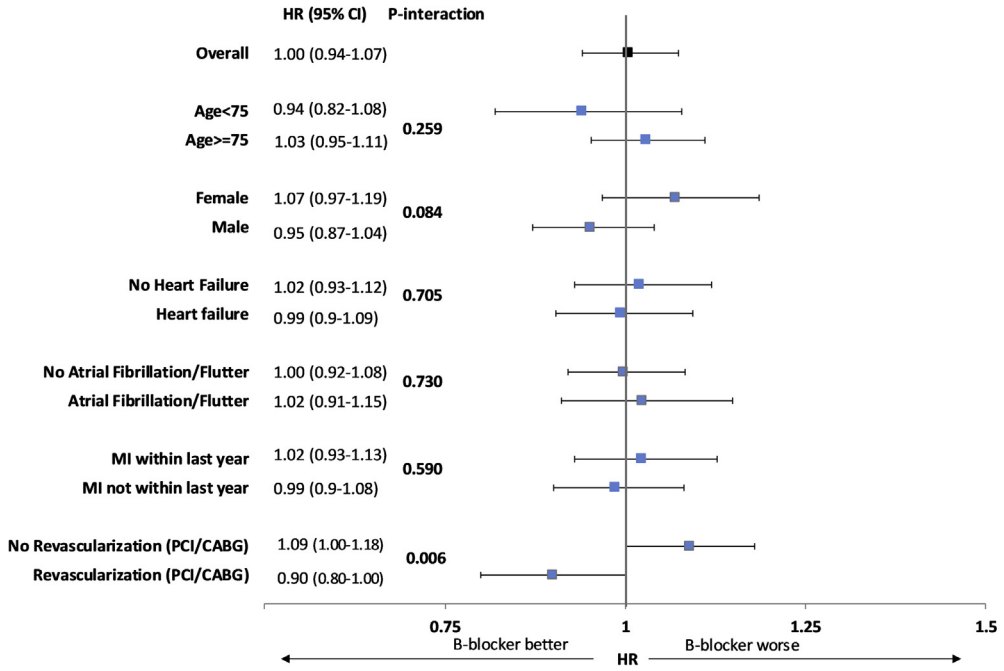

Figure 2. Forest plot of the subgroup results for the composite end point of death or hospitalization for myocardial infarction (MI) or angina at 1 year. CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

effect (HR 0.90, 95% CI 0.79-1.03). In our larger cohort of 33,811 patients at an average of 1.5 years after MI, we found no difference for the composite end point of death or hospitalization for MI or angina, with a greater precision around the HR estimate (HR 1.00, 95% CI 0.94-1.07).

Six cohort studies examined a mortality end point and found conflicting results. One of these 6 studies examined the association with BB discontinuation rather than BB initiation or use with outcomes.[12] Studies reporting short-term end points were more favourable, although lack of precision prevented firm conclusions for many studies[3,11-13,15,16] (Fig. 3). The point estimates for mortality varied widely, from an HR as low as 0.57 to one as high as 0.93, with the lowest estimate representing a 7% and the highest estimate representing a 43% relative hazard reduction in mortality. CIs ranging from a lower interval of 0.36 (64% mortality reduction) to an upper interval of 1.78 (78% mortality increase) reflect the imprecision of estimates of previous studies because of small sample

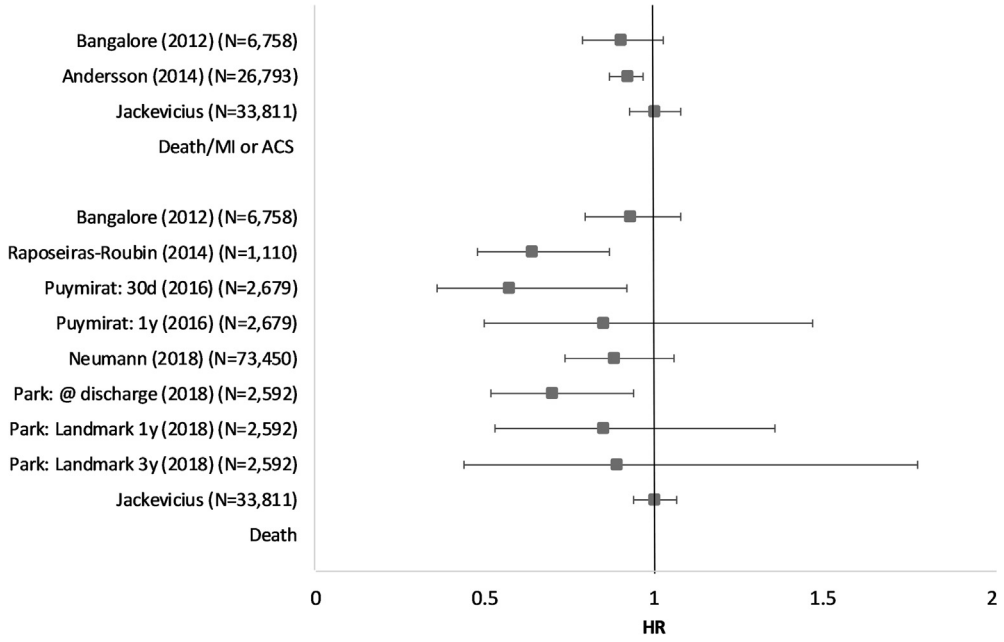

Figure 3. Point estimates and confidence intervals for the outcomes of death, myocardial infarction (MI), or acute coronary syndromes (ACS) or of death alone for the present study and previous published cohort studies examining the use of beta-blockers in post-MI patients.

size or few events, and they illustrate the inability to exclude a possible beneficial BB treatment effect. Our findings in a large, population-based, contemporary, and well balanced cohort of well treated patients with prior MI reports a more precise estimate showing no treatment effect for BBs both for a composite end point of major cardiovascular events and for mortality alone.

It has been suggested that type of BB may be an important variable in achieving a favourable BB effect after MI. Analogous to that for the heart failure indication, some preliminary research suggests improved outcomes in MI populations with the use of noncardioselective BBs and vasodilating BBs, both attributes of carvedilol.[20-22] We could not explore this further, because we excluded patients receiving carvedilol from our cohort to examine a non—heart failure population; future research can explore this hypothesis. There is renewed interest in targeting specific heart rates in various cardiovascular populations.[23] Although we did not have data on heart rate, we did not identify a dose-response gradient in our subgroup analysis, similarly to most previous research in post-MI populations.[24-26] Future research may explore dosing and heart rate targets further.

Since the landmark BB trials of the 1980s demonstrated a mortality benefit, the MI landscape has changed significantly.[5] We now have improved medical and interventional MI therapies, including more advanced coronary reperfusion approaches, particularly primary percutaneous coronary intervention for STEMI, as well as potent dual-antiplatelet therapy and high-intensity statins.[1,2] Furthermore, with the advent first of troponin and then of high-sensitivity troponin assays, our ability to detect smaller myocardial injury is now yielding a lower-risk MI population compared with MI that occurred in the era in which BBs were originally found to be beneficial.[1,2] The use of BBs indefinitely after MI has been ingrained in our therapeutic approach, but a reevaluation of this practice appears to be necessary to reflect the contemporary MI setting.[27]

The present study has several limitations. As an observational study, there is the possibility for residual confounding. We cannot know why some patients were treated with BB and others were not. However, our use of IPTW methods and use of a large unselected population-based database, with all standardized differences well below 0.1, indicate the creation of a well balanced cohort. Furthermore, potential confounding would most likely bias toward finding a benefit with BB, whereas we found no difference. Thus, residual confounding is unlikely to explain our findings. We did not have information on some cardiac risk factors, such as weight, smoking, and exercise status, given that these data are not typically available in administrative data sources. However, our cohort was well balanced for all other known baseline covariates and was also balanced for high levels of use of contemporary evidence-based medications for cardiovascular risk reduction. We did not have data available on ejection fraction. However, our exclusion of patients receiving carvedilol primarily excluded HFrEF patients from our population because carvedilol is used in Ontario solely for HFrEF. Therefore, our study results are applicable to patients without HFrEF. Furthermore, should some HFrEF patients have been included in our BB group, this again would have biased our findings toward benefit.

Conclusion

In summary, this large population-based cohort provides a precise estimate of treatment effect, finding that the use of BBs was not associated with a reduction in major cardiovascular events or mortality in stable patients with prior MI who were well treated with other evidence-based cardiovascular risk-reduction therapies. The conflicting results of recent observational studies and importance of this clinical question supports the conduct of randomized clinical trials of chronic BB use in a contemporary cohort of patients with prior MI.

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Disclosures

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2020.01.024.