

Are beta blockers still necessary for all survivors of acute myocardial infarction?

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In the previous decades, a huge number of clinical randomized controlled trials showed that beta blockers (BB) reduced incidence of all-cause death and adverse cardiac events in patients with acute myocardial infarction (AMI) (1-5). The Beta-blocker Heart Attack Trial (BHAT), which examined the efficacy of propranolol treatment initiated 5–21 days after AMI, showed that mortality was reduced by 25% during a mean follow-up period of 2 years (7% *vs.* 9.5%, respectively) (2,3). Similarly, the Norwegian trial, in which beneficial effect of timolol treatment from 6–27 days following AMI was examined, demonstrated nearly 40% reduction of mortality at 33 months (from 21.9% to 13.3%) (1). Furthermore, meta-analyses showed significant risk reduction via BB therapy for long-term mortality of post-AMI patients by 25% and 23% in the pre-reperfusion (6) and thrombolytic eras (7), respectively. Based on these findings, with respect to the use of BB in the secondary prevention settings after ST-elevation myocardial infarction (STEMI), the ACCF/AHA guideline for the management of STEMI recommends BB should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use as a class I indication. Whereas, European Society of Cardiology (ESC) (8) as well as Japanese Circulation Society (JCS) (9) guidelines recommend BB use, in the absence of contraindications, in patients with reduced systolic left ventricular (LV) function [LV ejection fraction (EF) ≤40%] as a class I, and routine use of BB in all patients as a class IIa

indication.

The favorable outcomes with BB treatment after AMI are likely attributable to protective effects for heart failure (HF) and sudden death caused by large infarct size, LV remodeling, residual ischemia, and LV arrhythmogenicity, and other factors (10-12). However, these benefits of BB could be reduced in the contemporary reperfusion era, since recent implementation of percutaneous coronary intervention (PCI) in acute managements of STEMI have greatly improved prognosis (13), possibly via limiting infarct size, residual ischemia, remodeling, and arrhythmia, for which BB have been prescribed to prevent for. In addition, we should notice that the mortality benefits of BB could have been further attenuated in the current era, since the increased implementation of evidence-based treatments other than PCI, such as cardiac rehabilitation, and administration of cardio-protective drugs including anti-platelets, renin-angiotensin system inhibitors, and statins, have likely reduced mortality (14), even without BB treatment. Thus, it is an emerging concern whether or how much BB treatment is still beneficial after AMI in the contemporary era.

In a recent issue of the *Journal of American College of Cardiology*, Dondo *et al.* addressed this issue by investigating the association between BB use and mortality in patients with AMI without HF or LV systolic dysfunction (LVSD) (15). A total of 179,810 survivors of hospitalization with AMI without HF or

LVSD, between January 1, 2007, and June 30, 2013 (final follow-up: December 31, 2013) were derived from the Myocardial Ischaemia National Audit Project in the United Kingdom. Although unadjusted 1-year mortality was lower for patients who received β -blockers compared with those who did not, after weighting and adjustment of the clinical background with survival-time inverse probability weighting propensity scores and instrumental variable analyses, mortality of AMI patients did not differ between those with and without BB use, regardless of STEMI or non-STEMI. Although this study by Dondo *et al.* has a limitation that almost 95% of the study subjects had received BB, which likely affected the results as a medication bias even after the state-of-the-art statistical analysis, their findings were consistent with recent analyses (16-19) and likely true in the contemporary PCI era.

The REduction of Atherothrombosis for Continued Health (REACH) Registry, an observational study enrolling a total of 44,708 patients with either risk factors of coronary artery disease (CAD) only, known prior myocardial infarction (MI), or known CAD without MI, the use of BB was not associated with a lower risk of composite cardiovascular events in patients with prior MI as well as in the overall patients (16). In the Osaka Acute Coronary Insufficiency Study (OACIS) (17,20-23), we recently reported that mortality rates did not differ between patients with and without BB therapy (5.2% *vs.* 6.2%, $P=0.786$) during a median follow-up period of 1,430 days (adjusted hazard ratio 0.935, 95% confidence interval 0.711 to 1.230, $P=0.534$) in 5,628 consecutive survivors for STEMI admitted within 24 hours after onset and treated with primary PCI, which was confirmed in the matching cohort selected using propensity score ($N=3,846$, hazard ratio 0.834, 95% confidence interval 0.643 to 1.082, $P=0.171$) (17). Ozasa *et al.* also reported a similar finding from the J-Cypher Registry that BB was not associated with better 3-year clinical outcomes in 910 STEMI patients who underwent PCI within 24 hours from the onset (18). Furthermore, a recent meta-analysis comprising 16,645 patients without LVSD and received percutaneous PCI for AMI did not show prognostic superiority for the use of BB (19). These lines of evidence strongly suggest that benefits of BB may be limited in AMI survivors, at least, in those without LVSD or at lower mortality risk.

It should be noted, however, that, as compared with the current era, mortality risk after AMI was much higher in the pre-reperfusion and thrombolytic eras, in which previous large clinical trials established a firm evidence that BB

treatment at discharge improved survival in post-MI patients (1-3,6,7). For example, the 2-year mortality rates in the Cooperative Cardiovascular Project, a retrospective analysis including over 200,000 post-MI patients, were 14.4% and 23.9% for those treated with BB and those without BB, respectively, even among low-risk individuals (4). In contrast, the overall mortality rates during a median follow-up period of 1,430 days in the OACIS study (17) were only 5.2% and 6.2% in the BB and non-BB groups, respectively, and particularly, mortality rates in non-BB group patients at low risk [Global Registry of Acute Coronary Events (GRACE) risk score (24) <121] was only 3.6%, which is significantly lower than those in the pre-reperfusion or thrombolytic eras (4,5). Importantly, however, even in the contemporary PCI era, the results from the OACIS study (17) also indicated benefits of BB therapy at discharge for high-risk patients: subgroup analyses among matched populations revealed that BB treatment was associated with a significantly decreased mortality for high-risk patients, who were defined as those with GRACE risk scores ≥ 121 or those administered diuretics, but not for lower risk patients (*Figure 1*), indicating that implementation of BB therapy for STEMI survivors may need to be assessed on the basis of individual mortality risk in the PCI era. Ozasa *et al.* also reported that BB treatment was associated with better survival (6.4% *vs.* 17.4%, $P=0.04$) and decreased incidence of major adverse cardiac events consisting of all-cause death, recurrent MI, and HF hospitalization in a subgroup of patients with LVEF of equal or less than 40% (18). In the OACIS study (17), however, survival classification and regression trees (CART) analysis (25) revealed no significant mortality risk reduction in patients with GRACE risk scores of ≥ 142 (*Figure 2*), while patients with GRACE risk scores between 121 and 141 were most benefitted by BB treatment with approximately 56% mortality risk reduction, indicating that the prescription of BB should be also considered with caution, particularly for individuals at extremely high risk.

In conclusion, in the contemporary era, in which evidence-based strategies have been implemented, the clinical significance of BB treatment after AMI has been likely attenuated, as compared with that in the thrombolytic and pre-reperfusion era, particularly for the AMI survivors without LVSD, HF or other severe clinical conditions, while BB could be still effective in high-risk patients. However, it is a pity that there have been, to date, no randomized controlled trials that examined whether BB treatment reduces incidence of clinical outcomes for AMI in the PCI era. In this regard, reports from a randomized

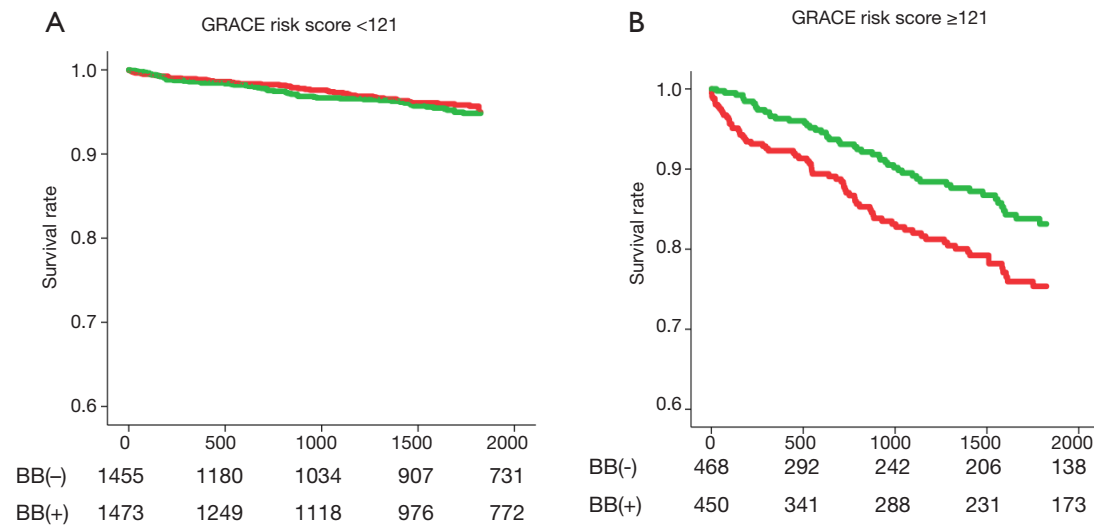


Figure 1 Cumulative incidence of mortality among STEMI patients who underwent PCI and were discharged alive with GRACE risk scores <121 (A) and ≥ 121 (B) (16). Green and red lines indicate estimates for those treated with BB and without BB, respectively. Numbers below the x-axis indicate the number of patients in each group at risk at the indicated time. STEMI, ST-elevation myocardial infarction; GRACE, Global Registry of Acute Coronary Events.

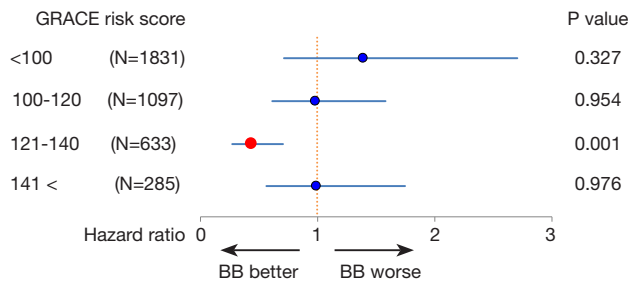


Figure 2 Prognostic impact of beta-blocker treatment at discharge of STEMI for mortality according to GRACE risk scores in the matched population (16). STEMI, ST-elevation myocardial infarction; GRACE, Global Registry of Acute Coronary Events.

controlled trial, Carvedilol Post-intervention Long-term Administration in Large-scale Trial (CAPITAL-RCT) (ClinicalTrials.gov Identifier: NCT01155635), which aims to examine efficacy of carvedilol on 6-year clinical outcomes in patients with STEMI treated with PCI and preserved EF more than 40%, have been awaited. The results of CAPITAL-RCT would help us to address the clinical question whether BB treatment is still effective on long-term outcome in STEMI survivors without LVSD as well as to give us an opportunity to re-assess the current guidelines for secondary prevention after AMI.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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