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Prior beta blockers use is independently associated with increased inpatient mortality in patients presenting with acute myocardial infarction

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ABSTRACT

Background: Beta blockers (BBs) are recommended for patients presenting with acute myocardial infarction. However, the effects of prior BBs use on inpatient mortality in patients presenting with acute myocardial infarction (AMI) are unknown.
Methods: This was a retrospective cohort study of patients presenting with AMI in Florida Hospital Orlando from January 1, 2013 to December 31, 2014. Data were collected prospectively, as part of the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry.
Results: 1128 patients were included in the analysis, with 354 (31.4%) patients on home BBs and 774 (68.6%) not on home BBs on presentation. Patients in prior BBs group were older, had higher incidence of multiple comorbidities, and were more likely to take cardiovascular medications. During hospitalization, Patients in prior BBs group were more likely to develop decompensated heart failure (9.9% vs. 3.6%, $P < 0.001$), less likely to have STEMI (33.9% vs. 54.4%, $P < 0.001$), and subsequently less PCI (73.2% vs. 81.3%, $P = 0.002$), but higher inpatient mortality (8.8% vs. 4.8%, $P = 0.009$). In multivariable logistic regression analysis, prior BBs use was independently associated with increased inpatient mortality (adjusted OR 3.15, 95% CI 1.44-6.87, $P = 0.004$), as well as in GRACE model (adjusted ratio = 1.83, 95% CI 1.01-3.34, $P < 0.047$). However, prior BBs use did not contribute significantly to predict inpatient mortality on the basis of GRACE model in terms of discrimination and calibration.
Conclusions: Prior BBs use was independently associated with increased inpatient mortality, and should be considered a high risk marker for patients presenting with acute myocardial infarction.

1. Introduction

Acute myocardial infarction (AMI) remains a leading cause of morbidity and mortality worldwide. In 2014, AMI accounted for 14.2% of cardiovascular deaths and 4.3% of all deaths in the United States (US) [1]. The estimated annual incidence of myocardial infarction in the US is 550,000 new attacks and 200,000 recurrent attacks [2]. Although its incidence has been steadily declining since mid-1990s, as well as its mortality [2], AMI remains one of the most expensive hospital discharge diagnoses with an estimated cost of $11.5 billion in 2011 [3].

One of the important factors contributing to the mortality decline of AMI was the introduction of new medications in the last two decades; beta-blockers (BBs) are one category of them. Based on randomized clinical trials, which demonstrated that BBs are effective in reducing cardiac events and mortality in patients who have had a recent myocardial infarction or left ventricular systolic dysfunction [4–8], current guidelines give a class I recommendation for oral BBs within the first 24 h in patients with myocardial infarction, and a class IIa for intravenous BBs for patients who are hypertensive or having ongoing ischemia [9,10]. However, most of these studies were conducted in the pre-reperfusion era and before the introduction of statins and antiplatelet agents. In recent years, the role of BBs in myocardial infarction became controversial, especially its use in post AMI patients with normal left ventricular systolic function, and in patients after percutaneous coronary interventions (PCI) [10,11]. Some studies even found that early use of BBs in

Abbreviation: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; BBs, beta blockers; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidential interval; NSTEMI, non-ST segment elevated myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST segment elevated myocardial infarction.

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myocardial infarction patients who underwent PCI was associated with worse clinical outcome [11–13], which reminded us of the "aspirin paradox" phenomenon [14]. In other words, prior BBs use may be a marker of a high-risk cohort of patients presenting with acute myocardial infarction.

In order to clarify the relationship between prior BBs use and hospital outcome in patients presenting with acute myocardial infarction, we designed and conducted this retrospective study.

2. Methods

The study was approved by the Florida Hospital institutional review board (IRB). Patient population and data collection have been described previously [15]. Briefly, data were collected as part of the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) registry at Florida Hospital Orlando between January 1, 2013 and December 31, 2014. The ACTION registry is a quality improvement registry of STEMI and non-STEMI (NSTEMI) patients. Data were collected prospectively for all patients who present within 24 h of onset of an ischemic event with primary diagnosis of myocardial infarction (STEMI or NSTEMI). Informed consent was obtained from all participants included in the study before enrolment in the ACTION registry.

Prior BBs use was defined as taking BBs at home before presentation. Non-prior BBs group and prior BBs group were compared in terms of demographic characteristics, comorbidities, home medications, presenting characteristics, and hospital outcome using univariate analysis. In the univariate analysis, *t*-test was used for continuous variable, and Fisher's exact test for count number analysis. We then performed multivariable analysis to investigate how each clinical factor was associated with inpatient mortality after controlling for the other factors. In the multivariable analysis, logistic regression models were used, and adjusted odds ratios (OR) were estimated for each factor hypothesized to predict inpatient mortality.

After the multivariable analysis, we further evaluated the contribution of prior BBs use for predicting inpatient mortality through comparing area under receiver operating characteristic curve (ROC) and calibration between GRACE model and GRACE model plus prior BBs. To be able to compare with previous studies, we did the same data transformation as in GRACE study with age transformed to every 10 years increase, systolic blood pressure to every 20 mm Hg decrease, heart rate to 30 beat/min increase, and creatinine to 1 mg/dL increase.

All analyses were performed by using Stata version 14 (StataCorp. 2015). All *p*-values were two tailed, and $\alpha < 0.05$ was set as the level of significance for all tests.

Table 1
Baseline characteristics.

Characteristic	Non-prior beta blocker use ($n = 774$)	Prior beta blocker use ($n = 354$)	*P* Value
Demographic			
Mean age, y	62.0	67.9	<0.001
Women, %	29.6	34.8	0.083
White, %	64.6	61.2	0.246
Medical history, %			
Hypertension	63.1	94.4	<0.001
Diabetes	29.8	51.7	<0.001
Hyperlipidemia	57.9	85.0	<0.001
Stroke	5.4	13.6	<0.001
Atrial fibrillation	4.3	6.8	0.073
Heart failure	3.8	17.0	<0.001
Myocardial infarction	14.2	42.6	<0.001
Home medication, %			
Aspirin	25.3	67.2	<0.001
P2Y12 inhibitors	5.2	31.6	<0.001
Statin	23.1	66.4	<0.001
ACEI/ARB	25.6	55.7	<0.001
Presenting characteristic, %			
Heart rate, mean	83.1	85	0.069
Systolic blood pressure, mean	144.5	148.7	0.011
ST-segment deviation	59.7	43.0	<0.001
Shock	2.3	2.3	0.946
Cardiac arrest	5.4	3.1	0.088
Decompensated heart failure	3.6	9.9	<0.001
STEMI vs NSTEMI, %			
STEMI	54.4	33.9	<0.001
NSTEMI	45.6	66.1	<0.001
Procedures, %			
PCI	81.3	73.2	0.002
CABG	8.5	6.5	0.241
In-hospital outcome, %			
Re-infarction	0.8	0.3	0.328
Stroke	0.5	1.4	0.117
Death	4.8	8.8	0.009

3. Results

In total, 1128 patients presented with STEMI or NSTEMI within 24 h were included in the study. Their baseline demographic and clinical characteristics are shown in Table 1. There were 774 (68.6%) patients who did not take BBs before admission, while 354 (31.4%) patients took BBs at home (Table 1). Patients who were not on prior BB were younger (mean age 62 vs. 67.9 years, $p < 0.001$). However, there was no significant difference between the non-prior BBs group and prior BBs group in terms of gender (29.6% vs. 34.8% of women, $P = 0.083$) and ethnic distribution (64.6% vs. 61.2% of white, $P = 0.246$). Unsurprisingly, when compared with non-prior BBs users, prior BBs users were more likely to associate with cardiac relevant comorbidities such as hypertension, diabetes, hyperlipidemia, stroke, heart failure and prior myocardial infarction (all $P < 0.001$), but atrial fibrillation; and more likely to take other cardiovascular medications preceding their presentation, including aspirin, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker (all $P < 0.001$).

On presentation, prior BBs users were more likely to have decompensated heart failure than non-prior BBs users (9.9% vs. 3.6%, $P < 0.001$), but there was no significant difference between these two groups in terms of heart rate, systolic blood pressure, or relative frequency of shock and cardiac arrest on admission. However, prior BBs users were less likely to have STEMI (33.9% vs. 54.4%, $P < 0.001$), and subsequently less PCI (73.2% vs. 81.3%, $P = 0.002$). More interestingly, inpatient mortality was significantly higher in prior BBs users compared with that in non-prior BBs group (8.8% vs. 4.8%, $P = 0.009$).

To further investigate the independent effects of prior BBs on inpatient mortality, multivariable analysis was performed while controlling other covariates (Fig. 1). Prior BBs use remained independently associated with elevated inpatient mortality (adjusted OR = 3.15, $P = 0.004$). Consistent with previous reports [16], factors such as age (adjusted OR = 1.57, $P = 0.002$), heart rate (adjusted OR = 1.57, $P = 0.010$), systolic blood pressure (adjusted OR = 1.68, $P < 0.001$), cardiac arrest (adjusted OR = 11.90, $P < 0.001$), and decompensate heart failure (adjusted OR = 6.79, $P < 0.001$) were significantly associated with elevated inpatient mortality; while other factors including all medical comorbidities and all other prior medications had no significant effects on inpatient mortality, although their frequency was higher in prior BBs users. One interesting finding was that female tended to have lower inpatient mortality (adjusted OR = 0.48, $P = 0.029$) compared to males in this study.

In order to evaluate how much contribution prior BBs made in predicting inpatient mortality, we incorporated prior BBs use into the GRACE model. As shown in Table 2, most of variables in GRACE model were significant predictors of inpatient mortality except positive initial cardiac enzyme and ST-segment deviation. The addition of prior BBs to GRACE model was significantly associated with increased inpatient mortality (adjusted ratio = 1.83, $P < 0.047$). However, the c-statistic showed no significant difference between the original GRACE model and GRACE model with prior BBs (Table 2 and Fig. 2A). Calibrations of predictions from GRACE model and GRACE model with prior BBs were similar as shown in Fig. 2B and C.

4. Discussion

The effect of prior use of BBs on patients presenting with AMI was not investigated before. Our study suggested that prior use of BBs was associated with increased NSTEMI incidence. It also was associated with increased presentation with cardiogenic shock and increased inpatient mortality. The increase in mortality was not explained by the difference in baseline characteristics of the patients. Therefore, prior BBs use should be considered a high risk marker for patients presenting