The effectiveness of β-blockers during and after acute myocardial infarction (AMI) was appraised in the early 1980s, when neither angiotensin-converting enzyme inhibitor (ACEI) therapy nor recanalization therapy (thrombolytic therapy or percutaneous coronary intervention [PCI]) was yet introduced. By virtue of their anti-ischemic, antiarrhythmic, and antiadrenergic properties, β-blockers did limit infarct size, reduced life-threatening arrhythmias, relieved chest pain and recurrent ischemia, and reduced mortality, including cardiac sudden death. Kjekshus demonstrated that a reduction in heart rate of at least 15beats/min during infarct evolution was associated with a reduction of infarct size ranging from 25% to 30%, and comparison of post-AMI trials indicated a significant linear relationship between the reduction of resting heart rate and percentage of reduction in mortality (r=0.60) and reduction in nonfatal re-infarction (r=0.59). In the 1990s, however, the introduction of thrombolytic therapy (TIMI II-B, GUSTO-I, etc) did not necessarily support routine early intravenous β-blocker use, at least when thrombolytic therapy or primary angioplasty was performed. In contrast, routine long-term use of oral β-blockers was supported, with substantial benefits in terms of reduced mortality and morbidity for AMI patients who did not have signs of heart failure (HF), low-output state, increased risk of cardiogenic shock, or relative contraindications to β-blockers.

In the 2000s, the focus of β-blocker therapy was as HF therapy (against symptomatic or asymptomatic left ventricular [LV] dysfunction) to be added to ACEI therapy. The CAPRICORN trial in AMI patients with LV dysfunction demonstrated that carvedilol therapy reduced the frequency of all-cause and cardiovascular mortality, and recurrent non-fatal MI. Furthermore, the CAPRICORN substudy displayed a beneficial effect of carvedilol on LV remodeling, namely improvements in changes in LV end-systolic volume for ACEI+carvedilol group−4.8 ml vs. ACEI group+4.5 ml, and changes in LV end-diastolic volume for ACEI+carvedilol group+0.6 ml vs. ACEI group+8.4 ml. The more important message from the CAPRICORN trial was that these beneficial effects were additional to those of evidence-based treatments for AMI, including ACEI therapy (98% of studied patients) and thrombolysis/primary angioplasty therapy (45% of studied patients). The CHRISTMAS trial suggested some of the beneficial effects of carvedilol would be mediated by improved function of hibernating or ischemic myocardium, or both, namely an important adjunct (or alternative) to recanalization therapy for patients with hibernating myocardium.

Implications in Post-Successful PCI Era

The ACC/AHA guidelines recommended routine use of β-blockers after AMI based on the evidence of studies performed in the pre-PCI era, partly described above. However, in the present era of primary PCI for AMI, few clinical trials have investigated the independent effects of β-blocker therapy on clinical outcomes after successful PCI.

“Does β-Blocker Therapy Improve Clinical Outcomes of AMI After Successful PCI?”

Retrospective analysis of pooled data from 2,442 patients who underwent successful PCI in the PAMI-2, noSOS, Stent-PAMI, and Air-PAMI trials revealed that patients receiving β-blockers (n=1,661, 68%) were less likely to die (2.2% vs. 6.6%) or experience major adverse cardiovascular events (MACE; death, re-infarction, and ischemia-driven target vessel revascularization, 14% vs. 17%) at 6 months, and these benefits were the greatest in the relatively high-risk group with low ejection fraction (EF; ≤50%) or multivessel coronary artery disease. Paradoxically, the low-risk group with preserved EF and those with single-vessel disease showed no statistically significant reduction in 6-month mortality or MACE with PCI and β-blocker therapy. It is enticing to speculate that successful PCI early in the evolving AMI and resultant preserved EF might reduce the patient’s future risk of cardiac events to a point where chronic β-blocker therapy becomes non-indispensable (unnecessary). However, it is possible that the retrospective analysis was largely influenced by selection bias, favoring use of β-blockers in relatively healthier and stable hemodynamic patients, and in fact, they found a lower percentage of Killip class ≥2 and sustained hypotension in the β-blocker patients.

The most recent report, in this issue of the Journal, by Konishi et al retrospectively analyzed the additive effects of β-blockers on renin-angiotensin system (RAS) inhibitors for 251 patients with AMI treated with primary PCI (mean...
EF 44%) during 2004–2009. Their data obtained in a representative teaching hospital in Japan is of real-practice value, even in a single-center retrospective analysis and not enough patients. The addition and choice/dosing of β-blockers were left to the discretion of the attending physician in the hospital. Although this created a significant selection bias, the 2 groups (171 patients in the β-blocker group: 68%; 80 patients in the no-β-blocker group: 32%) were well-balanced for the comparison, other than for the higher double dosage use of RAS inhibitors in the no-β-blocker group. After 12 months historical follow-up, the survival and cardiac event-free rates were significantly higher in the β-blockers group, and these benefits were observed in both the low-risk and high-risk groups. The levels of B-type natriuretic peptide, metalloproteinases 2 and 9, and EF improved significantly in the β-blockers group, which would support the beneficial effects on clinical outcomes in their study. However, comparative analysis between carvedilol and bisoprolol needs further prospective investigation.

The j-Cypher Subanalysis Report
The recently reported j-Cypher registry subanalysis should give a reply to the present issue. Of 12,824 consecutive patients undergoing sirolimus-eluting stent implantation in the j-Cypher registry, they identified 910 patients who underwent primary PCI for AMI and analyzed the clinical outcomes according to the use of β-blockers at hospital discharge. The β-blockers group (n=349, 38%) more frequently had hypertension, low EF, a left anterior descending artery infarct, and statin use compared with the no-β-blockers group (n=561, 62%). During 3-year follow-up, no difference was observed between the 2 groups in mortality (6.6% vs. 6.6%) or incidence of MACE (all-cause death, recurrent AMI, HF hospitalization, 13.5% vs. 12.1%). And better outcomes were observed in the β-blockers group only in the subgroup with EF ≤40%. That should influence the selection bias, but their findings were consistent with previous studies, namely, that the use of β-blockers was not associated with better clinical outcomes in patients with AMI who underwent successful PCI and had preserved EF.

Both reports from Japan have reappraised the contribution and/or limitation of β-blocker therapy in AMI in the post-successful PCI era. The ACC/AHA guideline also has pointed out uncertainty of oral β-blocker therapy in AMI on early (Day 0 to 1) safety issues and the post-PCI preserved EF effects. We need further research and additional investigation of real-world practice achievements and for the next revision of the AMI guideline.

References