

# $\beta$ -Blocker Therapy Prior to Admission for Acute Coronary Syndrome in Patients Without Heart Failure or Left Ventricular Dysfunction Improves In-Hospital and 12-Month Outcome: Results From the GULF-RACE 2 (Gulf Registry of Acute Coronary Events-2)

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**Background**—The prognostic impact of  $\beta$ -blockers (BB) in acute coronary syndrome (ACS) patients without heart failure (HF) or left ventricular dysfunction is controversial, especially in the postreperfusion era. We sought to determine whether a BB therapy before admission for ACS has a favorable in-hospital outcome in patients without HF, and whether they also reduce 12-month mortality if still prescribed on discharge.

**Methods and Results**—The GULF-RACE 2 (Gulf Registry of Acute Coronary Events-2) is a prospective multicenter study of ACS in 6 Middle Eastern countries. We studied in-hospital cardiovascular events in patients hospitalized for ACS without HF in relation to BB on admission, and 1-year mortality in relation to BB on discharge. Among the 7903 participants, 7407 did not have HF, of whom 5937 (80.15%) patients were on BB. Patients on BB tended to be older and have more comorbidities. However, they had a lower risk of in-hospital mortality, mitral regurgitation, HF, cardiogenic shock, and ventricular tachycardia/ventricular fibrillation. Furthermore, 4208 patients were discharged alive and had an ejection fraction  $\geq 40\%$ . Among those, 84.1% had a BB prescription. At 12 months, they also had a reduced risk of mortality as compared with the non-BB group. Even after correcting for confounding factors in 2 different models, in-hospital and 12-month mortality risk was still lower in the BB group.

**Conclusions**—In this cohort of ACS, BB therapy before admission for ACS is associated with decreased in-hospital mortality and major cardiovascular events, and 1-year mortality in patients without HF or left ventricular dysfunction if still prescribed on discharge. (*J Am Heart Assoc.* 2017;6:e007631. DOI: 10.1161/JAHA.117.007631.)

**Key Words:** acute coronary syndrome •  $\beta$ -adrenergic receptor blocker • heart failure • ST-segment elevation myocardial infarction

$\beta$ -Blockers (BB) have drastically improved the long-term prognosis of patients with heart failure (HF) for the past 2 decades,<sup>1</sup> which resulted in their classification as a first-line therapy in patients with HF and reduced ejection fraction by European and American cardiac societies.<sup>2,3</sup> However, their protective role in patients with acute coronary syndrome (ACS) is less clear. While robust data from randomized placebo-controlled trials and meta-analysis support their

efficacy on the short-term post-ACS,<sup>4</sup> controversies exist to their long-term beneficial effect in patients without HF or left ventricular (LV) dysfunction.

Most of the studies that reported a decrease in long-term mortality following the administration of BB post-ACS were done in the era before reperfusion therapy, and other treatments such as statins, new anti-platelets, and angiotensin-converting enzyme inhibitors/angiotensin receptor

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## Clinical Perspective

### What Is New?

- This study assessed the prognostic impact of β-blockers in patients without heart failure or left ventricular dysfunction.
- Previous β-blockade therapy on admission for acute coronary syndrome decreased in-hospital mortality, mitral regurgitation, heart failure, cardiogenic shock, and ventricular tachycardia/ventricular fibrillation in patients without heart failure.
- β-Blockers also decrease 12-month mortality in those patients if still prescribed at hospital discharge from acute coronary syndrome

### What Are the Clinical Implications?

- Our study suggested that β-blockers before admission for acute coronary syndrome in patients without heart failure or left ventricular dysfunction decrease in-hospital and 12-month mortality.
- It might be reasonable to consider β-blockers in primary prevention for high-risk patients—such as those with hypertension and diabetes mellitus—in order to improve mortality when those patients develop acute coronary syndrome.

blockers were not prescribed. In a systematic review of 31 of those trials published in the 1980s, BB decreased long-term mortality by 23% during the mean follow-up of 1.3 years.<sup>5</sup> However, those findings were challenged by recent studies performed in the postreperfusion era. A recent meta-analysis confirmed the superiority of BB over placebo in the old prereperfusion therapy era, but failed to demonstrate any long-term reduction of mortality in the reperfusion era.<sup>6</sup>

However, in most of those studies, patients were randomized to BB irrespective of their LV function. Moreover, it is not known whether a previous β-blockade therapy in patients presenting with ACS is beneficial. The aim of this article is to report on the association between BB on admission for ACS and in-hospital cardiovascular outcome, as well as 1-year mortality in relation to BB on discharge, in patients without HF or LV dysfunction. Here, we demonstrated that a BB therapy before admission for ACS is associated with better in-hospital outcome and decreased 1-year mortality in patients without HF, included in a large prospective Middle Eastern cohort that was conducted in the postreperfusion period.

## Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

## Study Group

The Gulf RACE-2 (Gulf Registry of Acute Coronary Events-2) was a prospective multicenter study of ACS patients recruited for 9 months (October 2008 to June 2009), from 6 Arab Gulf countries: Bahrain, Kingdom of Saudi Arabia, Qatar, Oman, United Arab Emirates, and Yemen, aiming at describing clinical characteristics and cardiovascular outcome of ACS. Details of patients' recruitment, study design, and methods have been previously published.<sup>7,8</sup> Briefly, we collected data, as per the case report form, of consecutive patients hospitalized for ACS in the 65 participating hospitals across the participating countries. The registry data were collected online using a dedicated website and included clinical characteristics, demographic distribution, past medical history, treatment plans, echocardiographic data, and in-hospital and long-term outcome. Patients were followed up at 90 days and at 1 year either by telephone or by a clinic visit. ACS included unstable angina, ST-elevation myocardial infarction (STEMI) and non-ST-elevation MI, and all cardiovascular outcomes were measured as defined by the American College of Cardiology/American Heart Association task force on clinical data standards guidelines for ACS.<sup>9</sup> All other clinical diagnoses, patient-related variables, and outcomes used standardized definitions. Each participating center's institutional review board approved the registry protocol. A written informed consent was obtained from all patients and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

In this analysis, we first studied in-hospital cardiovascular outcome in patients without a history of HF and/or HF symptoms, who were admitted for ACS, in relation to BB on admission (study group 1). Furthermore, we assessed 1-year mortality in patients who were discharged alive from the hospital, without LV dysfunction, as defined by a left ventricular ejection fraction (LVEF)  $\geq 40\%$ , in relation to BB prescription on discharge (study group 2). The primary outcome in both study groups was mortality, and the secondary outcomes (only for study group 1) were recurrent ischemia, mitral regurgitation, acute HF, ventricular tachycardia and/or ventricular fibrillation (VF), and stroke/transient ischemic attacks (TIAs).

## Statistical Analysis

Baseline categorical variables and outcome measures were summarized using frequency distributions, while means and SDs were used for continuous variables. Outcome measures and baseline characteristics of patients were compared between the 2 groups: BB and no BB using the  $\chi^2$  test (or Fisher exact test when expected cell counts fell below 5) for categorical variables and the Student *t* test or Wilcoxon rank sum test for numeric variables. Multivariable logistic regression analysis was performed for in-hospital and 12-month mortality; and for each analysis, 2 models were done. The first

model included age, sex, and a history of ischemic heart disease only for in-hospital mortality. The second model included variables that were statistically significant ( $P < 0.05$ ) between both groups, except for variables that have a high risk of co-linearity. The model for in-hospital mortality included age, sex, ischemic heart disease, smoking, hypertension, diabetes mellitus, dyslipidemia, body mass index, stroke/TIAs, clopidogrel, creatinine, and heart rate. The model for 12-month mortality included age, sex, hypertension, diabetes mellitus, dyslipidemia, stroke/TIAs, aspirin, statins, angiotensin-converting enzyme inhibitors, and/or angiotensin receptor blockers. The ability to discriminate the outcome between “Dead versus Alive” of the regression model was assessed using the Area Under the Receiver Operating Characteristic<sup>10</sup> and C-statistics with 95% confidence intervals (CI) for accurate prediction of the outcome. Adjusted odds ratios (OR) and 95% CI with  $P$  values are presented. Statistical significance was set at the 5% level (2-tailed test). All analyses were done using IBM-SPSS version 22.0.

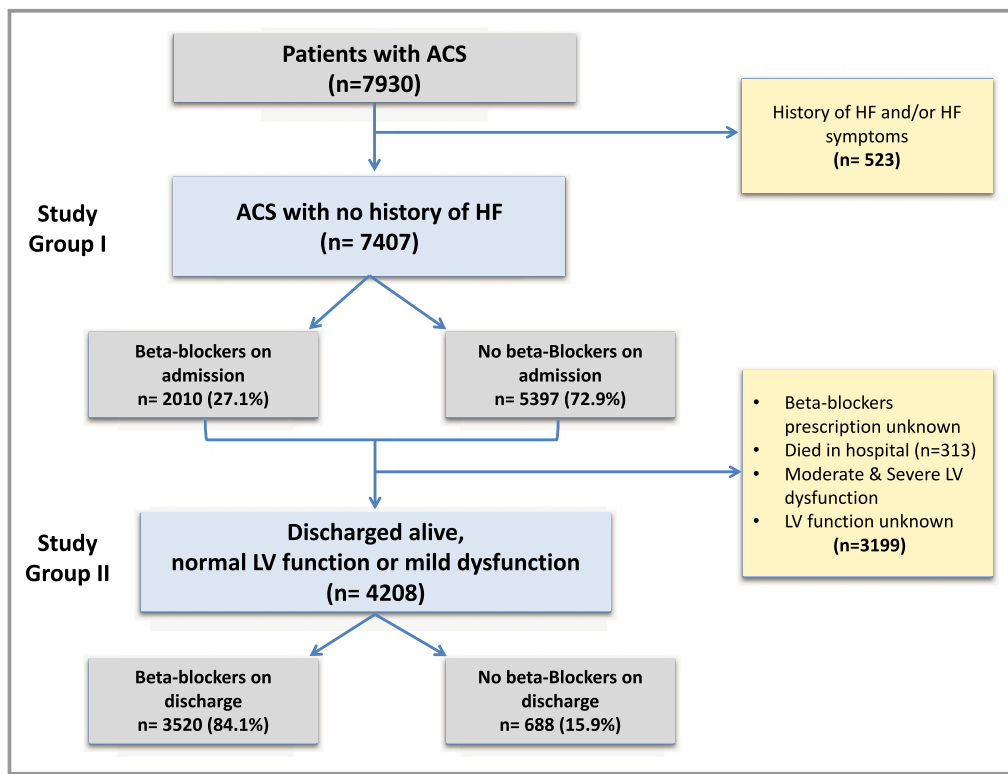
## Results

### Baseline Characteristics

Out of the total 7903 participants in the Gulf-RACE-2, 523 patients were excluded because of a history and/or

presentation for HF; hence, 7407 patients were included in study group 1 (see flow chart, Figure 1). Among those, 5937 (72.9%) patients were on BB while almost one third (27.1%) were not. Baseline characteristics of patients in study group 1 are shown in Table 1. Patients on BB tended to have more comorbidities. They were older (58 years old versus 55.6 years old,  $P = 0.001$ ), more likely to be males (26.1% versus 18.4%,  $P = 0.001$ ), had a higher prevalence of dyslipidemia, hypertension, diabetes mellitus, ischemic heart disease, and chronic kidney disease than in the non-BB group. Patients not on BB tended to smoke more and were more likely to have STEMI rather than non-ST-elevation MI. Interestingly, aspirin was prescribed in >98% of patients and statins in >96% in both groups.

Of the 5937 patients, 4208 were discharged alive and had normal LV function or mild dysfunction as confirmed by an echocardiogram on discharge (study group 2), while 3199 patients had moderate or severe LV dysfunction, an unknown LV function or BB prescription on discharge, or died ( $n = 313$ ). As shown in Table 2, the vast majority of patients with a LVEF  $\geq 40\%$  were discharged with BB (84.1%). Baseline characteristics of study group 2 were very similar to study group 1, since the proportion of males was also higher in the BB group; furthermore, the prevalence of dyslipidemia, hypertension, and diabetes mellitus was also higher. Patients on BB had more invasive interventions



**Figure 1.** Flow chart of the study. ACS indicates acute coronary syndrome; HF, heart failure; LV, left ventricular.

**Table 1.** Baseline Characteristics of Patients Admitted for ACS at the GULF-RACE-2, Without a History of HF and/or Symptoms of HF at Admission, According to BB on Admission

Variable	BB on Admission N=2010 (27.1%)	No BB on Admission N=5397 (72.9%)	P Value
<b>Demographics</b>			
Age, y	58.0±12.0	55.6±12.6	0.001
Sex (male)	525 (26.1)	991 (18.4)	0.001
BMI, kg/m <sup>2</sup>	27.8±5.8	26.7±5.3	0.001
Smoking	517 (25.7)	2235 (41.4)	0.001
<b>Race</b>			
Gulf-Arabs	1562 (77.7)	3647 (67.6)	0.001
Non-Gulf-Arabs	448 (23.3)	1750 (32.4)	
<b>Past medical history</b>			
Dyslipidemia	1035 (56.9)	1238 (26.8)	0.001
Hypertension	1486 (74.2)	1878 (35.3)	0.001
Diabetes mellitus	1022 (50.8)	1796 (33.3)	0.001
IHD	732 (37.9)	477 (9.0)	0.001
Stroke/TIAs	108 (5.4)	168 (3.1)	0.001
CKD	115 (5.8)	94 (1.8)	0.001
<b>Grace score</b>			
Low	801 (40.1)	2207 (41.6)	0.33
Intermediate	805 (40.3)	2040 (38.4)	
High	391 (19.6)	1150 (20.0)	
<b>Discharge diagnosis</b>			
STEMI	508 (25.3)	2964 (54.9)	0.001
NSTEMI	700 (34.8)	1399 (25.9)	
Unstable angina	802 (39.9)	1034 (19.2)	
<b>Clinical parameters</b>			
SBP, mm Hg, mean±SD	138.0±29.0	135.0±28.5	0.001
DBP, mm Hg, mean±SD	80.9±16.7	81.5±17.7	0.20
HR, bpm, mean±SD	82.1±19.0	84.8±20.3	0.001
Creatinine, μmol/L, mean±SD	105±87.0	98±65.2	0.001
<b>Medications at admission</b>			
Aspirin	1979 (98.5)	5313 (98.4)	0.97
ACE-inhibitors and/or ARBs	1487 (79)	4003 (74.1)	0.83
Statins	1930 (96.0)	5123 (94.9)	0.05
Clopidogrel	361 (18)	377 (7)	0.004

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; BB, β-blockers; BMI, body mass index; bpm, beats per minute; CKD, chronic kidney disease; DBP, diastolic blood pressure; GULF-RACE-2, Gulf-Registry of Acute Coronary Events-2; HF, heart failure; HR, heart rate; IHD, ischemic heart disease; NSTEMI, non-ST-elevation myocardial infarction; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; TIAs, transient ischemic attacks.

(thrombolysis, primary percutaneous coronary intervention, and coronary artery bypass grafts during hospital stay) than their non-BB counterparts. Among those who had a coronary angiogram (37.4% in the BB group and 20.65% in the non-BB group), more severe coronary artery disease was observed in the BB group. On discharge, more patients

with BB were given prescriptions for aspirin, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, statins, and clopidogrel than the non-BB group. In both groups, normal LV function was present in up to 37% while a mild LV dysfunction (40%<LVEF<50%) was more pronounced.

**Table 2.** Baseline Characteristics of Patients Discharged Alive From ACS in the GULF-RACE-2, With a LVEF ≥40%, According to BB on Discharge

Variable	BB on Discharge N=3520 (84.1%)	No BB on Discharge N=668 (15.9%)	P Value
<b>Demographics</b>			
Age, y	55±12	56±13	0.05
Sex (male)	2876 (81.7)	502 (75.1)	0.001
BMI, kg/m <sup>2</sup>	27.0±5.0	26.9±5.6	0.14
Smoking	1391 (39.5)	238 (20.2)	0.12
<b>Race</b>			
Gulf Arabs	2363 (67.1)	533 (78.8)	0.001
Non-Gulf Arabs	1157 (32.9)	135 (20.2)	
<b>Past medical history</b>			
Dyslipidemia	1709 (52.6)	156 (23.4)	0.001
Hypertension	2522 (77.6)	260 (38.9)	0.001
Diabetes mellitus	1567 (48.2)	222 (33.2)	0.02
Stroke/TIAs	103 (2.9)	32 (4.8)	0.01
CKD	88 (2.5)	16 (2.4)	0.87
<b>Discharge diagnosis</b>			
STEMI	1604 (45.5)	320 (48.0)	0.27
NSTEMI	1058 (30.1)	174 (26.0)	0.04
Unstable angina	858 (24.4)	174 (26.0)	0.41
<b>Clinical parameters on discharge</b>			
SBP, mm Hg, mean±SD	139±27	134±28.5	0.001
DBP, mm Hg, mean±SD	83±16	79±17	0.001
HR, bpm, mean±SD	82±18	81±20	0.06
<b>Interventions</b>			
Thrombolysis	800 (56.2)	124 (40.5)	0.001
Primary PCI	714 (20.7)	65 (9.7)	0.001
CABG	324 (9.2)	33 (4.9)	0.001
<b>Coronary angiogram*</b>			
Significant double-vessel disease	363 (10.3)	40 (6.0)	0.001
Significant triple-vessel disease	409 (11.6)	41 (6.1)	0.001
<b>LV function</b>			
Normal (LVEF ≥50%)	1313 (37.3)	250 (37.4)	0.95
Mild LV dysfunction (LVEF 40–50%)	2207 (62.7)	418 (62.6)	
<b>Medications at discharge</b>			
Aspirin	3447 (98.0)	582 (87.4)	0.001
ACE-inhibitors and/or ARBs	2966 (84.3)	464 (69.6)	0.001
Statins	3416 (97.0)	568 (85.2)	0.001
Clopidogrel	2802 (79.6)	439 (65.7)	0.001

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; BB, β-blockers; BMI, body mass index; bpm, beats per minute; CABG, coronary artery bypass graft; CKD, chronic kidney disease; DBP, diastolic blood pressure; GULF-RACE-2, Gulf-Registry of Acute Coronary Events-2; HR, heart rate; LV, left ventricular; LVEF, left ventricular ejection fraction; NTSEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; TIAs, transient ischemic attacks.

\*Performed only in 37.4% of patients on BB and 20.65% of patients not on BB.



### In-Hospital Outcome

In-hospital outcome data were available in all patients of study group 1. There were 313 deaths and the cumulative mortality since admission was 4.2%. However, it was lower in patients on BB (OR 0.64, 95% CI, 0.48–0.85, *P*=0.002) (Table 3), as was the risk of mitral regurgitation (OR 0.15, 95% CI, 0.07–0.32, *P*=0.001), ventricular tachycardia and/or VF (OR 0.52, 95% CI, 0.38–0.71, *P*=0.001), cardiogenic shock (OR 0.66, 95% CI, 0.52–0.81, *P*=0.001), and acute HF (OR 0.50, 95% CI, 0.24–0.78, *P*=0.001). However, both groups had a similar risk for stroke/TIAs and recurrent ischemia. Multivariable analysis of in-hospital mortality showed that age was associated with an increased risk, whereas male sex was associated with a better prognosis (Table 4). Interestingly, dyslipidemia was independently associated with a lower mortality risk (OR 0.59, 95% CI, 0.44–0.80, *P*=0.001); that might be because patients with dyslipidemia are more often prescribed statins and/or given higher doses. As expected, creatinine and heart rate are associated with a worse outcome. Even after correcting for several variables, BB conferred protection in patients hospitalized for ACS in both models (OR 0.55, 95% CI, 0.41–0.75, *P*=0.001; OR 0.68, 95% CI, 0.49–0.97; model 1 and model 2; respectively). Subgroup analysis showed that BB protect both males and females, patients <65 years and elderly patients, patients with diabetes mellitus as well as nondiabetics, patients without a history of MI, and hypertensive patients. However, women on BB had a lower magnitude of benefit than male counterparts (OR 0.62, 95% CI, 0.39–0.99, *P*=0.05; OR 0.58, 95% CI, 0.40–0.83, *P*=0.001; females versus males, respectively). Interestingly, nonhypertensive patients were not protected (OR 0.75, 95% CI, 0.46–1.30, *P*=0.26), nor were those with a history of MI despite the presence of a clear trend (OR 0.61, 95% CI, 0.35–1.09, *P*=0.09) (Figure 2A).

### Twelve-Month Outcome

At 12 months, survival data were available in all patients. There were 216 deaths and the cumulative mortality since hospital discharge was 5.13%. However, mortality was lower in the BB group than in patients discharged home without BB (4.1% versus 10.6%, OR 0.64, 95% CI, 0.48–0.87, *P*=0.001; respectively). Multivariable analysis showed that age and a previous history of TIAs increase the mortality risk. Surprisingly, hypertension is associated with a lower risk, probably because hypertensive patients are treated more aggressively and prescribed cardiovascular protective drugs to lower the total cardiovascular risk. Even after correcting for different variables, BB conferred protection in patients initially discharged with BB hospitalized for ACS in both models (OR 0.37, 95% CI, 0.27–0.50, *P*=0.001; OR 0.58, 95% CI, 0.41–0.82; model 1 and model 2; respectively) (Table 5). Subgroup analysis showed that BB confer protection to a large subgroup

**Table 3.** In-Hospital Outcome of Patients Admitted for ACS at the GULF-RACE-2, Without a History of HF and/or Symptoms of HF at Admission, According to BB on Admission

	Mortality	Recurrent Ischemia	Acute MR	CHF	Cardiogenic Shock	VT and/or VF	Stroke/TIAs
	Number of Events OR 95% CI	Number of Events OR 95% CI	Number of Events OR 95% CI	Number of Events OR 95% CI	Number of Events OR 95% CI	Number of Events OR 95% CI	Number of Events OR 95% CI
<b>BB on admission</b>							
No	61 OR=1	842 OR=1	124 OR=1	611 OR=1	331 OR=1	247 OR=1	12 OR=1
Yes	252 OR=0.64 (0.48–0.85)	283 OR=1.13 (0.98–1.31)	7 OR=0.15 (0.07–0.32)	159 OR=0.50 (0.24–0.78)	83 OR=0.66 (0.52–0.81)	49 OR=0.52 (0.38–0.71)	37 OR=0.87 (0.45–1.67)
<i>P</i> value	0.002	0.11	0.001	0.001	0.001	0.001	0.68

ACS indicates acute coronary syndrome; BB, β-blockers; CHF, congestive heart failure; CI, confidence interval; GULF-RACE-2, Gulf-Registry of Acute Coronary Events-2; HF, heart failure; MR, mitral regurgitation; OR, odds ratio; TIAs, transient ischemic attacks; VF, ventricular fibrillation; VT, ventricular tachycardia.

**Table 4.** Multivariable Analysis of In-Hospital Mortality in Patients Admitted for ACS at the GULF-RACE-2, Without a History of HF and/or Symptoms of HF at Admission

Variable	Model 1			Model 2		
	Adjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value
Age, y	1.04	1.03 to 1.05	0.001	1.04	1.03 to 1.05	0.001
Sex (male)	0.62	0.48 to 0.80	0.001	0.56	0.42 to 0.75	0.001
IHD	1.02	0.73 to 1.41	0.91	1.24	0.90 to 1.72	0.19
Smoking				0.91	0.70 to 1.19	0.51
Hypertension				0.78	0.60 to 1.02	0.07
Diabetes mellitus				1.13	0.88 to 1.45	0.35
Dyslipidemia				0.73	0.53 to 0.98	0.04
Statins				0.72	0.50 to 1.04	0.08
BMI, kg/m <sup>2</sup>				0.99	0.97 to 1.01	0.45
Stroke/TIAs				1.13	0.68 to 1.90	0.63
Clopidogrel				1.30	0.86 to 1.98	0.22
Creatinine, μmol/L				1.42	1.32 to 1.53	0.001
HR, bpm				1.01	1.0 to 1.01	0.03
BB on admission						
No	1	Reference group		1	Reference group	
Yes	0.55	0.41 to 0.75	0.001	0.68	0.49 to 0.97	0.03

ACS indicates acute coronary syndrome; BB, β-blockers; bpm, beats per minute; CI, confidence interval; GULF-RACE-2, Gulf-Registry of Acute Coronary Events-2; HF, heart failure; HR, heart rate; IHD, ischemic heart disease; OR, odds ratio; TIAs, transient ischemic attacks.

of the following: both males and females, patients <65 years and the elderly, patients with diabetes mellitus as well as nondiabetics, patients admitted either for STEMI or non-ST-elevation MI, and patients with normal LV function (LVEF >50%) and mild dysfunction (LVEF from 40% and 50%) (Figure 2B).

### Sensitivity Analysis

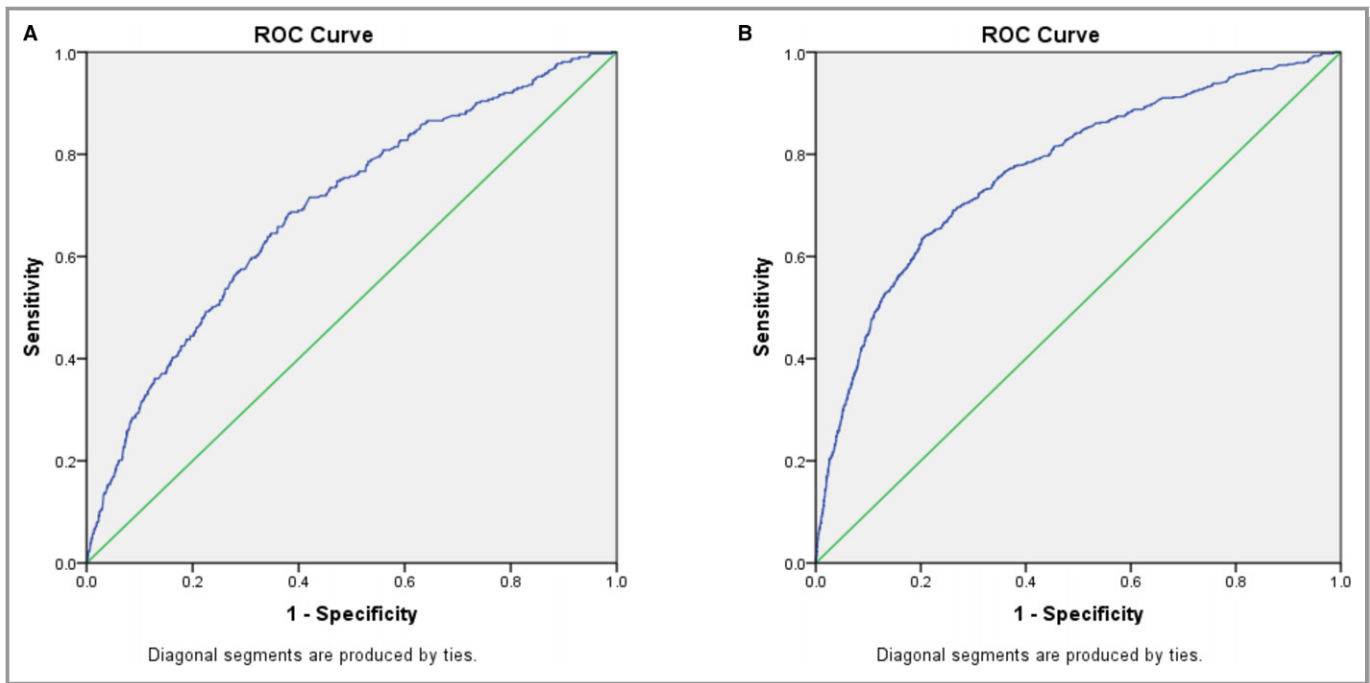
We performed sensitivity analysis by conducting a receiver operating characteristic curve analysis. In the first analysis, BB on admission are shown to be good predictors for in-hospital mortality, and the area under the curve was 0.69 (95% CI, 0.663–0.723; *P*=0.015) (Figure 3A). In the second analysis, BB on discharge were also good predictors of 12-month mortality; the area under the curve was 0.770 (95% CI, 0.75–0.79; *P*=0.010) (Figure 3B).

### Discussion

This observational study demonstrates that BB therapy before admission for ACS in patients without a history of HF and/or HF symptoms is associated with decreased in-hospital mortality, and major in-hospital cardiovascular events such

as acute HF, mitral regurgitation, cardiogenic shock, and ventricular tachycardia and/or VF. Furthermore, BB prescription on discharge from ACS is also associated with an increased 12-month survival in patients with normal LV function or a mild dysfunction.

To our knowledge, we are the first to report that BB therapy before admission for ACS is associated with a better in-hospital outcome in the postreperfusion era with mechanical intervention such as with stents. Interestingly, patients on BB had more comorbidities but there were fewer deaths and they developed fewer in-hospital cardiovascular events. This could be because a long-term β-blockade therapy confers protection from mortality, acute HF, and arrhythmias, despite the occurrence of myocardial ischemia. However, patients on BB were more often prescribed statins and clopidogrel. Statins reduce cardiovascular events and improve mortality post-MI on the short term and long term.<sup>11,12</sup> In a recent analysis of the French registry of FAST-MI (Acute ST- and Non-ST-Elevation Myocardial Infarction),<sup>13</sup> statins were associated with decreased mortality post-MI, even after 5 years from the event. Clopidogrel also confers cardiovascular protection and lowers mortality following an ACS,<sup>14</sup> even in patients not undergoing a percutaneous coronary intervention.<sup>15</sup> Nevertheless, BB conferred protection even after taking into account those variables.



**Figure 2.** Receiver operating characteristic (ROC) curve analysis of in-hospital mortality in relation to  $\beta$ -blockers on admission for ACS (A) and 12-month mortality in relation to  $\beta$ -blockers on discharge from ACS (B). ACS indicates acute coronary syndrome.

Several trials and meta-analyses have firmly demonstrated that BB reduce mortality and rehospitalization in patients with HF.<sup>16</sup> We have also demonstrated that BB therapy in patients hospitalized for acute HF was associated with better in-hospital outcome<sup>17</sup>; furthermore, we have also shown that nonwithdrawal of BB during acute HF is also associated with decreased in-hospital mortality.<sup>18</sup> However, whether BB are associated with improved survival and decreased rehospitalization for HF in patients without a history of HF—which is the case of our study group—or in patients with normal LV function, is not known. In the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry, BB did not decrease mortality, rehospitalization, or the combined end point in patients with HF and preserved ejection fraction.<sup>19</sup> However, the decreased arrhythmic risk associated with BB therapy has been demonstrated in several studies because BB inhibit the autonomic nervous system,<sup>20</sup> hyperactivation of which could trigger arrhythmias.<sup>21</sup>

We also demonstrated that BB on discharge from ACS decrease 12-month mortality. The long-term cardiovascular outcome associated with BB prescription following an ACS is controversial. Although BB were proven to decrease the infarct size and limit the LV remodeling on the short- and medium term,<sup>1,22</sup> several studies questioned its use in the long term, especially in the past 2 decades when reperfusion and secondary prevention have become a common clinical practice. In the COMMIT (Clopidogrel and Metoprolol in

Myocardial Infarction) trial that randomized >45 000 patients with ACS to metoprolol versus placebo, the co-primary end point of decreased mortality was not met, whereas only the risk of reinfarction and VF was decreased at the price of an excess cardiogenic shock.<sup>23</sup> Concordant with those results, BB did not improve mortality in patients with stable coronary artery disease with a prior history of ACS or in those with high cardiovascular risk during the median follow-up of 44 months in the REACH (Reduction of Atherothrombosis for Continued Health) registry.<sup>24</sup> Although the co-primary end point of decreased cardiovascular mortality, nonfatal MI, and stroke was met with BB in patients with a previous MI without HF, included in a post hoc analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial, mortality alone was unaffected over 2 years of follow-up.<sup>25</sup>

Our results regarding 12-month mortality reduction are discordant with 2 recent registries of ACS.<sup>13,26</sup> Puymirat and colleagues reported in the recent analysis of the FAST-MI registry a neutral effect of BB post-MI on mortality at 1 and 5 years (adjusted hazard ratio: 0.77, 95% CI, 0.46–1.30; 1.19, 95% CI, 0.65–2.18; respectively).<sup>13</sup> Likewise, an English and Welsh mixed cohort study of  $\approx$ 180 000 patients with ACS but without HF or LV dysfunction on discharge did not demonstrate any benefits of BB on 1-year mortality.<sup>26</sup> However, our results are aligned with 2 recent studies: OBTAIN (The Outcomes of Beta-blocker Therapy After Myocardial Infarction) registry<sup>27</sup> and a retrospective analysis of electronic



**Table 5.** Multivariable Analysis of 12-Month Mortality in Patients Discharged Alive From ACS in the GULF-RACE-2, With a LVEF ≥40%

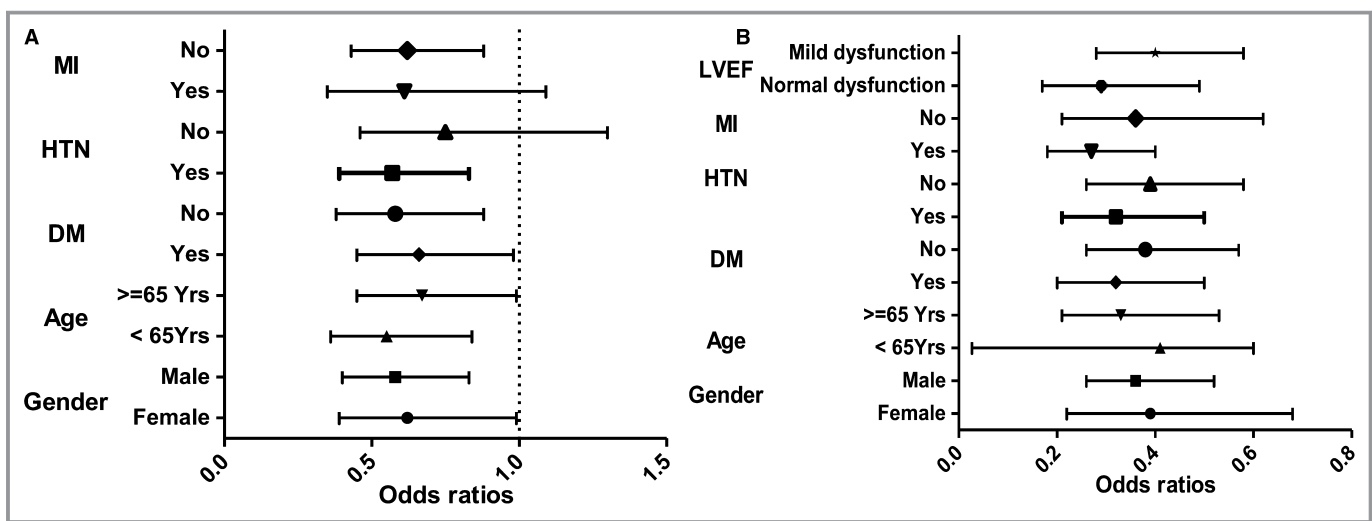
Variable	Model 1			Model 2		
	Adjusted OR	95% CI	P Value	Adjusted OR	95% CI	P Value
Age, y	1.04	1.03 to 1.05	0.001	1.03	1.02 to 1.04	0.001
Sex (male)	0.82	0.60 to 1.36	0.24	0.86	0.61 to 1.23	0.41
Hypertension				0.70	0.50 to 0.98	0.04
Diabetes mellitus				1.57	1.15 to 2.15	0.005
Dyslipidemia				0.70	0.47 to 1.01	0.06
Stroke/TIAs				2.40	1.33 to 3.95	0.003
Aspirin				1.23	0.85 to 1.82	0.31
ACE-inhibitors and/or ARBs				0.90	0.44 to 1.84	0.77
Statins				1.17	0.74 to 1.85	0.50
Clopidogrel				0.92	0.56 to 1.52	0.75
<b>BB on discharge</b>						
No	1	Reference group		1	Reference group	
Yes	0.37	0.27 to 0.50	0.001	0.58	0.41 to 0.82	0.001

ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; BB, β-blockers; CI, confidence interval; GULF-RACE-2, Gulf-Registry of Acute Coronary Events-2; LVEF, left ventricular ejection fraction; OR, odds ratio; TIAs, transient ischemic attacks.

health records from a healthcare delivery system at California.<sup>28</sup> In the OBTAIN study, BB on discharge from an ACS were associated with a decreased 2-year mortality.<sup>27</sup> Similarly, in the California study, β-blockade therapy reduced mortality in patients with newly diagnosed coronary artery disease post-MI, during the follow-up of almost 4 years.<sup>28</sup>

European and American guidelines regarding BB use post-MI are conflicting, especially regarding the duration of

the treatment. The American Heart Association/American College of Cardiology 2013 guidelines for STEMI recommend that BB should be used in the long term in patients without HF, unless contraindicated.<sup>29</sup> The 2014 NSTEMI suggest that it might be reasonable to prescribe BB in non-HF patients indefinitely (Class IIa).<sup>30</sup> However, in both scenarios, the long term is limited to 3 years according to the 2011 AHA/American College of Cardiology secondary



**Figure 3.** Subgroup analysis of in-hospital mortality in patients with β-blockers on admission (A), and 12-month mortality in patients discharged with β-blockers (B). DM indicates diabetes mellitus; HTN, hypertension; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

prevention update (Class I), and any therapy beyond 3 years might be reasonable (Class IIa).<sup>31</sup> In the absence of trials in the postreperfusion era, the European Society of Cardiology 2012 STEMI guidelines have switched the level of recommendation of long-term BB therapy from class I to IIa in 2012,<sup>32</sup> and kept the same class in the recently published 2017 guidelines.<sup>33</sup> Interestingly, no specific guidance for the use of BB in patients without HF was published in the 2015 European Society of Cardiology non-ST-elevation MI guidelines.<sup>34</sup> In the light of our results, it might be reasonable to consider BB in primary prevention for high-risk patients—such as those with hypertension and diabetes mellitus—in order to improve mortality when those patients develop an ACS. Nevertheless, replication of our data in other registries and doing a randomized clinical trial are mandatory before any formal recommendation.

We acknowledge the presence of several limitations. First, this was an observational study and not a randomized controlled trial that compared BB versus placebo in patients with ACS and no HF or LV dysfunction. LVEF on admission for ACS was missing in many patients, many of whom were hospitalized for a cardiovascular event for the first time; thus, we relied only on the medical history of HF that was collected by investigators and/or symptoms of HF on presentation for ACS. Hence, selection bias is possible as we could have included in our analysis patients with reduced ejection fraction who have never been diagnosed with HF, or excluded patients with HF and preserved LVEF. Although patients in the BB group had more extensive disease on cardiac catheterization, we cannot generalize that finding to patients who did not have that procedure, knowing that they represent the majority of the cases. Additionally, we included in our multivariable models all possible predictors of ACS mortality, but we cannot exclude the existence of other possible parameters that were not recorded by investigators of this cohort. The study population consists of Arabs; thus, these findings may not apply to other ethnic groups. Finally, there was a lack of information regarding BB type, dose, and the duration of the therapy. We recognize that all of those factors are confounding and could have influenced the outcome.

## Conclusions

Our results suggest that previous β-blockade therapy in patients admitted for ACS without a history of HF and/or HF symptoms on admission is associated with decreased in-hospital mortality, ventricular tachycardia and/or VF, congestive HF, and cardiogenic shock. Moreover, BB on discharge are also associated with decreased 12-month mortality in patients with normal LV function or mild dysfunction.

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