



## Should $\beta$ -Blockers Be Prescribed More Frequently to Japanese Patients With Coronary Artery Disease?

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In the era of percutaneous coronary intervention (PCI), the importance of medical treatment for coronary artery disease (CAD) seems to have decreased. However, half of the decline in rates of death from CAD over the past 2 decades in the USA has been attributed to reductions in risk factors, and half to medical treatments, the main contributor being the secondary-prevention medications, of which  $\beta$ -blockers account for the largest portion.<sup>1</sup> The ACC/AHA Secondary Prevention Guidelines for Patients with Coronary and Other Atherosclerotic Vascular Diseases state that  $\beta$ -blockers should be part of routine therapy and continued indefinitely in all patients with myocardial infarction (MI), acute coronary syndrome or left ventricular (LV) dysfunction unless contraindicated. Calcium antagonists for the secondary prevention of MI are not recommended in Western populations.

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Beta-blockers are also strongly recommended in Japan for the secondary prevention of MI. In this issue of the Journal, Kohro et al report that although  $\beta$ -blockers were prescribed for only 30% of patients with CAD in Japan, the continuation rate when prescribed at the time of discharge was 91%. Although  $\beta$ -blockers do not confer additional benefits in reducing all-cause mortality, cardiac events and cerebrovascular events, all-cause mortality is more effectively reduced by lipophilic than hydrophilic  $\beta$ -blockers.<sup>2</sup> The essential message from the study is that, despite it being observational and thus limited, the continuation rate of  $\beta$ -blockers was high, and that lipophilic rather than hydrophilic  $\beta$ -blockers may more effectively reduce mortality rates of Japanese patients with CAD.

The earlier and largest landmark trials of  $\beta$ -blockers in MI before the era of reperfusion therapy (the Norwegian study of timolol and the BHAT of propranolol) revealed that  $\beta$ -blockers reduce mortality. However, the cardiovascular event rate after MI is substantially lower among Japanese patients who undergo recent therapies such as direct PCI than in those reported before the era of reperfusion. The CAPRICORN randomized trial of carvedilol in the era of reperfusion showed not only an effective reduction in all-cause mortality,<sup>3</sup> but also a positive benefit on LV remodeling,<sup>4</sup> and less than 50% of patients underwent reperfusion therapy. From this view-

point, the value of  $\beta$ -blockers for managing patients after acute MI in the era of direct PCI, especially direct coronary stenting, has not been described.

The JBCMI comparison of  $\beta$ -blockers and long-acting calcium antagonists to treat post-acute MI patients in Japan showed that more than 80% of patients underwent reperfusion therapy upon admission. Notably, both types of drug similarly affected cardiovascular event rates,<sup>5</sup> which may be explained in part by the fact that Japanese patients exhibit a 3-fold-greater incidence of coronary spasm soon after acute MI than Caucasians.<sup>6</sup> The JBCMI findings were encouraging for Japanese cardiologists, but calcium antagonists are not recommended as a class I drug by the 2006 Japanese Circulation Society Guidelines for the Secondary Prevention of MI. They outline the class I recommendations that  $\beta$ -blockers be prescribed to all patients with post-MI, except when normal or subnormal LV function is preserved after successful reperfusion therapy, to those with post-infarct angina or hypertension, and to those who do not presently have heart failure but who have had heart failure upon admission or a large MI. Nonetheless, the rate of prescribing  $\beta$ -blockers after MI in Japan remains low. Three successive multicenter studies (JAMIS, 1999; MUSASHI-AMI, 2006; OACIS, 2007) found incremental prescription rates for  $\beta$ -blockers of 5.3%, 25.6% and 38.0%, respectively, after acute MI in Japan. Japanese health insurance providers have not yet approved the use of  $\beta$ -blockers to treat patients after MI.

The use of  $\beta$ -blockers after MI in the USA increased from 41.8% to 71.6% between 1995 and 2004, in association with a 3% reduction in mortality each year.<sup>7</sup> On the other hand, an investigation of hospitals that submitted data to the Hospital Quality Alliance in the USA indicated that although  $\beta$ -blockers were prescribed to 93% of patients after acute MI,<sup>8</sup> the continuation rate was 76% at least at 6 months after discharge.<sup>9</sup>

A recent meta-analysis revealed that a PCI-based invasive strategy may improve long-term survival compared with a medical treatment-only strategy in patients with stable CAD. However, the COURAGE trial suggests that medical therapy is still important for the management of stable CAD, even in the era of PCI therapy. Over 85% of patients in that trial received  $\beta$ -blockers, a rate similar to that of statin administration. In contrast, only 33% of Japanese patients with stable CAD receive  $\beta$ -blockers,<sup>11</sup> because of the higher incidence

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of coronary artery spasm than in Caucasians. However, the use of  $\beta$ -blockers in combination with calcium antagonists to treat coronary spastic angina with organic stenosis significantly increased after 1990. Notably,  $\beta$ -blockers exerted a significantly worse prognostic effect before, but not after, 1990.<sup>12</sup> Beta-blockers are combined with calcium antagonists to treat coronary spastic angina with organic stenosis according to the Guidelines for Diagnosis and Treatment of Patients with Coronary Spastic Angina (class IIa recommendation).

The beneficial effect of long-acting calcium antagonists on cardiovascular events in a Western population with CAD and normal blood pressure has been demonstrated by the CAMELOT study.<sup>13</sup> Long-acting calcium antagonists also demonstrated a beneficial effect on Western patients after PCI.<sup>14</sup> Importantly, more than 75% and 85% of patients, respectively, received  $\beta$ -blockers in those studies. During the past decade, randomized control trials using calcium antagonists for CAD patients with or without hypertension revealed that long-acting calcium antagonists are superior to placebo and equivalent to  $\beta$ -blockers in preventing cardiovascular events. In addition, calcium antagonists are the only drugs recommended for combination with  $\beta$ -blockers as therapy for hypertensive patients in the Guidelines for the Management of Hypertension published by the Japanese Society of Hypertension.

Propensity score matching by Kohro et al found that  $\beta$ -blockers did not reduce cardiovascular events in a Japanese population with CAD, which might be explained partly as a limitation of any observational study,<sup>2</sup> a racial difference or a consequence of PCI therapy. Because the JBCMI trial did not have a control group, the actual effectiveness of  $\beta$ -blockers in secondary prevention among Japanese patients after acute MI is inconclusive. However, that  $\beta$ -blockers reduce cardiac events after MI has been identified by a retrospective Japanese study.<sup>15</sup> All-cause mortality in Japanese patients with CAD was reduced more effectively by lipophilic than hydrophilic  $\beta$ -blockers.<sup>2</sup> Bisoprolol, sustained-release metoprolol and carvedilol, which should not be considered indicative of a  $\beta$ -blocker class effect, are the only  $\beta$ -blockers recommended for patients with chronic heart failure according to the AHA/ACC Guidelines for the Diagnosis and Management of Chronic Heart Failure. Lipophilic  $\beta$ -blockers might modulate the sympathetic balance and be associated with risk reduction in sudden cardiac death and LV hypertrophy. Likewise, the beneficial effects conferred on patients with CAD might be more pronounced with lipophilic than with hydrophilic  $\beta$ -blockers.

Long-term use of  $\beta$ -blockers is safe and tolerated by Japanese patients with CAD, and lipophilic  $\beta$ -blockers might help reduce all-cause mortality. Gradual dose titration of  $\beta$ -blockers is required to attain a high rate of continuation of these drugs for secondary prevention after acute MI. In any case, evidence of the value of  $\beta$ -blockers for Japanese patients with CAD is scant and a randomized control trial is required

to confirm the efficacy of  $\beta$ -blockers and the superiority of lipophilic over hydrophilic  $\beta$ -blockers in reducing mortality or cardiovascular events in Japanese patients with CAD in the era of PCI therapy.

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