Relationship Between β-Blocker Therapy at Discharge and Clinical Outcomes in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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Background—The evidence supporting the use of β-blockers in patients with acute coronary syndrome after successful percutaneous coronary intervention has been inconsistent and scarce.

Methods and Results—Between March 1, 2009, and December 30, 2014, a total of 3180 eligible patients with acute coronary syndrome undergoing percutaneous coronary intervention were consecutively enrolled. The primary end point was all-cause death and the secondary end point was a composite of all-cause death, nonfatal myocardial infarction, heart failure readmission, and cardiogenic hospitalization. Patients were compared according to the use of β-blockers at discharge. Compared with the no β-blocker group, the risk of all-cause death was significantly lower in the β-blocker group (hazard ratio [HR], 0.33; 95% CI, 0.17–0.65 [P=0.001]). A consistent result was obtained in multiple adjusted model and propensity score–matched analysis. The use of β-blockers was also associated with decreased risk of composite of adverse cardiovascular events (HR, 0.47; 95% CI, 0.28–0.81 [P=0.006]), although statistical significance disappeared after multivariable adjustment and propensity score matching. Furthermore, we performed post hoc analysis for the subsets of patients and the results revealed that patients with non–ST-segment elevation myocardial infarction benefited the most from β-blocker therapy at discharge (HR, 0.04; 95% CI, 0.00–0.27 [P=0.001]), and the use of <50% of target dose was significantly associated with better outcome compared with no β-blocker use, rather than ≥50% of target dose.

Conclusions—The administration of relatively low β-blocker dose is associated with improved clinical outcomes among patients with acute coronary syndrome after successful percutaneous coronary intervention, especially for patients with non–ST-segment elevation myocardial infarction. (J Am Heart Assoc. 2016;5:e004190 doi: 10.1161/JAHA.116.004190)

Key Words: acute coronary syndrome • β-blocker • clinical outcomes

β-Blockers, as one of secondary prevention medications, can diminish myocardial oxygen demand by reducing heart rate, blood pressure, and myocardial contractility, thereby being widely used to relieve ischemic symptoms in patients with acute coronary syndrome (ACS). The updated American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend the use of β-blockers for the management of ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation myocardial infarction (NSTEMI). However, evidence supporting the clinical benefit of β-blockers is largely based on studies in patients with acute MI for STEMI, and was extrapolated to patients with unstable angina pectoris (UAP) and NSTEMI. In the percutaneous coronary intervention (PCI) era, patients with ACS, a spectrum of clinical presentations ranging from UAP to NSTEMI and STEMI, mostly constituted those undergoing PCI. However, few studies are available to systematically describe the contemporary pattern of β-blocker use and determine its impact on clinical outcomes in ACS patients after PCI. As Shachamet et al pointed out, many physicians remain unconvinced of either a short- or long-term benefit of β-blocker use following PCI. Moreover, much less attention has been paid to specifying which subgroup of patients with ACS benefits the most from β-blocker therapy. Thus, we sought to evaluate the impact of β-blocker therapy on clinical outcomes in patients...
with ACS after PCI and specified subgroups in a “real-world” clinical setting.

Methods

Study Population

All patients diagnosed with coronary heart disease at Tongji Hospital in Wuhan, China, were consecutively recruited in the Clinical Outcomes of Coronary Heart Diseases in Tongji Hospital registry from March 1, 2009. Demographics, clinical profiles, and concomitant medications were collected with standardized case report forms by professional investigators in the department of cardiology, and all participants were prospectively contacted at 1, 6, and 12 months by cardiology nurses and research coordinators through patient interview, chart review, and serial telephone contacts. Written informed consent was obtained from each patient at admission.

Between March 1, 2009, and December 30, 2014, all patients in the database were searched. For inclusion, patients were required to meet the following criteria: (1) age older than 18 years; (2) have an ascertained diagnosis of ACS at admission, and (3) undergoing PCI. In addition, the following patients were excluded from this analysis: (1) patients discharging unstable, (2) patients with the absence of β-blocker information at discharge, or (3) contraindication to β-blocker therapy such as significant bradycardia (heart rate <50 beat per min) or hypotension (systolic blood pressure <90 mm Hg). This strategy was approved by the ethics committee of Tongji Medical College and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The study was supported by grants from the National Program on Key Basic Research Project (973 Program) (No. 2012CB518004), the National Nature Science Foundation Key project (No. 91439203), and the National Health and Family Planning Commission of China (No. 201202025, No. 2011BAI11B04).

Definitions and Clinical End Points

For the purpose of calculating the proportion of β-blocker dose administered (daily dosage of β-blockers/target dose), the target dose was in line with β-blocker doses used in large randomized trials, defined as follows: metoprolol 200 mg/d,7 carvedilol 50 mg/d,8 timolol 20 mg/d,9 bisoprolol 10 mg/d,10 atenolol 100 mg/d,11 and propanolol 180 mg/d.12 In addition, patients who were diagnosed with ACS must present with ischemic symptoms within 24 hours and have at least one of the following conditions: (1) electrocardiographic changes consistent with ACS, (2) an increase in serum cardiac biomarkers (troponin or creatine kinase-MB), or (3) documentation of angina pectoris.13 Successful PCI was identified as a patent vessel at the treatment site with anterograde thrombolysis in myocardial infarction flow 3 and angiographic residual stenosis <50%. In the present study, we evaluated two study end points: (1) the primary outcome was all-cause mortality, which was regarded as cardiac origin unless obvious noncardiac cause could be identified; and (2) the secondary outcome was a composite end point of all-cause death, nonfatal MI, heart failure readmission, and cardiogenic hospitalization. Of these, MI referred to symptoms with new electrocardiographic changes (pathologic Q waves, persistent ST-segment elevation, or ST-segment depression) as well as cardiac markers at least one value above the 99th percentile of the upper reference limit.14 The identification of heart failure readmission was consistent with the guidelines of the European Society of Cardiology.15 In addition, cardiogenic hospitalization was considered as a hospitalization for cardiovascular cause, including UAP, transient ischemic attack, or revascularization procedure. The occurrence of clinical outcomes was systematically adjudicated by two independent physicians.

Statistical Analysis

Characteristics of study participants were expressed as mean±SD or percentage. We divided patients into two groups with regard to whether β-blocker therapy was received at discharge. Categorical variables were compared using chi-square test and continuous variables were analyzed by means of Wilcoxon rank-sum test or Student t test according to its distribution. Characteristics of study participants were further compared with respect to the following: no β-blocker use, <50% of target dose, and ≥50% of target dose. Differences among groups were examined in the same way for categorical variables and 1-way ANOVA analysis or Kruskal–Wallis rank test if deviated from normality for continuous variables. Survival curves were depicted by Kaplan–Meier method and compared with the log-rank test. Multivariable Cox proportional hazard regression was applied to identify the independent factors associated with end points. The variables entered into the multivariate model were age, sex, hypertension, diabetes, dyslipidemia, stroke, prior infarction, recent infarction within 3 weeks, heart failure status (Canadian heart class or Killip heart class), arrhythmia, and medications at discharge (aspirin, clopidogrel, statins, β-blocker, angiotensin-converting enzyme inhibitors [ACEIs]/angiotensin receptor blockers [ARBs], nitrates). In addition, clinical factors related to treatment selection may confound the event rates, therefore, we performed propensity score–matched analysis to address the issue. To estimate the propensity score, a logistic regression model developed with the variables, including age, sex, hypertension, diabetes, dyslipidemia, stroke, prior
infarction, recent infarction within 3 weeks, heart failure status (Canadian heart class or Killip heart class), arrhythmia, and medications at discharge (aspirin, clopidogrel, statins, ACEIs/ARB, nitrates), was used to predict the use of β-blockers. Patients in the β-blocker group were 1:1 matched to patients in the no β-blocker group on the basis of their propensity score and the value of caliper equal to 0.2. Absolute standardized differences <10% for a given covariate indicate a relatively small imbalance. For the propensity score–matched cohort, McNemar test was used for paired categorical variables and paired t test or paired sample Wilcoxon rank test for continuous variables, depending on the normality of the variables. The associations of β-blocker use with clinical outcomes were evaluated by use of Cox regression models.

SPSS version 20.0 (IBM Corp, Armonk, NY) was used for statistical analysis. All comparisons were two-sided, and P<0.05 was considered statistically significant. The power of the study was calculated by PASS version 11.0 (NCSS, Kaysville, UT).

Results

Study Cohort

Between March 1, 2009, and December 30, 2014, there were 5063 patients recruited in the database, and only 3453 patients underwent the PCI procedure. Of these, 23 patients were discharged unstably, 183 were not diagnosed with ACS at admission, 43 had a contraindication to β-blocker use, and 24 could not provide complete information about the administration of β-blockers at discharge, and were excluded from the analysis. Finally, 3180 patients were included in the evaluation cohort. The details are shown in Figure 1.

β-Blocker Management at Discharge and Baseline Characteristics

In the overall evaluation cohort, 2423 patients (76.2%) were discharged on β-blockers, while 757 patients (23.8%) were not. Compared with β-blocker users, patients who were not administrated β-blockers were older (60.79±10.39 versus

![Figure 1. Study flow profile. ACS indicates acute coronary syndrome; CHD, coronary heart disease; PCI, percutaneous coronary intervention.](image)
58.44±10.47, *P*<0.001), had lower diastolic blood pressure (DBP) (79.01±13.18 versus 80.57±13.18, *P*=0.005), lower heart rate (74.40±15.15 versus 75.10±12.42, *P*=0.009), and were more likely to have arrhythmia (11% versus 7.1%, *P*<0.001). For concomitant medication use, the prescriptions of aspirin, statins, and ACEIs/ARBs were more common in the -blocker group compared with the no -blocker group (99.4% versus 98.4% [*P*=0.007]; 98.6% versus 95.5% [*P*<0.001]; 81% versus 58.4% [*P*<0.001]). Table 1 summarizes the baseline characteristics and other medication management according to the use of -blockers at discharge. The differences in the baseline characteristics in the 3 subgroups are also shown in Tables 2 through 4. In the propensity score-matched model, there was no significant difference in the baseline characteristics between the -blocker group and the no -blocker group.

**Clinical Outcomes**

At 1 year after index admission, completed follow-up information was obtained in 3153 patients (99.2%). A total of 33 patients died of all-cause diseases, 14 patients occurred nonfatal MI, 34 patients had heart failure, and 214 patients died of all-cause diseases, 14 patients occurred nonfatal MI, 34 patients had heart failure, and 214 patients were readmitted for cardiogenic reasons during follow-up. -blocker therapy was associated with a lower incidence of all-cause death (unadjusted hazard ratio [HR], 0.33; 95% CI, 0.17–0.65 [*P*=0.001]). After adjusting for confounders, the risk of all-cause death remained consistently lower in the -blocker group (adjusted HR, 0.38; 95% CI, 0.17–0.83 [*P*=0.015]) (Table 5). In the propensity score-matched cohort, the -blocker group still had decreased all-cause mortality (HR, 0.27; 95% CI, 0.08–0.97 [*P*=0.045]) (Table 6). A lower rate of secondary end point was also observed in the -blocker users (unadjusted HR, 0.76; 95% CI, 0.59–0.98 [*P*=0.035], although the statistical difference disappeared after adjustment (adjusted HR, 0.87; 95% CI, 0.66–1.16 [*P*=0.355]). In addition, the associations of -blocker use with the rate of nonfatal MI, heart failure readmission, and cardiogenic hospitalization were computed, respectively. The results are illustrated in Table 5, and Figure 2 describes the association between the use of -blockers and clinical end points.

**Subgroup Analyses**

At baseline, 728 patients (22.9%) had STEMI, 576 patients (18.1%) had NSTEMI, and 1876 patients (59.0%) had UAP. We evaluated the relative -blocker treatment effects in the subsets of patients with ACS. Notably, a greater benefit of -blocker use was found in patients with NSTEMI whose incidence of all-cause death was significantly lower in the -blocker group (0.2% versus 6.4%; unadjusted HR, 0.04; 95% CI, 0.00–0.27 [*P*=0.001]), and the relationship remained even after performing multivariable Cox proportional hazard regression analysis (adjusted HR, 0.00; 95% CI, 0.00–0.14 [*P*=0.005]). In addition, -blocker use was associated with a lower risk of the secondary end point (7.8% versus 15.7%; unadjusted HR, 0.47; 95% CI, 0.28–0.81 [*P*=0.006]), but no statistical difference was observed after adjustment (adjusted HR, 0.65; 95% CI, 0.35–1.21 [*P*=0.171]). In the patients with STEMI and UAP, however, there was no statistical difference between the two groups for all-cause mortality (1.1% versus 1.9%; adjusted HR, 0.40; 95% CI, 0.08–1.94 [*P*=0.257] in patients with STEMI and 0.7% versus 0.9%; adjusted HR, 0.96; 95% CI, 0.29–3.10 [*P*=0.938] in patients with UAP) and the secondary end point (8.5% versus 16.1%; adjusted HR, 1.13; 95% CI, 0.59–2.16 [*P*=0.720] in patients with STEMI and 9.0% versus 9.9%; adjusted HR, 0.97; 95% CI, 0.66–1.41 [*P*=0.852] in patients with UAP (Table 5 and Figure 2). The associations of -blocker therapy with the clinical outcomes across the 3 subgroups were consistent in the propensity score-matched cohorts (Table 6).

**Doses of -Blockers**

Among the patients discharged on -blockers, receiving <50% of target dose was reported in 2012 patients (83.0%), while 411 patients (17%) were prescribed ≥50% of target dose and the administration of metoprolol accounted for the majority (85.4%). The baseline characteristics according to the treatment of -blocker use are exhibited in Table 1 through 4. For overall patients, all-cause mortality was 0.7% in <50% of target dose group, significantly lower than in the no -blocker group (0.7% versus 2.1%; adjusted HR, 0.40; 95% CI, 0.19–0.82 [*P*=0.012]), while the rate of all-cause death was not different between ≥50% of target -blocker dose group and no -blocker group (0.7% versus 2.1%; adjusted HR, 0.46; 95% CI, 0.13–1.59 [*P*=0.221]) (Figure 3), and no differences were observed in the incidence of secondary end point between the three different -blocker dose groups. Similar results were also obtained in patients with NSTEMI (Figure 3).

**Discussion**

In this observational study, we investigated the association of -blocker use with the clinical outcomes in patients with ACS undergoing PCI. We found that nearly 77% of eligible patients with ACS undergoing PCI were treated with -blockers at discharge, and those not prescribed -blockers were more likely to be older and have a history of arrhythmia. Importantly, -blocker therapy at discharge, especially a relatively low -blocker dosage, were independently associated with improved survival, and the efficacy was more significant in patients with NSTEMI. -Blocker therapy also

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Table 1. Baseline Characteristics in the Overall Patients

|                         | Before Matching          |                   | After Matching          |                   | β-Blocker Use (% of Target Dose) | Among 3 β-Blocker Doses |
|-------------------------|--------------------------|-------------------|-------------------------|-------------------|----------------------------------|-------------------------|
|                         | All (N=3180)             | β-Blocker Group   | No β-Blocker Group      | β-Blocker Group   | No β-Blocker Group              |                          |
|                         | (n=2423)                 | (n=757)           | (n=651)                 | (n=651)           | (n=512)                          | (n=411)                 |
| **Before Matching**     |                          |                   |                         |                   |                                 |                          |
| **No β-Blocker Group**  |                          |                   |                         |                   |                                 |                          |
| **After Matching**      |                          |                   |                         |                   |                                 |                          |
| **P Value**             |                          |                   |                         |                   |                                 |                          |
| **β-Blocker Group**     |                          |                   |                         |                   |                                 |                          |
| **Age, y**              | 59.00±10.50              | 58.44±10.47       | 60.79±10.39             | 0.001             | 60.78±10.43                     | 60.87±10.39             |
|                         | 133.84±20.35             | 133.20±20.93      | 132.50±20.73            | 0.032             | 132.85±19.31                    | 132.24±20.73            |
| **Male, %**             | 75.9                     | 75.6              | 76.9                    | 0.467             | 76.7                            | 76.8                    |
|                         | 79.07±13.18              | 79.01±13.18       | 78.86±13.08             | 0.005             | 79.70±12.52                     | 78.64±13.08             |
| **Hypertension, %**     | 66.3                     | 66.6              | 65.5                    | 0.568             | 64.7                            | 66.5                    |
|                         | 74.94±13.10              | 75.10±12.42       | 74.40±15.15             | 0.009             | 74.73±12.45                     | 74.40±15.11             |
| **Diabetes, %**         | 32.4                     | 32.9              | 30.9                    | 0.297             | 31.2                            | 31.6                    |
|                         | 85.23±55.46              | 84.10±43.38       | 88.90±73.86             | 0.330             | 89.53±68.88                     | 88.49±75.41             |
| **Dyslipidemia, %**     | 46.1                     | 46.8              | 43.8                    | 0.146             | 47.6                            | 45.8                    |
|                         | 8.5                      | 8.8               | 7.3                     | 0.185             | 6.9                             | 7.1                     |
| **Stroke, %**           | 8.5                      | 8.8               | 7.3                     | 0.185             | 6.9                             | 7.1                     |
| **Recent MI within 3 weeks, %** | 41.0                 | 41.4              | 39.7                    | 0.410             | 37.0                            | 38.1                    |
| **Prior MI, %**         | 6.6                      | 6.8               | 6.1                     | 0.507             | 6.0                             | 5.8                     |
| **Canadian heart class II, III, or IV, %** | 14.2                  | 14.3              | 13.9                    | 0.763             | 14.1                            | 14.0                    |
| **Killip heart class II, III, or IV, %** | 11.6                  | 11.0              | 13.5                    | 0.060             | 9.7                             | 11.8                    |
| **Anxiety, %**          | 8.0                      | 7.1               | 11.0                    | 0.001             | 12.0                            | 10.6                    |
| **Smoker, %**           | 49.3                     | 48.8              | 50.8                    | 0.353             | 50.5                            | 50.5                    |
| **Drinker, %**          | 30.9                     | 30.5              | 32.0                    | 0.472             | 30.9                            | 32.1                    |
| **SBP, mm Hg**          | 133.52±20.49             | 133.84±20.35      | 132.50±20.93            | 0.232             | 132.85±19.31                    | 132.24±20.73            |
| **DBP, mm Hg**          | 80.20±13.19              | 80.57±13.18       | 79.01±13.18             | 0.005             | 79.70±12.52                     | 78.86±13.08             |
| **Heart rate, beats per min** | 74.94±13.10            | 75.10±12.42       | 74.40±15.15             | 0.009             | 74.73±12.45                     | 74.40±15.11             |
| **Creatinine, µmol/L**  | 85.23±55.46              | 84.10±43.38       | 88.90±73.86             | 0.330             | 89.53±68.88                     | 88.49±75.41             |
| **Betablockers, %**     | 65.1                     | 85.4              | —                       | —                 | 83.6                            | —                       |
| **Statins, %**          | 96.0                     | 95.8              | 96.7                    | 0.266             | 96.5                            | 96.6                    |
| **ACE/ARB, %**          | 97.0                     | 98.6              | 95.5                    | 0.001             | 97.1                            | 96.8                    |
| **Statins, %**          | 75.6                     | 81.0              | 58.4                    | 0.001             | 59.8                            | 58.8                    |
| **Medication at discharge** | 34.0                  | 33.3              | 36.3                    | 0.127             | 35.9                            | 35.6                    |

**Variables are expressed as mean±SD or percentage. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; MI, myocardial infarction; SBP, systolic blood pressure.**
Table 2. Baseline Characteristics in Patients With STEMI

| Clinical Characteristics | All (n=728) | Before Matching | After Matching | After Matching |
|--------------------------|-------------|-----------------|---------------|---------------|
| Age, y                   | 55.89±11.03 | 55.36±11.05     | 58.12±10.71   | 58.77±10.60   |
| Male, %                  | 89.4        | 94.0            | 81.7          | 84.0          |
| Hypertension, %          | 55.8        | 59.4            | 55.7          | 54.4          |
| Diabetes, %              | 33.4        | 32.7            | 38.1          | 35.9          |
| Dyslipidemia, %          | 45.1        | 47.0            | 38.5          | 42.0          |
| Systolic BP, mm Hg       | 126.2       | 127.4           | 124.6         | 124.8         |
| Diastolic BP, mm Hg      | 78.1        | 78.3            | 77.3          | 77.6          |
| Heart rate, beats per min| 78.2        | 78.1            | 78.1          | 78.1          |
| Medication at discharge  | Aspirin, %  | 99.7            | 98.8          | 99.0          |
| Medication at discharge  | β-Blocker type |               |               |               |

Variables are expressed as mean ± SD or percentage. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; MI, myocardial infarction; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction.
Table 3. Baseline Characteristics in Patients With NSTEMI

|                         | Before Matching | After Matching | β-Blocker Use (% of Target Dose) | Among 3 β-Blocker Doses |
|-------------------------|-----------------|----------------|---------------------------------|-------------------------|
|                         | β-Blocker Group (n=436) | No β-Blocker Group (n=140) | P Value | β-Blocker Group (n=109) | No β-Blocker Group (n=109) | P Value | <50% (n=350) | ≥50% (n=86) | P Value |
| Clinical characteristics |                 |                |                                 |                         |
| Age, y                  | 58.59±11.78     | 57.63±11.67    | 61.61±11.64 0.001              | 59.32±10.77 60.01±11.24 0.590 | 58.21±11.66 55.35±11.52 0.001 |
| Male, %                 | 79.1            | 78.0           | 82.6 0.245                 84.4 79.8 0.511 | 77.2 81.2 0.367 |
| Hypertension, %         | 66.6            | 67.8           | 62.9 0.279                 70.6 64.2 0.360 | 66.5 73.3 0.273 |
| Diabetes, %             | 37.6            | 38.0           | 36.4 0.736                 42.2 38.5 0.678 | 36.2 45.3 0.277 |
| Dyslipidemia, %         | 44.6            | 46.2           | 39.9 0.194                 51.4 43.1 0.298 | 46.1 46.5 0.429 |
| Stroke, %               | 8.4             | 8.3            | 8.8 0.876                 10.1 7.3 0.581 | 8.7 7.0 0.869 |
| Prior MI, %             | 3.7             | 2.8            | 6.4 0.044                 1.8 3.7 0.625 | 3.2 1.2 0.089 |
| Killip heart class II, III, or IV, % | 25.0           | 24.6           | 26.4 0.664                 26.6 22.0 0.542 | 24.6 24.4 0.909 |
| Arrhythmia, %           | 7.1             | 5.3            | 12.9 0.002                 7.3 9.2 0.774 | 6.0 2.3 0.005 |
| Smoker, %               | 53.2            | 53.6           | 52.0 0.743                 56.9 52.3 0.560 | 52.5 58.4 0.609 |
| Drinker, %              | 32.7            | 33.6           | 30.1 0.470                 30.3 30.3 >0.999 | 32.7 37.3 0.573 |
| SBP, mm Hg              | 131.73±20.57    | 132.32±19.89   | 130.00±22.44 0.141         | 132.41±18.34 129.15±22.18 0.429 | 131.40±19.73 136.20±20.21 0.048 |
| DBP, mm Hg              | 79.66±13.22     | 80.34±13.22    | 77.68±13.06 0.027         | 79.59±12.29 78.06±13.16 0.460 | 79.76±12.97 82.74±14.06 0.026 |
| Heart rate, beats per min | 75.50±14.75   | 75.61±12.83    | 75.19±19.63 0.032         | 74.55±12.79 74.35±19.73 0.123 | 74.55±12.79 79.74±12.23 0.001 |
| Creatinine, µmol/L      | 97.51±92.86     | 87.95±54.02    | 120.92±148.67 0.001       | 85.67±54.48 124.71±161.70 0.229 | 85.67±54.48 106.12±47.86 0.000 |
| Medication at discharge |                 |                |                                 |                         |
| Aspirin, %              | 99.0            | 99.5           | 97.1 0.051                 100.0 100.0 — | 99.7 98.8 0.028 |
| β-Blocker type, %       |                 |                |                                 |                         |
| Metoprolol              | 63.0            | 83.3           | — 76.1 0.001               | — 76.1 — >0.999 | 87.7 65.1 <0.001 |
| Clopidogrel, %          | 96.0            | 96.6           | 94.3 0.032               96.3 96.3 >0.999 | 96.9 95.3 0.414 |
| Statins, %              | 97.9            | 98.9           | 95.0 0.005               99.1 99.1 >0.999 | 98.9 98.8 0.040 |
| ACEI/ARB, %             | 75.7            | 82.6           | 62.9 <0.001               74.3 67.9 0.248 | 80.6 90.7 <0.001 |
| Nitrates, %             | 35.9            | 34.4           | 40.7 0.176               34.9 41.3 0.371 | 34.3 34.9 0.398 |

Variables are expressed as mean±SD or percentage. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; SBP, systolic blood pressure.
Table 4. Baseline Characteristics in Patients With UAP

| Variable                                      | All (n=1876) | Before Matching | After Matching | P Value | β-Blocker Use (% of Target Dose) | Among 3 β-blocker Doses |
|-----------------------------------------------|--------------|----------------|---------------|---------|---------------------------------|------------------------|
|                                               |              | β-Blocker Group | No β-Blocker Group |        |                                |                        |
|                                               |              | (n=1420)       | (n=456)        |         |                                |                        |
| Age, y                                        | 60.32±9.58   | 59.95±9.50     | 61.48±9.73     | 0.003   | 61.77±8.98                     | 61.64±9.70            |
|                                               |              |                |                |         | 0.817                           | 60.04±9.59            |
| Male, %                                       | 71.6         | 71.3           | 72.7           | 0.575   |                                | 73.6                  |
|                                               |              |                |                |         | 73.8                            | >0.999                |
| Hypertension, %                               | 70.3         | 70.5           | 69.7           | 0.754   |                                | 73.3                  |
|                                               |              |                |                |         | 69.9                            | 0.304                 |
| Diabetes, %                                   | 30.4         | 31.4           | 27.3           | 0.100   | 30.9                            | 28.1                  |
|                                               |              |                |                |         | 0.431                           | 30.3                  |
| Dyslipidemia, %                               | 46.9         | 46.9           | 46.8           | 0.958   | 49.1                            | 48.4                  |
|                                               |              |                |                |         | 0.883                           | 46.4                  |
| Stroke, %                                     | 9.7          | 10.5           | 7.3            | 0.050   | 6.4                             | 7.2                   |
|                                               |              |                |                |         | 0.775                           | 10.0                  |
| Prior MI, %                                   | 9.2          | 9.8            | 7.5            | 0.134   | 6.2                             | 6.9                   |
|                                               |              |                |                |         | 0.784                           | 9.4                   |
| Canadian heart class II, III, or IV, %        | 24.1         | 24.4           | 23.0           | 0.540   | 23.5                            | 22.5                  |
|                                               |              |                |                |         | 0.808                           | 26.9                  |
| Arhythmia, %                                  | 9.3          | 8.7            | 11.4           | 0.080   | 11.6                            | 11.9                  |
|                                               |              |                |                |         | >0.999                          | 8.2                   |
| Smoker, %                                     | 44.5         | 43.9           | 46.4           | 0.380   | 43.7                            | 45.9                  |
|                                               |              |                |                |         | 0.580                           | 45.0                  |
| Drinker, %                                    | 28.9         | 28.3           | 30.9           | 0.300   | 32.8                            | 31.6                  |
|                                               |              |                |                |         | 0.758                           | 27.7                  |
| SBP, mm Hg                                    | 136.63±19.94 | 136.94±19.96   | 135.71±19.89   | 0.647   | 137.12±19.35                    | 135.59±19.63          |
|                                               |              |                |                |         | 0.072                           | 136.19±19.44          |
|                                            |              |                |                |         | 140.87±22.13                    |                        |
| DBP, mm Hg                                    | 80.97±12.93  | 81.30±12.95    | 79.97±12.80    | 0.070   | 80.12±12.31                     | 79.83±12.76           |
|                                               |              |                |                |         | 0.530                           | 80.98±12.84           |
|                                            |              |                |                |         | 83.00±13.43                     |                        |
| Heart rate, beats per min                     | 73.36±11.37  | 73.56±11.12    | 72.69±12.12    | 0.110   | 73.41±11.32                     | 72.87±12.30           |
|                                               |              |                |                |         | 0.543                           | 73.24±11.13           |
|                                            |              |                |                |         | 75.29±12.98                     |                        |
| Creatinine, μmol/L                            | 83.23±48.10  | 84.07±51.81    | 80.33±32.15    | 0.291   | 88.41±64.75                     | 80.10±32.58           |
|                                               |              |                |                |         | 0.051                           | 84.37±52.02           |
| Medication at discharge                       |              |                |                |         | 82.00±50.65                     |                        |
| Aspirin, %                                    | 99           | 99.2           | 98.7           | 0.535   | 98.5                            | >0.999                |
|                                               |              |                |                |         | 98.5                            | 99.2                  |
|                                               |              |                |                |         | 99.1                            | 0.664                 |
| β-Blocker type, %                             |              |                |                |         |                                |                        |
| Metoprol                                       | 66.1         | 87.3           | —              | 0.483   | 94.8                            | 96.3                  |
|                                               |              |                |                |         | 0.405                           | 96.3                  |
|                                               |              |                |                |         | 94.1                            |                        |
|                                               |              |                |                |         | 0.214                           |                        |
| Clopidogrel, %                                | 96.2         | 96.0           | 96.7           | <0.001  | 96.5                            | 96.0                  |
|                                               |              |                |                |         | 0.824                           | 98.8                  |
|                                               |              |                |                |         | 96.8                            |                        |
|                                               |              |                |                |         | <0.001                          |                        |
| Statins, %                                    | 97.8         | 98.5           | 95.6           | <0.001  | 98.5                            | 56.8                  |
|                                               |              |                |                |         | 0.200                           | 78.9                  |
|                                               |              |                |                |         | 80.8                            |                        |
|                                               |              |                |                |         | <0.001                          |                        |
| ACEI/ARB, %                                   | 73.9         | 79.2           | 57.5           | <0.001  | 58.8                            | 56.8                  |
|                                               |              |                |                |         | 0.200                           | 78.9                  |
|                                               |              |                |                |         | 80.8                            |                        |
|                                               |              |                |                |         | <0.001                          |                        |
| Nitrates, %                                   | 35.2         | 34.3           | 37.9           | 0.159   | 40.2                            | 36.0                  |
|                                               |              |                |                |         | 0.261                           | 33.7                  |
|                                               |              |                |                |         | 37.9                            |                        |
|                                               |              |                |                |         | 0.179                           |                        |

Variables are expressed as mean±SD or percentage. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; MI, myocardial infarction; SBP, systolic blood pressure; UAP, unstable angina pectoris.
Table 5. Clinical Outcomes and Unadjusted/Multivariable Adjusted HRs During 1-Year Follow-Up

|                                | [β-Blocker Group] | No [β-Blocker Group] | Univariable Analysis | Multivariable Analysis |
|--------------------------------|-------------------|----------------------|----------------------|------------------------|
|                                | n=2423            | n=757                | HR       | 95% CI | P Value | HR       | 95% CI | P Value |
| All patients                    |                   |                      |                      |                       |                      |                      |
| All-cause death                | 17 (0.7%)         | 16 (2.1%)            | 0.33     | 0.17–0.65 | 0.001 | 0.38 | 0.17–0.83 | 0.015 |
| Nonfatal MI                    | 8 (0.3%)          | 6 (0.8%)             | 0.41     | 0.14–1.19 | 0.100 | 0.62 | 0.19–2.02 | 0.423 |
| HF readmission                 | 23 (0.9%)         | 11 (1.5%)            | 0.65     | 0.32–1.32 | 0.233 | 1.09 | 0.45–2.65 | 0.849 |
| Cardiogenic hospitalization    | 162 (6.7%)        | 52 (6.9%)            | 0.96     | 0.70–1.31 | 0.804 | 1.02 | 0.72–1.46 | 0.839 |
| Secondary end point            | 210 (8.7%)        | 85 (11.2%)           | 0.76     | 0.59–0.98 | 0.035 | 0.87 | 0.66–1.16 | 0.355 |
| Patients with STEMI            | n=567             | n=161                |          |        |        |        |        |        |
| All-cause death                | 6 (1.1%)          | 3 (1.9%)             | 0.57     | 0.14–2.29 | 0.429 | 0.40 | 0.08–1.94 | 0.257 |
| Nonfatal MI                    | 4 (0.7%)          | 2 (1.2%)             | 0.57     | 0.10–3.10 | 0.514 | 0.38 | 0.02–6.27 | 0.501 |
| HF readmission                 | 6 (1.1%)          | 4 (2.5%)             | 0.43     | 0.12–1.51 | 0.186 | 0.59 | 0.15–2.31 | 0.451 |
| Cardiogenic hospitalization    | 32 (5.6%)         | 9 (5.6%)             | 1.01     | 0.48–2.12 | 0.979 | 1.33 | 0.54–3.29 | 0.534 |
| Secondary end point            | 48 (8.5%)         | 18 (16.1%)           | 0.76     | 0.44–1.30 | 0.317 | 1.13 | 0.59–2.16 | 0.720 |
| Patients with NSTEMI           | n=436             | n=140                |          |        |        |        |        |        |
| All-cause death                | 1 (0.2%)          | 9 (6.4%)             | 0.04     | 0.00–0.27 | 0.001 | 0.00 | 0.00–0.14 | 0.005 |
| Nonfatal MI                    | 2 (0.5%)          | 2 (1.4%)             | 0.31     | 0.04–2.16 | 0.235 | 0.23 | 0.03–1.72 | 0.151 |
| HF readmission                 | 7 (1.6%)          | 3 (2.1%)             | 0.70     | 0.18–2.72 | 0.610 | 1.14 | 0.25–5.23 | 0.863 |
| Cardiogenic hospitalization    | 24 (5.5%)         | 8 (5.7%)             | 0.92     | 0.41–2.04 | 0.828 | 0.99 | 0.48–2.41 | 0.973 |
| Secondary end point            | 34 (7.8%)         | 22 (15.7%)           | 0.47     | 0.28–0.81 | 0.006 | 0.65 | 0.35–1.21 | 0.171 |
| Patients with UAP              | n=1420            | n=456                |          |        |        |        |        |        |
| All-cause death                | 10 (0.7%)         | 4 (0.9%)             | 0.80     | 0.25–2.55 | 0.705 | 0.96 | 0.29–3.10 | 0.938 |
| Nonfatal MI                    | 2 (0.1%)          | 2 (0.4%)             | 0.32     | 0.05–2.28 | 0.255 | 0.36 | 0.04–2.88 | 0.333 |
| HF readmission                 | 10 (0.7%)         | 4 (0.9%)             | 0.80     | 0.25–2.55 | 0.705 | 1.01 | 0.27–3.79 | 0.993 |
| Cardiogenic hospitalization    | 106 (7.4%)        | 35 (7.7%)            | 0.97     | 0.66–1.42 | 0.865 | 0.99 | 0.66–1.51 | 0.956 |
| Secondary end point            | 128 (9.0%)        | 45 (9.9%)            | 0.91     | 0.65–1.28 | 0.581 | 0.97 | 0.66–1.41 | 0.852 |

The benefit at 1 year was estimated by the Kaplan–Meier method. The multivariable Cox regression was used to adjust potential confounders. HF indicates heart failure; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UAP, unstable angina pectoris.

showed a trend in improved clinical outcomes in the STEMI and UAP patients.

ACS as a major cause of emergency medical care and hospitalization worldwide has been well improved by the introduction of PCI. Optimal secondary medication remains important after successful PCI. Predecessors have highlighted the importance of β-blocker therapy in patients with acute myocardial infarction. However, there are a few studies reporting that β-blocker use is not associated with improved outcome. One meta-analysis of randomized trials on the clinical outcomes of β-blocker use indicated no mortality benefit but reduced recurrent myocardial infarction and angina (short-term) at the expense of increased heart failure, cardiogenic shock, and drug discontinuation. In this meta-analysis, data used in the reperfusion era were mainly recruited from the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) and the Japanese β-blockers and Calcium Antagonists Myocardial Infarction (JCBAMI) trial. In COMMIT, the association between metoprolol allocation and risk of clinical outcomes was only assessed in a mean period of 15 days among AMI patients. On the other hand, only post-myocardial infarction patients were enrolled in the JCBAMI trial, which could not reflect the benefit of early β-blocker therapy on improvement in prognosis. Yet, our study proved the benefit of early use of β-blockers on long-term survival among patients with ACS. Nevertheless, Chan et al reported the mortality benefit of β-blockers in patients undergoing successful elective PCI; however, they did not discuss which type of patients with ACS benefited the most. In the present study, our results showed that β-blocker use was better associated with decreased incidence of all-cause death in patients with NSTEMI. The published Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA...
Guidelines (CRUSADE)\textsuperscript{32} and Global Registry of Acute Coronary Events (GRACE)\textsuperscript{33} studies also revealed that early β-blocker therapy had a beneficial impact on hospital and 6-month mortality in patients with NSTEMI. In addition, Yang et al\textsuperscript{24} demonstrated that β-blocker therapy at discharge was associated with improved survival in STEMI patients treated with primary PCI and recommended long-term β-blocker therapy in all patients with STEMI regardless of risk profile. In our analysis, the use of β-blockers was not statistically associated with a lower risk of all-cause death in STEMI patients, but the trend of improved survival was obvious. Additionally, the observational data from the Outcome of β-blocker Therapy After Myocardial Infarction (OBTAIN) study suggested that increased survival was not observed in patients treated with β-blocker doses approximating those used in previous randomized clinical trials compared with lower doses,\textsuperscript{34} which was consistent with our conclusions that relatively low β-blocker dose actually decrease the rate of all-cause mortality.

Even though several investigators have studied the benefits of β-blocker use among patients with myocardial infarction, our study stressed the impact of β-blocker therapy, especially relatively low β-blocker dose, on reducing all-cause mortality in patients after elective PCI, and provided the evidence to support the idea that the benefit of oral β-blocker therapy might be confined to patients with NSTEMI.\textsuperscript{35} Evidence has suggested that the benefit of β-blockers for patients with NSTEMI may be due to the multivessel disease commonly presenting in them and its sympathetic hyperactivity.\textsuperscript{36–39} However, further exploration of the clinical usefulness of β-blocker therapy in patients with ACS warrants large-scale clinical trials such as a recently registered project (NCT02648243). Finally, we cannot claim generalizability to patients with STEMI/UAP for it was underpowered to detect the difference.

| Table 6. | Clinical Outcomes and HRs After Propensity Score Matching During 1-Year Follow-Up |
|----------|---------------------------------------------------------------------------------|
|          | β-Blocker Group | No β-Blocker Group | HR    | 95% CI  | P Value |
| All patients | n=651 | n=651 | 0.27 | 0.08–0.97 | 0.045 |
| All-cause death | 3 (0.5%) | 11 (1.7%) | 0.80 | 0.21–2.96 | 0.733 |
| Nonfatal MI | 4 (0.6%) | 5 (0.8%) | 0.71 | 0.23–2.23 | 0.556 |
| HF readmission | 5 (0.8%) | 7 (1.1%) | 0.92 | 0.60–1.42 | 0.714 |
| Cardiogenic hospitalization | 40 (6.1%) | 43 (6.6%) | 0.78 | 0.54–1.12 | 0.184 |
| Secondary end point | 52 (8.0%) | 66 (10.1%) | 1.37 | 0.31–6.10 | 0.683 |
| All patients with STEMI | n=131 | n=131 | 1.03 | 0.07–16.50 | 0.982 |
| All-cause death | 4 (3.1%) | 3 (2.3%) | 1.55 | 0.26–9.25 | 0.634 |
| Nonfatal MI | 1 (0.8%) | 1 (0.8%) | 1.21 | 0.41–3.59 | 0.736 |
| HF readmission | 3 (2.3%) | 2 (1.5%) | 1.29 | 0.60–2.75 | 0.513 |
| Cardiogenic hospitalization | 7 (5.3%) | 6 (4.6%) | —* | —* | —* |
| Secondary end point | 15 (11.5%) | 12 (9.2%) | 0.80 | 0.21–2.96 | 0.733 |
| Patients with NSTEMI | n=109 | n=109 | 1.99 | 0.18–21.96 | 0.574 |
| All-cause death | 0 (0.0%) | 6 (5.5%) | 1.50 | 0.25–8.98 | 0.657 |
| Nonfatal MI | 0 (0.0%) | 1 (0.9%) | 0.91 | 0.55–1.49 | 0.697 |
| HF readmission | 2 (1.8%) | 2 (1.8%) | 0.95 | 0.60–1.48 | 0.808 |
| Cardiogenic hospitalization | 33 (8.1%) | 30 (7.4%) | 0.95 | 0.60–1.48 | 0.808 |
| Secondary end point | 39 (9.6%) | 37 (9.1%) | 0.95 | 0.60–1.48 | 0.808 |
| Patients with UAP | n=405 | n=405 | 1.03 | 0.07–16.50 | 0.982 |
| All-cause death | 3 (0.7%) | 2 (0.5%) | 1.29 | 0.60–2.75 | 0.513 |
| Nonfatal MI | 1 (0.2%) | 2 (0.5%) | 0.92 | 0.13–6.55 | 0.935 |
| HF readmission | 6 (5.5%) | 5 (4.6%) | 0.54 | 0.23–1.30 | 0.170 |
| Cardiogenic hospitalization | 8 (7.3%) | 14 (12.8%) | 0.54 | 0.23–1.30 | 0.170 |
| Secondary end point | 39 (9.6%) | 37 (9.1%) | 0.95 | 0.60–1.48 | 0.808 |

HF indicates heart failure; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UAP, unstable angina pectoris.

*The hazard ratio (HR) and 95% CI could not be evaluated that no event occurred in the β-blocker group.
**Figure 2.** The cumulative incidence in the study population. The hazard curves for the primary and secondary end points in the overall population (A), in the patients with ST-segment elevation myocardial infarction (STEMI) (B), in the patients with non–ST-segment elevation myocardial infarction (NSTEMI) (C), and in the patients with unstable angina pectoris (UAP) (D). The curves were described by Kaplan-Meier methods and the P values were calculated using the log-rank tests.
**Study Limitations**

There were several limitations that deserve consideration. First, the nonrandomized nature of this observational study could have resulted in selection bias. Although randomized controlled trials are considered the highest standard for evaluating treatment efficacy, observational studies can still provide unique and valuable insights into treatment effectiveness and generalizability in practice. Our findings imply that the efficacy demonstrated in randomized clinical trials can be translated into tangible clinical benefits in the real world. Second, a 1-year follow-up period may be too short for conclusive determination of the long-term efficacy of β-blockers in the setting of ACS. Third, the STEMI group and the UAP group were underpowered to discriminate the benefit of β-blocker use.

**Conclusions**

This large observational study has shown that the higher survival rate in patients following PCI is associated with the appropriate use of β-blockers at discharge and this benefit is consistent in the patients with NSTEMI.

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