Randomized controlled trials (RCT) and meta-analyses conducted in the pre-reperfusion era have demonstrated beneficial effects of oral β-blocker therapy on survival in patients with acute myocardial infarction (AMI). Current clinical practice guidelines recommend oral β-blockers for secondary prevention in AMI patients with reduced systolic left ventricular function or heart failure, in the absence of contraindications (class I). It is unclear, however, whether oral β-blocker therapy is effective in uncomplicated AMI patients who have undergone percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) after AMI and received state-of-the-art medication such as strong statins and renin-angiotensin-aldosterone system antagonists (RAAS antagonists). Furthermore, the optimal type, dose, and duration of β-blocker therapy are not clearly defined.

In this issue of the Journal, Hwang et al examine the association between oral β-blocker dose and 1-year risk of cardiac death after AMI using data from a multicenter, prospective registry, the Korea Acute Myocardial Infarction Registry—National Institutes of Health (KAMIR-NIH). Eighty-three percent of patients were discharged on a β-blocker. Beta-blocker type and dose were chosen by the individual physician. The majority of patients received either bisoprolol or carvedilol. Patients discharged on a β-blocker were classified as low-dose or high-dose, according to the percent of target dose prescribed (<25%, ≥25%). The majority of patients were discharged on low-dose β-blockers. All patients in the study were compliant in maintaining the type and dose of β-blocker up to 1 year after discharge. The mean ejection fraction was 52%, and most patients received revascularization via either PCI or CABG (no β-blocker group, 77.1%; low-dose group, 94.6%; high-dose group, 91.2%; P=0.0001). Dual antiplatelet therapy was performed in >99% of patients, and most patients received RAAS antagonists and statins (RAAS antagonists/statins: 54.5/86.1% in no β-blocker group, 84.9/95.2% in the low-dose group, and 84.7/93.8% in high-dose group, P<0.0001). The rate of 1-year cardiac death was lower for patients discharged on β-blocker compared with no use of β-blockers. A significant dose-effect of β-blockers on heart rate reduction was observed (no β-blocker group, 3.7±20.5; low-dose group, 6.3±18.8; high-dose group, 8.7±19.9 beats/min; P<0.001), and significantly higher blood pressure reduction was observed in the high-dose group compared with the no β-blocker and the low-dose groups. There was no significant additional benefit, however, of high-dose β-blockers compared with low-dose β-blockers for risk of cardiac death.

The main mechanism of the beneficial effects of β-blockers in patients with AMI is considered to be attenuation of the myocardial oxygen demand by decreases in heart rate, blood pressure, and myocardial contractility. Although

### Table. β-Blocker Target Dose vs. Type and Dose of β-Blockers Prescribed

<table>
<thead>
<tr>
<th>β-Blocker</th>
<th>Target dose (mg/day)</th>
<th>OBTEIN Study</th>
<th>IHCS Registry</th>
<th>CREDO-Kyoto AMI Registry</th>
<th>KAMIR-NIH Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>200</td>
<td>67.7</td>
<td>80.0</td>
<td>–</td>
<td>1.7</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>50</td>
<td>24.3</td>
<td>10.0</td>
<td>90.2</td>
<td>44.4</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>10</td>
<td>2.8</td>
<td>–</td>
<td>–</td>
<td>48.3</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100</td>
<td>3.8</td>
<td>7.0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Propranolol</td>
<td>160&lt;sup&gt;1&lt;/sup&gt; or 180&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>10</td>
<td>1.1</td>
<td>3.0</td>
<td>9.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Others</td>
<td>–</td>
<td>61.2</td>
<td>86.6</td>
<td>73.5</td>
<td>83.4</td>
</tr>
</tbody>
</table>

<sup>1</sup>Less than 25% of target dose.
the hemodynamic effects of β-blockers are considered as dose dependent, observational studies reported that patients who had had AMI were being treated with lower doses of β-blockers than that used in clinical trials. The discrepancy between the target dose and prescribed dose in the real-world patients is perhaps due to the adverse effects of β-blockers such as hypotension, bradycardia, coronary spasm, fatigue, depression, and metabolic disorders.

The main finding of the present study suggesting no significant additional benefit of high-dose β-blockers compared with low-dose β-blockers for risk of cardiac death would be robust, because the baseline characteristics, severity of AMI, prevalence of early revascularization, and concomitant medications were remarkably similar between the low-dose and high-dose β-blockers groups. The fundamental question, however, is whether oral β-blocker therapy could improve clinical outcomes in contemporary uncomplicated AMI patients or not. The present study as well as several other observational studies have suggested the clinical benefit of β-blockers in patients with uncomplicated AMI, while we reported no benefit of β-blockers in ST-segment elevation AMI (STEMI) patients treated with primary PCI in the 2 Japanese large-scale observational studies.

Selection bias for use of β-blockers in the present study might be due to 17% vs. 56% and 62% in the present study and the 2 Japanese studies was the very low prevalence of no β-blocker use in the present study. Given that β-blocker in AMI is the guideline-recommended medication, very low prevalence of no β-blocker use might indicate that a large proportion of patients in the no β-blocker group were those who were deemed to have very poor prognosis, and in whom β-blocker was regarded as futile. It is noteworthy that patients in the present no β-blocker group less frequently received early revascularization and guideline-recommended medications. Indeed, in the CAPITAL–RCT trial, which is the only RCT exploring the effectiveness of an oral β-blocker in uncomplicated STEMI patients, the event rate for a composite of all-cause death, myocardial infarction, hospitalization for heart failure, and hospitalization for acute coronary syndrome at median 4-year follow-up was very low, and the event rate did not differ with regard to β-blocker use. The lack of a dose-response relationship for β-blockers in the present study might be explained very well, if β-blockers are not at all effective in preventing cardiovascular events in patients with uncomplicated AMI. A large RCT (REDUCE–SWEDHEART: ClinicalTrials.gov NCT 03278509) is ongoing to evaluate the role of β-blocker after AMI in contemporary practice.

Disclosures

The authors declare no conflicts of interest.

References