Admission Heart Rate Is a Determinant of Effectiveness of Beta-Blockers in Acute Myocardial Infarction Patients

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**Background:** Beta-blockers are standard therapy for acute myocardial infarction (AMI). However, despite current advances in the management of AMI, it remains unclear whether all AMI patients benefit from β-blockers. We investigated whether admission heart rate (HR) is a determinant of the effectiveness of β-blockers for AMI patients.

**Methods and Results:** We enrolled 3,283 consecutive AMI patients who were admitted to 28 participating institutions in the Japanese Registry of Acute Myocardial Infarction Diagnosed by Universal Definition (J-MINUET) study. According to admission HR, we divided patients into 3 groups: bradycardia (HR <60 beats/min, n=444), normocardia (HR 60 to ≤100 beats/min, n=2,013), and tachycardia (HR >100 beats/min, n=342). The primary endpoint was major adverse cardiac events (MACE), including all-cause death, non-fatal MI, non-fatal stroke, heart failure (HF), and urgent revascularization for unstable angina, at 3-year follow-up. Beta-blocker at discharge was significantly associated with a lower risk of MACE in the tachycardia group (23.6% vs. 33.0%; P=0.033), but it did not affect rates of MACE in the normocardia group (17.8% vs. 18.4%; P=0.681). In the bradycardia group, β-blocker use at discharge was significantly associated with a higher risk of MACE (21.6% vs. 12.7%; P=0.026). Results were consistent for multivariable regression and stepwise multivariable regression.

**Conclusions:** Admission HR might determine the efficacy of β-blockers for current AMI patients.

**Key Words:** Acute myocardial infarction; Beta-blockers; Heart rate

Beta-blockers are recommended for long-term management of patients with acute myocardial infarction (AMI), but many of the studies that established the effectiveness of β-blockers for AMI patients were conducted several decades ago. During the past few decades, advances in the management of AMI, such as reperfusion therapy, and the use of statins, and angiotensin-converting enzyme inhibitors, have dramatically improved the clinical outcomes of AMI patients. Many observational studies of long-term β-blocker therapy for current AMI patients have...
been conducted, but the results are inconsistent. Some of these observational studies have suggested that β-blockers are no longer effective for all AMI patients, but that their use is associated with improved outcomes for some specific subgroups, such as patients with reduced left ventricular ejection fraction (EF), multivessel disease, or high Global Registry of Acute Coronary Events (GRACE) risk scores. These findings indicated the importance of current evidence-based therapy and that not all patients should be treated with β-blockers after AMI.

Recent data for 6,168 patients presenting with MI in a German registry showed that admission tachycardia or bradycardia was associated with adverse outcomes. Furthermore, higher heart rate (HR) at discharge was associated with an increased risk of death. Resting HR reduction was also shown to be a driving factor of the beneficial effects of β-blockers. Therefore, we evaluated whether admission HR is a determinant of the effectiveness of β-blockers for AMI patients in a retrospective analysis of the Japanese Registry of Acute Myocardial Infarction Diagnosed by Universal Definition (J-MINUET) study.

Methods

Study Design and Subjects

The analyses were based on data from the J-MINUET study (the design and primary results of the J-MINUET study have been published previously). Briefly, the J-MINUET study was a prospective observational multicenter study conducted at 28 nationwide institutions; 3,283 consecutive AMI patients were enrolled between July 2012 and March 2014. AMI was diagnosed according to the European Society of Cardiology, ACC Foundation, American Heart Association, and World Heart Foundation Task Force for the Universal Definition of Myocardial Infarction. ST-segment elevation AMI (STEMI) was diagnosed in the presence of new ST elevation at the J point in at least 2 continuous leads of ≥2 mm (0.2 mV) in men or ≥1.5 mm (0.15 mV) in women in leads V2–3 and/or of ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads. A new or presumably new left bundle branch block was considered as a STEMI equivalent. Up to 3 years of clinical follow-up data were obtained from medical records, telephone contact, and mailed questionnaires. The indications for and methods of revascularization and the use of β-blockers were at the discretion of the treating physicians. The J-MINUET study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committee of each participating institution.

Study Populations

Based on the admission HR, patients with data regarding β-blocker use at discharge were divided into 3 groups: bradycardia (HR <60 beats/min), normocardia (HR, 60 to ≤100 beats/min) or tachycardia (HR >100 beats/min). Furthermore, each of these groups was divided into 2 subgroups based on β-blocker use at discharge: the β-blocker group and the no β-blocker group. Figure 1 shows the study flowchart. The primary endpoint was major adverse cardiac events (MACE) such as all-cause death, non-fatal MI, non-fatal stroke, heart failure (HF), and urgent revascularization for unstable angina at the 3-year follow-up. Non-fatal MI included only type 1 (spontaneous MI) and type 2 (MI secondary to an ischemic imbalance). HF was defined as HF requiring hospital admission. The secondary endpoints included the following: death; composite of death and non-fatal MI; composite of death, non-fatal MI, and non-fatal stroke; and composite of death, non-fatal MI, non-fatal stroke, and HF.

Statistical Analysis

All continuous variables are described as median values and interquartile range. All categorical variables are described using absolute and relative frequency distributions. Differences between groups of continuous variables were evaluated with the Kruskal-Wallis test. The chi-square test was used for non-continuous and categorical variables. We created Kaplan-Meyer curves for patients treated with or without β-blockers, and the differences between groups were assessed by the log-rank test. Univariate and multivariate Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals (CI) for all events. Because differences in baseline characteristics could significantly affect outcomes, sensitivity analyses were performed to adjust for confounders using 2 Cox regression models. In the first model, we selected covariates (age, sex, STEMI, urgent revascularization, multivessel disease, Killip class >2, and MI history) based on their potential to be associated with cardiac events. In the second model, we selected covariates that were significantly different (P<0.1) among 3 HR groups. In this model, we used stepwise-backward selection with probability to remove the effect of regression at P>0.05. Throughout the present study, P<0.05 was considered significant. Statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), and STATA (version 12; StataCorp LP, College Station, TX, USA).

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Figure 1. Flowchart of patients enrolled in the registry. AMI, acute myocardial infarction; BB, β-blocker; HR, heart rate on admission.

Table 1. Baseline Characteristics and Management of AMI According to Admission Heart Rate

|                          | Bradycardia group (n=444) | Normocardia group (n=2,013) | Tachycardia group (n=342) | P value |
|--------------------------|---------------------------|-----------------------------|---------------------------|---------|
| Age (years)              | 70 (63–79)                | 69 (60–77)                  | 69 (58–78)                | 0.028   |
| Male                     | 339 (76.4%)               | 1,541 (76.6%)               | 246 (71.9%)               | 0.177   |
| Vitals                   |                           |                             |                           |         |
| SBP (mmHg)               | 120 (100–144)             | 142 (122–162)               | 147 (120–171)             | <0.001  |
| HR (beats/min)           | 52 (45–56)                | 79 (69–87)                  | 112 (106–122)             | <0.001  |
| Arrhythmia on admission  |                           |                             |                           |         |
| Atrial fibrillation      | 26 (5.9%)                 | 71 (3.5%)                   | 37 (10.8%)                | <0.001  |
| Ventricular tachycardia/fibrillation | 15 (3.4%) | 51 (2.5%) | 29 (8.5%) | <0.001 |
| Complete AV block        | 78 (17.6%)                | 23 (1.1%)                   | 1 (0.3%)                  | <0.001  |
| Concomitant diseases     |                           |                             |                           |         |
| Hypertension             | 278 (62.9%)               | 1,350 (67.2%)               | 241 (71.1%)               | 0.051   |
| Diabetes                 | 139 (31.7%)               | 704 (35.5%)                 | 154 (45.6%)               | <0.001  |
| Dyslipidemia             | 230 (52.0%)               | 1,076 (53.8%)               | 184 (54.3%)               | 0.768   |
| CKD                      | 215 (48.4%)               | 770 (38.3%)                 | 185 (54.1%)               | <0.001  |
| Previous history         |                           |                             |                           |         |
| Previous MI              | 43 (9.7%)                 | 251 (12.5%)                 | 49 (14.4%)                | 0.120   |
| Prior stroke             | 46 (10.8%)                | 209 (10.7%)                 | 41 (12.4%)                | 0.658   |
| Previous PAD             | 20 (4.7%)                 | 74 (3.9%)                   | 25 (7.6%)                 | 0.009   |
| Diagnosis                |                           |                             |                           |         |
| NSTEMI                   | 103 (23.2%)               | 633 (31.4%)                 | 139 (40.6%)               | <0.001  |
| STEMI                    | 341 (76.8%)               | 1,380 (68.6%)               | 203 (59.4%)               |         |
| Killip class >2          | 61 (13.7%)                | 126 (6.3%)                  | 107 (31.5%)               | <0.001  |
| Multivessel disease      | 188 (44.2%)               | 782 (41.4%)                 | 155 (52.2%)               | 0.002   |
| Urgent revascularization | 407 (91.7%)               | 1,773 (88.1%)               | 270 (78.9%)               | <0.001  |
| Medications at discharge |                           |                             |                           |         |
| β-blockers               | 278 (62.6%)               | 1,387 (68.9%)               | 254 (74.3%)               | 0.002   |
| ACEIs                    | 249 (57.1%)               | 1,031 (52.1%)               | 158 (47.0%)               | 0.02    |
| ARBs                     | 112 (25.9%)               | 569 (28.7%)                 | 97 (28.7%)                | 0.495   |
| Statins                  | 384 (87.5%)               | 1,758 (87.8%)               | 278 (82.2%)               | 0.018   |
| Aspirin                  | 423 (95.5%)               | 1,926 (96.2%)               | 315 (92.9%)               | 0.025   |
| P2Y12 inhibitors         | 346 (82.0%)               | 1,551 (79.9%)               | 246 (73.7%)               | 0.013   |

ACEI, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; AV, atrioventricular; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; HR, heart rate; MI, myocardial infarction; NSTEMI, non-ST-elevated myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.
Among the 3,283 patients registered in the J-MINUET study, we identified 2,799 consecutive patients with data regarding admission HR and β-blocker use at discharge. Of them, 444 patients (15.9%) were classified into the bradycardia group, 2,013 (71.9%) into the normocardia group, and 342 (12.2%) into the tachycardia group. Baseline clinical characteristics and management according to admission HR are shown in Table 1. There were several important differences among the groups. Complete atrioventricular block was more frequently observed in the bradycardia group, whereas ventricular tachycardia, fibrillation, and atrial fibrillation were more frequently observed in the tachycardia group. The proportions of STEMI and urgent revascularization were highest in the bradycardia group and lowest in the tachycardia group. The prevalences of hypertension, diabetes, chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m²) and high Killip class (>2) were highest in the tachycardia group. Medications at discharge are also shown in Table 1. Most patients were prescribed evidence-based secondary prevention medications such as renin-angiotensin-aldosterone system inhibitors and statins. In the tachycardia group, β-blockers were more likely to be prescribed, whereas angiotensin-converting enzyme inhibitors were less likely to be prescribed. The Kaplan-Meier curves for death and the primary endpoint according to admission HR are shown in Supplementary Figure. At the 3-year follow-up, the tachycardia group had significantly higher incidences of death (bradycardia group vs. normocardia group vs. tachycardia group: 4.8% vs. 8.8% vs. 13.6%; log-rank test P<0.001) and the primary endpoint (bradycardia group vs. normocardia group vs. tachycardia group: 24.3% vs. 23.9% vs. 35.7%; log-rank test P<0.001).

### Bradycardia Group

Among the 444 patients included in the bradycardia group (HR <60 beats/min), 278 (62.6%) were treated with β-blockers at discharge. Figure 2 and Figure 3 show the Kaplan-Meier curves for the primary endpoint and the secondary endpoints at 3 years. At 3-year follow-up, the β-blocker group had a significantly higher incidence of the primary endpoint (β-blocker group vs. no β-blocker group: 21.6% vs. 12.7%; log-rank test P=0.026; unadjusted hazard ratio, 1.74; 95% CI, 1.06–2.87; P=0.028). In terms of the secondary endpoints, both groups had comparable outcomes. Sensitivity analyses using multivariable Cox regression and stepwise Cox regression showed a significantly higher incidence of the primary endpoint (Table 2).

### Normocardia Group

Among the 2,013 patients included in the normocardia group (HR ≥60 to ≤100 beats/min), 1,387 (69.2%) were treated with β-blockers at discharge. Figure 2 and Figure 4 show the Kaplan-Meier curves for the primary endpoint and the secondary endpoints at 3 years. At 3-year follow-up, the β-blocker group had a comparable incidence of the primary endpoint (β-blocker group vs. no β-blocker group: 17.6% vs. 12.7%; log-rank test P=0.062; unadjusted hazard ratio, 1.74; 95% CI, 1.06–2.87; P=0.028). In terms of the secondary endpoints, both groups had comparable outcomes. Sensitivity analyses using multivariable Cox regression and stepwise Cox regression showed a significantly higher incidence of the primary endpoint (Table 2).

### Tachycardia Group

Among the 342 patients included in the tachycardia group (HR >100 beats/min), 254 (74.3%) were treated with
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Discussion

In this prospective, observational multicenter study including consecutive patients who were hospitalized within 48 h of the onset of MI and mostly treated with urgent revasc-

Figure 3. Unadjusted Kaplan-Meier curves according to β-blocker use in the bradycardia group. Kaplan-Meier curve for (A) mortality shows no difference between patients who did or did not use β-blockers. Kaplan-Meier curves for (B) composite of mortality and non-fatal MI, (C) composite of mortality, non-fatal MI, and non-fatal stroke, and (D) composite of mortality, non-fatal MI, non-fatal stroke, and heart failure show trends towards a higher incidence of each outcome for patients who used β-blockers. However, the differences were not statistically significant. MI, myocardial infarction.

β-blockers at discharge. Figure 2 and Figure 5 show the Kaplan-Meier curves for the primary endpoint and the secondary endpoints at 3 years. At 3-year follow-up, the β-blocker group had a significantly lower incidence of the primary endpoint (β-blocker group vs. no β-blocker group: 23.6% vs. 33.0%; log-rank test P=0.033; unadjusted hazard ratio, 0.62; 95% CI, 0.40–0.97; P=0.035). In terms of secondary endpoints, including all-cause death, the β-blocker group had significantly better outcomes (Figure 4). Sensitivity analyses using multivariable Cox regression and stepwise Cox regression showed a significantly lower incidence of the primary endpoint (Table 2).
larization and evidence-based medical therapy, the use of β-blockers at discharge was significantly associated with a lower risk of death and MACE for patients with tachycardia (HR >100 beats/min) on admission; however, β-blocker use did not affect long-term mortality or MACE for patients with normocardia (HR 60 to ≤100 beats/min) on admission. Moreover, interestingly, for patients with bradycardia (HR <60 beats/min) on admission, the use of β-blockers at discharge was associated with a higher risk of MACE.

The current American Heart Association guidelines recommend oral β-blockers as a Class I indication for all AMI patients without contraindications. However, these recommendations are mainly based on evidence from AMI patients before the reperfusion era; therefore, the evidence for β-blocker use in current AMI patients is lacking. Although the COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) study indicated that the beneficial effects of β-blockers were observed for overall mortality and MACE in patients with tachycardia on admission. Therefore, for contemporary management of AMI, it is important to know who should be treated with β-blockers and who should not.

Table 2. Comparison of the Primary Endpoint According to Beta-Blocker Use

| Group          | Beta-blocker group | No-β-blocker group | Unadjusted Hazard ratio (95% CI) | P value | Multivariable-Adjusted Hazard ratio (95% CI) | P value | Stepwise-Adjusted Hazard ratio (95% CI) | P value |
|----------------|--------------------|--------------------|---------------------------------|---------|---------------------------------------------|---------|----------------------------------------|---------|
| Bradycardia    | (n=278)            | (n=166)            | 60 (21.6%)                      | 21 (12.7%) | 1.74 (1.06–2.87)                          | 0.028   | 1.72 (1.02–2.89)                       | 0.040   |
| Primary endpoint |                   |                    | 1.67 (1.00–2.79)               | 0.048   |
| Normocardia    | (n=1,387)          | (n=626)            | 247 (17.8%)                     | 115 (18.4%) | 0.95 (0.77–1.19)                          | 0.681   |
| Primary endpoint |                   |                    | 0.57 (0.34–0.95)               | 0.032   |
| Tachycardia    | (n=254)            | (n=88)             | 60 (23.6%)                      | 29 (33.0%) | 0.62 (0.40–0.97)                          | 0.035   | 0.49 (0.28–0.85)                       | 0.011   |

The primary endpoint includes all-cause death, non-fatal myocardial infarction, non-fatal stroke, heart failure, and urgent revascularization for unstable angina at 3 years.

More recently, a retrospective analysis of 2,310 STEMI patients who were treated with PCI at a regional tertiary center showed that β-blockers improved the post-discharge survival of patients with elevated admission HR. Those findings support our results indicating that β-blockers reduce overall mortality and MACE in patients with tachycardia on admission.

In the normocardia group, no significant differences according to β-blocker use were observed for overall mortality and MACE. Although the results were consistent with those of previous studies, β-blocker use was associated with significant reduction of the composite endpoint of death, non-fatal MI, and non-fatal stroke in this patient group. This was because the incidence rates of death, non-fatal MI, and non-fatal stroke were numerically lower in the β-blocker group, whereas the incidence rates of HF and urgent revascularization for unstable angina were numerically higher in the β-blocker group (Supplementary Table 1). However, none of the components showed significant difference. These numerical differences might be explained by residual confounding factors. Careful interpretation seems to be necessary to conclude the effectiveness of β-blockers in this patient group.

In the bradycardia group, indications for β-blockers should be more carefully considered because β-blockers are known to be a cause of iatrogenic bradycardia such as acquired complete atrioventricular block. A meta-analysis of 14 randomized trials of β-blockers and calcium-channel blockers for AMI patients suggested that the magnitude of resting HR reduction was associated with the beneficial effects of β-blockers. In the BEAUTIFUL (Ivabradine for patients with stable coronary artery disease and left ventricular systolic dysfunction) study, the beneficial effects of rate reduction by ivabradine for patients with stable coronary artery disease and left ventricular dysfunction were observed only in patients with HR ≥70 beats/min. More recently, a prospective analysis of 2,310 STEMI patients who were treated with PCI at a regional tertiary center showed that β-blockers improved the post-discharge survival of patients with elevated admission HR. Those findings support our results indicating that β-blockers reduce overall mortality and MACE in patients with bradycardia on admission.
Study Limitations

Our study had several important limitations that should be noted when interpreting the findings. First, this was not a randomized controlled study; therefore, potential biases in measured and unmeasured variables existed. Statistical techniques may not have been sufficient to adjust for these confounding factors. Second, this study lacked important data regarding β-blockers. We only knew whether patients were using β-blocker therapy at discharge. Unfortunately,
there was no information regarding the type or dose of β-blocker, the timing of initial administration, discontinuation, adherence, dose change, or new prescription after discharge, which can affect the long-term efficacy of β-blocker therapy. Third, there were too many missing EF values. When considering the effectiveness of β-blockers for AMI patients, the EF value, which is a well-known strong predictor of the effectiveness of β-blockers, is critically important. However, in our registry data, missing EF values were observed for approximately one-third of the total population; therefore, we considered it inappropriate to add this value to our analysis. Finally, the initial diagnosis and adverse clinical events were not centrally adjudicated in our registry. All diagnoses and events were identified by physicians and confirmed by the principal investigator of each hospital. Therefore, inaccuracies in diagnoses and clinical events were possible.
Conclusions

In our multicenter registry data, β-blocker therapy at discharge was associated with improved long-term survival and clinical outcomes for current AMI patients with tachycardia on admission. In contrast, for patients with bradycardia on admission, β-blocker therapy was associated with worse long-term clinical outcomes. Our study suggested that admission HR might be a determinant of the efficacy of β-blocker therapy for current AMI patients. However, further investigations are warranted to confirm our findings.

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Supplementary Files

Please find supplementary file(s):
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