β-Blockers in the Post–Myocardial Infarction Patient

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Case 1: A 76-year-old man was diagnosed with an ST-segment elevation anterior wall myocardial infarction (MI) and underwent primary percutaneous coronary intervention with stent placement. After 3 days, the left ventricular ejection fraction was 35%. He was prescribed aspirin, clopidogrel, an angiotensin-converting enzyme (ACE) inhibitor, and a statin.

Case 2: A 67-year-old woman with history of hypertension was diagnosed with a non–ST-elevation MI. The left ventricular ejection fraction was 50%. She initially was given an intravenous β-blocker, nitrates, aspirin, an ACE inhibitor, and a statin.

Should long-term β-blockers be recommended for both of these patients?

The 2001 American Heart Association and American College of Cardiology (AHA/ACC) guidelines for secondary prevention of MI and death recommend initiating β-blockade in all post-MI patients and continuing therapy indefinitely.1

Despite strong evidence supporting the use of β-blockers in the post-MI period, less than half of MI patients are prescribed β-blockers in the chronic setting.2,3 Physician reluctance to use β-blockers after acute MI may be related to: (1) a perceived decline of benefits due to the introduction of antiplatelet agents, ACE inhibitors, statins, and revascularization procedures; (2) concerns about safety in patients with heart failure (HF), chronic obstructive pulmonary disease (COPD), diabetes mellitus, and/or old age; (3) side effect profile; and (4) perceived lack of benefit in non–ST-elevation MI.

Use of β-Blockade in Contemporary Management of Post-MI Patients

Since it was first reported in 1965 that administration of propranolol after acute MI reduced mortality,4 a number of studies have been conducted to confirm this observation.5 The largest were the β-Blocker Heart Attack Trial (BHAT)6 and the Norwegian Multicenter Study Group7 trial studying nonselective β-blockers. In the BHAT trial (which monitored 3837 post-MI patients for 27 months), propranolol significantly reduced overall mortality by 26% compared with placebo.6 The Norwegian Multicenter Study Group (which monitored 1884 post-MI patients for 12 to 33 months) demonstrated a 39% reduction in mortality and a 28% reduction in the reinfarction rate with timolol (Table 1).7

Although the results of these studies represented a major advance in post-MI management, they predated the era of modern therapy and did not include patients with HF. With the addition of ACE inhibition into post-MI management algorithms, some clinicians questioned the added value of β-blockers. Nevertheless, the Survival and Ventricular Enlargement (SAVE) and Acute Infarction Ramipril Efficacy (AIRE) trials showed that β-blockers provided an additional reduction in cardiovascular mortality independent of the use of ACE inhibitors.9,10 In addition, a meta-analysis of 31 long-term β-blocker studies with follow-up lasting 1 to 4 years found marked benefits in terms of reducing mortality and morbidity in post-MI patients.5 The benefits of β-blockers were maintained in the era in which fibrinolytics and aspirin were used. In fact, the substantial effect of β-blockers in reducing mortality compared favorably with other therapies: The number of unselected patients needed to treat to avoid one death over 2 years was 24 for fibrinolytics and aspirin used for 4 weeks, 42 for β-blockers, 94 for statins, and 153 for antiplatelet agents.5

The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial evaluated the effects of adding carvedilol (a nonselective β-blocker with α-blocking capability) to standard therapy in patients with acute MI and left ventricular systolic dysfunction (ejection fraction ≤0.40), with or without HF symptoms. In this study, mortality or nonfatal reinfarction (which was not the primary end point)
was significantly reduced by carvedilol (Table 2).\textsuperscript{11} Almost all patients in CAPRICORN were given ACE inhibitors, 85% were on aspirin, and 45% received reperfusion therapy.\textsuperscript{11}

\section*{β-Blockers in Post-MI Patients With Relative Contraindications}

A review of $\geq$200,000 patient records in the Cooperative Cardiovascular Project found that only 34% of patients received β-blockers after MI.\textsuperscript{12} The percentage was lower among African Americans, the elderly, and patients with HF, COPD, low heart rate or blood pressure, or type 1 diabetes mellitus.\textsuperscript{12} When all risk factors were accounted for, however, there was notably less mortality in each of these subgroups when β-blockers were administered.\textsuperscript{12,16}

\section*{β-Blocker Use in HF}

Because of their initial transient negative inotropic effects, β-blockers traditionally were considered contraindicated in HF. However, in a subset analysis in BHAT of patients who had HF before randomization, propranolol reduced total mortality and sudden death.\textsuperscript{13} In CAPRICORN, carvedilol reduced mortality and reinfarction in post-MI patients with left ventricular systolic dysfunction, with or without signs of HF (Table 2).

Present ACC/AHA guidelines advise that in patients with systolic HF, most of whom have coronary artery disease,\textsuperscript{14} an ACE inhibitor should be used first, and a β-blocker such as carvedilol or metoprolol CR/XL should be started at low doses (see Figure 1) and gradually increased over $\approx$12 weeks.\textsuperscript{15} There is now conclusive evidence that long-term β-blocker use results in improved rates of mortality and morbidity in patients with HF.\textsuperscript{16–18,19}

\section*{β-Blockade in Patients With COPD}

COPD of itself is not a contraindication unless there is significant reactive airway disease. The Cooperative Cardiovascular Project found that patients with COPD had a major reduction in mortality with β-blockers.\textsuperscript{12,20} In fact, even patients who are prescribed β-agonists may actually benefit

\begin{table}[h]
\centering
\caption{Comparison of Major β-Blocker Trials in the Chronic Post-MI Period}
\begin{tabular}{|l|c|c|c|c|c|}
\hline
 & \textbf{CAPRICORN}\textsuperscript{11} & & \textbf{BHAT}\textsuperscript{8} & & \textbf{Norwegian}\textsuperscript{7} \\
 & Carvedilol & Placebo & Propranolol & Placebo & Timolol \\
 & (n=975) & (n=984) & (n=1916) & (n=1921) & (n=945) \\
\hline
Starting dose, titration, and target dose & 6.25 mg starting dose, increased progressively to max 25 mg twice daily during 4- to 6-wk period & 180–240 mg daily & 5 mg starting dose, increased to 20 mg daily \\
\hline
Mean no. days after entry from MI (range) & 10 (3–21) & 13.8 (5–21) & 11.5 (7–28) \\
\hline
Exclusion criteria & Documented MI & Documented MI & Documented MI \\
Left ventricular ejection fraction $\leq$40% or wall motion score $<1.3$ & Marked bradycardia & History of HF or asthma & Uncontrolled HF, heart rate $<50$ bpm, 2° or 3° atrioventricular block, blood pressure $<100$ mm Hg, unstable diabetes mellitus, COPD, intermittent claudication \\
\hline
Mean age, y (range) & 63 (29–88) & 63 (25–90) & 54.7 (30–69) & 54.9 (30–69) & 60.3 (20–75) \\
Men/women, % & 73/27 & 74/26 & 84/16 & 85/15 & 80/20 \\
Mean left ventricular ejection fraction, % (SD) & 33 (6.4) & 33 (6.4) & NP & NP & NP \\
Previous MI, % & 31 & 29 & 14 & 13 & 19 \\
Previous angina, % & 57 & 54 & 36 & 36 & 38 \\
Previous hypertension, % & 55 & 52 & 41 & 40 & 18 \\
Previous diabetes mellitus, % & 21 & 23 & 12 & 11 & N/A \\
Revascularization, % & 12 & 11 & N/A & N/A & N/A \\
Thrombolyis/percutaneous coronary intervention, % & 45 & 47 & N/A & N/A & N/A \\
ACE inhibitor, % & 98 & 97 & N/A & N/A & N/A \\
Aspirin-converting enzyme, % & 86 & 86 & N/A & N/A & N/A \\
Anticoagulant, % & 63 & 65 & 14 & 15 & N/A \\
Nitrates, % & 73 & 73 & N/A & N/A & N/A \\
IV Diuretics, % & 35 & 33 & N/A & N/A & N/A \\
\hline
\end{tabular}
\end{table}

N/A indicates not available; NP, not performed.
from the addition of a β-blocker. Nevertheless, β2-blockade may cause bronchoconstriction and should be used with caution. In patients with mild reactive airway disease, short-acting β1-selective agents such as metoprolol or atenolol at low dose may be safer because of limited interaction with the β2-receptor. Their selectivity, however, may be lost at higher doses.

β-Blockade in Patients With Diabetes Mellitus and Hyperlipidemia

Diabetes is an important risk factor for early and late mortality after MI. The use of β-blockers in diabetes has been questioned because of their modulating effect on hypoglycemic symptoms and potential interference with insulin release. In patients with diabetes, it was found that those who were prescribed β-blockers had a significantly lower 1-year mortality rate than those not receiving these agents, regardless of type and severity of diabetes.

Some β-blockers decrease HDL and increase triglycerides. In spite of this, BHAT data showed that propranolol improves survival after MI. Low-dose metoprolol CR/XL alone or in combination with a statin resulted in significant slowing of the progression of carotid artery’s intima-media thickness over a 3-year period.

β-Blockade in Elderly Patients

Fewer than 51% of elderly patients (older than 65) hospitalized with an acute MI and without any contraindications to β-blockers received early β-blocker therapy. However, those who did receive this therapy (mean age, 75.1 years) had

### TABLE 2. Comparison of Major β-Blocker Trials in the Chronic Post-MI Period: Clinical Outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>CAPRICORN</th>
<th>BHAT</th>
<th>Norwegian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol, %</td>
<td>Placebo, %</td>
<td>Reduction, %</td>
<td>P</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>11.9</td>
<td>15.3</td>
<td>23</td>
</tr>
<tr>
<td>Sudden death</td>
<td>5</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Nonfatal reinfarction</td>
<td>3</td>
<td>75</td>
<td>40</td>
</tr>
<tr>
<td>All-cause mortality and reinfarction</td>
<td>14</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

N/A indicates not analyzed; NS, not significant.

*Coronary heart disease mortality and reinfarction.

AV indicates atrioventricular; BP, blood pressure; DM, diabetes mellitus; HR, heart rate; LV, left ventricular; PVD, peripheral vascular disease.
a significantly lower rate of in-hospital mortality than those not receiving early β-blockade. A subgroup analysis of all-cause mortality on patients <70 years and ≥70 years of age was performed in CAPRICORN. The point estimates favoring carvedilol use regardless of age are consistent with the findings of the overall study group (unpublished data, 2002). The Cardiovascular Cooperative Project also reported that mortality was 32% lower in patients ≥80 years of age.12

β-Blocker Use in African Americans

It has been suggested that African Americans with HF may not respond as well to ACE inhibitors and β-blockers. However, a 40% decrease in the relative risk of death was reported for African-American patients receiving β-blockers at hospital discharge. In BHAT, β-blocker benefits for African-American patients were observed. In the US Carvedilol Heart Failure Trial Program, carvedilol mortality benefit was apparent and of similar magnitude in both African-American and non–African-American HF patients.31

β-Blocker Use in Patients With Peripheral Vascular Disease

Although there is concern that β-blockers could increase claudication in patients with peripheral vascular disease, clinical studies do not support this concept. Indeed, β-blockers are well tolerated.32

β-Blockers and Side Effects

All too often, β-blockers are not used because of their perceived side effects, namely fatigue, decreased heart rate, hypotension, and reduced sexual activity. In the BHAT trial, reduced sexual activity was reported by 43.2% in the propranolol group and 42.0% in the placebo group; the difference was not statistically significant. Similarly, fatigue was present in 66.8% in the propranolol group compared with 62.1% in the placebo group. Propranolol had to be discontinued in only 0.7% because of bradycardia, in 1.2% because of hypotension, in 1.5% because of fatigue, in 0.4% because of depression, and in only 0.2% because of reduced sexual activity. It is clear from this study that even high doses of β-blockers are well tolerated in post-MI patients.32

β-Blocker Use in Patients With Non–ST-Elevation MI

The role of β-blockers in patients with non–ST-elevation MI has been questioned in the retrospective analysis of the BHAT trial. However, the Norwegian Multicenter Study Group7 and Gottlieb et al12 found that β-blocker therapy was associated with an improvement in survival rate. Although not as strong for a non–ST-elevation MI, evidence shows that β-blockers should be used in this group of patients, with the same β-blockers and doses that are being used for patients with an ST-elevation MI. It should also be noted that patients with non–ST-elevation MI may also be at high risk, because they are older, have extensive coronary artery disease, and have a higher rate of residual ischemia or reinfarction.34

Which β-Blocker?

β-Blockers have important differences with regard to receptor selectivity, receptor affinity, lipophilicity, and intrinsic sympathomimetic agonism. It is not clear that these pharmacological distinctions translate into meaningful differences in efficacy and safety. However, the choice and dose of β-blocker should be based on its proven effectiveness in large, randomized clinical trials (Figure).

Conclusion

The level of evidence supporting the use of β-blockers in the chronic post-MI period is very strong. On the basis of much of the evidence presented here, the American Medical Association and 5 other collaborating medical organizations recently issued a “Quality of Care Alert,” which recommends that the benefits of β-blockers in reducing mortality and reinfarction may actually outweigh their risks, even in patients with relative contraindications such as asthma, diabetes mellitus, COPD, severe peripheral vascular disease, PR interval >0.24 seconds, and moderate or severe left ventricular failure.5 Taken as a whole, this evidence leads to the conclusion that β-blockers should be administered to all post-MI patients without a contraindication and should be continued indefinitely, as recommended in the recent 2001 AHA/ACC Scientific Statement.1

References


