MORE THAN 1 MILLION PATIENTS SUFFER a myocardial infarction (MI) in the United States each year. Despite significant advances in pharmacologic and interventional therapies, 25 percent of men and 38 percent of women still die within one year of an acute MI. In addition, nearly half will experience subsequent physical disability from heart failure (HF). Prognosis after an MI is determined by several factors including the extent of left ventricular systolic dysfunction (LVD) (a left ventricular ejection fraction [EF] of less than or equal to 40 percent) with or without clinical HF; the progression of underlying coronary artery disease (CAD); patient age; and comorbidities. These factors lead to death due to progressive HF; sudden arrhythmic death, and reinfarction. Randomized clinical trials have shown that long-term beta-blocker use reduces the risk of death and disability in MI survivors. Current guidelines state that all patients should be prescribed a beta-blocker after an MI unless there is an absolute contraindication to therapy. Contraindications include symptomatic Bradycardia, hypotension (systolic blood pressure <80 mmHg), signs of peripheral hypoperfusion, cardiogenic shock, acute pulmonary edema, advanced heart block (without pacemaker), or reactive airway disease.

The 2004 American Heart Association/American College of Cardiology (AHA/ACC) STEMI guidelines give a Class Ia recommendation (procedure/treatment should be performed/administered) for the in-hospital and long-term post discharge use of beta-blockers in MI (ST elevation MI [STEMI]) patients without contraindications. The presence of decompensated heart failure early in the course of STEMI should preclude the use of early IV beta-blockade until the HF has been compensated, but LVD and/or HF is a strong indication for the oral use of beta-blockers in MI (ST elevation MI [STEMI]) patients without contraindications. The 2002 ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction supports the use of beta-blocker therapy as a Class Ib recommendation.

Despite compelling evidence and recommendations,
beta-blockers remain an underutilized therapy in the post-MI period. Physician concerns may exist regarding the safety and benefits of beta-blockers in post-MI patients with LVD, with or without HF symptoms, despite clinical trial evidence to the contrary. This is especially important as many post-MI patients will have LVD with or without symptoms of HF. In the Trandolapril Cardiac Evaluation (TRACE) registry involving more than 6,500 MI patients, HF and LVD were assessed within the first few days of an MI. This study found that 64 percent of post MI patients had either HF or LVD, or both. In addition, misunderstandings may persist regarding the safety and benefits in elderly patients or patients with diabetes or chronic obstructive airway disease. A number of beta-blockers have demonstrated safety and efficacy in large-scale, long-term, placebo-controlled, randomized clinical trials of MI survivors in which the target doses were well defined. Nevertheless, MI patients are often treated with agents whose long-term use has not been shown to be effective and for which optimal dosing has not been defined.

**Risk after Myocardial Infarction**

Within six years of a myocardial infarction, approximately 18 percent of men and 35 percent of women will have a recurrent MI. Post-MI patients also have a sudden death rate that is four to six times that of the general population. Compared with post-MI patients without LVD, patients with LVD have an even worse prognosis. Post-MI patients with LVD have a fourfold increase in the rate of in-hospital mortality and a twofold to threefold increase in the rate of mortality at 30 days and at 6 months. Post-MI patients with LVD also have a twofold increase in the rate of reinfarction and are at the highest risk for sudden death. Approximately 50 percent of patients with LVD do not have symptoms of HF, but despite being asymptomatic they remain at similar risk as patients with symptoms of HF.

**Beta-Blocker Use after Myocardial Infarction**

**Immediate Post-MI Period**

Beta-blocker use in the immediate post-MI period is a Class I recommendation in the AHA/ACC guidelines. The use of intravenous beta blockers is a Class IIa recommendation. Some, but not all, trials of beta-blockers in the early stage after an MI have shown a reduced risk of reinfarction, arrhythmias, and mortality. Beta-blockers are believed to limit the damage to the injured myocardium. Meta-analysis of clinical trials have demonstrated that immediate (within 24 hours) post-MI beta-blocker use can provide reductions in all-cause mortality; however, these agents remain unproven in reducing nonfatal reinfarction. Most of these trials were conducted before the use of thrombolysis for MI.

The recent large-scale Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) showed no mortality difference with the use of IV beta-blockade, supporting the weaker recommendation previously made by the ACC/AHA guidelines. In this study, 45,852 patients were randomly allocated metoprolol (up to 15 mg IV, then 200 mg oral daily; n=22,929) or matching placebo (n=22,923), and study treatment was to continue until discharge or up to four weeks in hospital (mean=15 days in survivors). Eligible patients included those presenting with ST-segment elevation, left-bundle branch block, or ST-segment depression (7 percent) within 24 hours of onset of symptoms of suspected acute MI, unless their physician considered them to have clear indications for, or contraindications to, any of the study treatments. Patients scheduled for primary percutaneous coronary intervention (PCI) were excluded. Other reasons for excluding patients were determined by the physician and included either a small likelihood of worthwhile benefit (e.g., other life-threatening disease or unconvincing history of MI) or high risk of adverse effects with the study treatments (which for metoprolol would have included persistently low blood pressure [e.g., systolic blood pressure below 100 mm Hg], or low heart rate [e.g., below 50 bpm], heart block, or cardiogenic shock). Evidence of moderate HF (Killip class II or III) was not an exclusion criterion; approximately 20 percent of patients were in Killip class II and almost 5 percent were classified as Killip class III. There was no difference in overall mortality between the placebo and metoprolol groups (RR=1 percent, P=0.7). Of importance, patients in this study had a significantly increased risk (30 percent, P<0.00001) of cardiogenic shock when administered IV metoprolol followed by oral metoprolol succinate versus placebo.

**Intermediate and Long-Term Post MI Period**

Long-term beta-blocker therapy has been associated with significant mortality reductions in MI patients as demonstrated in three large-scale, randomized, clinical trials: the Beta-Blocker Heart Attack Trial (BHAT), the Norwegian Timolol Trial (NTT), and the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial (Exhibit 1). Although HF or LVD is present in a large number of MI patients, individuals with significant cardiac decompensation have generally been excluded from randomized beta-blocker trials; only 19 percent of BHAT and 33 percent of NTT participants had a history or some degree of HF on admission. In BHAT, patients with a history of severe HF were excluded, and in NTT, patients with uncontrolled cardiac failure were excluded. CAPRICORN specifically enlisted only patients with documented HF or LVD, or both. Approximately 50 percent of post MI patients had either HF or LVD, or both.
LVD and was performed in the era of thrombolysis, angioplasty, and angiotensin-converting enzyme (ACE) inhibitor therapy. Patients were randomized to carvedilol as early as the day following the infarct, and the majority were randomized within the first two weeks of the trial. CAPRICORN demonstrated that when carvedilol was added to standard care (including antiplatelet therapy, ACE inhibitors, lipid-lowering, and if indicated, reperfusion therapy) compared to placebo added to standard care, there was a statistically significant 23 percent reduction in all-cause mortality (Exhibit 2). CAPRICORN further demonstrated that carvedilol reduced the risk of reinfarction by 40 percent. Approximately half of the patients in CAPRICORN were asymptomatic (no HF symptoms), and approximately 46 percent were given acute interventional therapy (either thrombolytic therapy or angioplasty). Carvedilol resulted in similar benefit in those patients with no symptoms of HF (RR=31 percent) as in those who had undergone revascularization (RR=32 percent). In a subset analysis, carvedilol also significantly increased left ventricular ejection fraction (LVEF) whereas placebo caused no change after six months of treatment.
Evidence-Based Strategy for Post-MI Beta-Blocker Therapy

Although large-scale randomized clinical trials have demonstrated a reduced post-MI mortality risk in patients with normal ventricular function treated with long-term propranolol (BHAT) and timolol (NTT) and patients with LVD treated with carvedilol (CAPRICORN), no similar evidence has been reported for the commonly used Beta1-selective blockers metoprolol or atenolol. In general, although anti-adrenergic agents are discussed as being interchangeable, the currently available clinical trial evidence does not support the view that clinical benefits of beta-blockers post MI are a class effect.

Evidence-Based Algorithm for Beta Blockers Post MI

Patients with Suspected MI Admitted to the Hospital

Initiating IV β-Blockers

In MI patients with significant ongoing chest pain, hypotension, or marked sinus tachycardia without contraindications, IV dosing may be considered; otherwise oral dosing should be initiated. MI patients receiving IV beta-blockers require strict monitoring of heart rate, blood pressure, electrocardiogram, and clinical status during initiation, and administration should be discontinued if abnormalities occur. The AHA/ACC guidelines state that intravenous β-blocker use is a Class IIa recommendation.

Many patients are initiated intravenously on Beta1-selective agents in-hospital, converted to oral treatment, and discharged on these Beta1-selective agents despite their failure to demonstrate significant improvement in long-term survival after MI.

Implementation of evidence-based therapy may prompt consideration of switching patients from Beta1-selective blockers to evidence-based nonselective Beta-blockers. Switching was performed safely in MI patients during the CAPRICORN trial, in which prior Beta-blockade did not exclude participation. A post-hoc analysis that included the approximately 15 percent of CAPRICORN patients who had received at least one dose of IV or oral beta-blockade was performed. The agent was discontinued prior to randomization. Although some of these patients were switched to carvedilol on the same day, the majority had one or more intervening days with no beta-blocker therapy. Carvedilol resulted in clinical benefits regardless of whether patients had initially been started on a different beta-blocker or were started de novo at randomization. Patients initiated on an IV or oral beta-blocker and subsequently receiving carvedilol had the same improved outcomes as those initiated directly on carvedilol.

Among patients randomized in the hospital in CAPRICORN, there was no significant heterogeneity between those newly started on or those switched to carvedilol with regard to in-hospital HF or bradycardia adverse events. Importantly, patients newly started on carvedilol had similar rates of in-hospital HF and bradycardia as those on placebo (HF: placebo 2 percent, carvedilol 4 percent, \( P=0.06 \); bradycardia: placebo 2 percent, carvedilol 1 percent, \( P=0.77 \)). This pattern was also seen for patients who had previously received IV or oral beta-blockade (HF: placebo 1 percent, carvedilol 2 percent, \( P=0.28 \); bradycardia: placebo 2 percent, carvedilol 3 percent, \( P=0.56 \)). For in-hospital hypotensive events, there was a trend toward heterogeneity among these subgroups (interaction \( P \) value=0.08). Eleven percent of patients newly started on carvedilol experienced a hypotensive event, compared to 6 percent on placebo (\( P=0.0007 \)); however, there were nearly equal rates (7 percent placebo, 8 percent carvedilol) among patients previously receiving IV or oral beta-blockade as part of their post-MI treatment.

No difference was observed between carvedilol and placebo in the incidence of HF adverse events reported any time during the study regardless of prior β-blocker treatment. For bradycardia, patients newly started on carvedilol had a rate of 7.5 percent any time during the study versus 4 percent for placebo (\( P=0.0005 \)); for patients who previously received a β-blocker, this rate was 8 percent for carvedilol and 5 percent for placebo (\( P=0.06 \)). For hypotension any time during the study, patients newly started on carvedilol had a rate of 24 percent versus 15 percent on placebo (\( P<0.0001 \)); for patients who previously received β-blockade this rate was 21 percent on carvedilol versus 14 percent on placebo (\( P=0.03 \)).

Withdrawal of medication, both for events in-hospital and events reported for the entire study, showed no heterogeneity based on prior beta-blocker use, and no difference between carvedilol and placebo. Although these data primarily reflect a population that was not directly switched from IV or oral beta-blocker to carvedilol in the peri-MI period, they do suggest both the safety and efficacy of carvedilol in such patients.

Initiating Oral Beta-Blockers

Oral beta-blockers may be started before, during, or after initiation and titration of ACE-inhibitor therapy in patients with or without reperfusion therapy. The evidence-based beta-blockers for post-MI patients without LVD include propranolol and timolol (Exhibit 3). Both metoprolol tartrate and atenolol are FDA-indicated for post-MI use, although their safety and efficacy, specifically in post-MI patients with LVD, have not been studied. Evidence from
CAPRICORN shows that patients with LVD, regardless of the presence of HF symptoms, benefit greatly from treatment.9,24 Left ventricular function should be assessed in the hospital before the patient is discharged, and LVEF less than 40 percent warrants the use of carvedilol preferentially.24

In patients with LVD, carvedilol should be started at 6.25 mg bid and increased to 12.5 bid and 25 mg bid at three- to 10-day intervals (Exhibit 4).9,24 The recommended dosing regimen need not be altered in patients who received treatment with an IV or oral beta-blocker during the acute phase of the MI. Treatment should be initiated as soon as possible and the target dose should be continued indefinitely. If patients are unable to achieve the full recommended dose due to severe bradycardia or hypotension, a lower dose should be maintained and dose escalation should be reattempted after several weeks. Dose-related clinical benefits have been demonstrated at below target doses of carvedilol in patients with chronic HF.29

Concomitant Drug Therapy
The ACC/AHA recommendations for pharmacologic therapy in the acute phase after MI and long-term management are listed in Exhibits 4 and 5. Patients with MI should be treated with ACE inhibitors and beta-blockers in the absence of contraindications, irrespective of left ventricular function. In post-MI patients with LVD and HF, aldosterone antagonists are also indicated; in the absence of contraindications or intolerance, ACE inhibitors are recommended for initiation 12 to 24 hours after admission for MI. Thus, patients may be started on beta-blockers before, during, or after initiation of ACE inhibitors. ACE inhibitors need not be at target doses prior to the initiation of a beta-blocker. Subsequent uptitration of the ACE inhibitor can be done after optimization of the beta-blocker dose, and both agents may be titrated to target doses over time. Aldosterone antagonists are recommended in post-MI patients with LVD, HF, or diabetes in the absence of contraindications or significant renal
dysfunction. Patients must be closely monitored for the development of hyperkalemia. Aldosterone antagonists can be initiated, continued, or dose-adjusted before or during beta-blocker treatment. Although both ACE inhibitors and beta-blockers are Class I recommendations in the guidelines and the evidence is strong that both should ultimately be used in post-MI patients without contraindications or intolerance, the question frequently arises of which to initiate first. In the major clinical trials of ACE inhibitors in MI, most patients were already on beta-blocker therapy when randomized to ACE inhibitor or placebo. In CAPRICORN, by study design, patients needed to be on ACE inhibitor therapy prior to randomization to carvedilol or placebo. The recent CIBIS III trial indicates that the initiation of bisoprolol prior to enalapril in HF may result in better outcomes for the patient. In another clinical trial, HF patients were randomized to initiation and uptitration of ACE inhibitor therapy followed by carvedilol compared to initiation and uptitration of carvedilol followed by ACE inhibitor. Patients started first on carvedilol had better clinical status, greater LVEF, and lower B-type natriuretic peptide (BNP) levels at the end of one year compared to those started on ACE inhibitors first. Thus, in post-MI patients with LVD and borderline blood pressures, initiation of beta-blocker therapy first, followed by subsequent initiation of ACE inhibitors should be considered.

If overt HF develops in patients with asymptomatic LVD or worsens in those who already have signs or symptoms of decompensation, diuretics should be increased and the rate of uptitration should be slowed. If hypotension limits carvedilol uptitration, the ACE inhibitor dose should be decreased temporarily.

**Switching**

In all MI patients without contraindication, a beta-blocker should be started as soon as possible, LVD should be assessed, and then either the initiation or switching to an evidence-based beta-blocker should occur. Dosing of carvedilol remains the same whether the patient is newly initiated or switched from another agent. Patients should remain on β-blocker therapy for life.

Switching to evidence-based beta-blockade with carvedilol may be considered in select patients. After patients have been clinically stable for 72 hours, oral metoprolol and atenolol can be switched to carvedilol (for LVEF ≤0.40). Patients with LVD not at further increased risk due to persistent ischemia, arrhythmias, hypotension, HF, or large areas of jeopardized myocardium may be safely switched directly from metoprolol or atenolol to carvedilol. Other patients should be stabilized prior to switching. Patients taking metoprolol or atenolol should discontinue these agents and then begin carvedilol 12 hours after the last dose: carvedilol 12.5 mg bid for those taking metoprolol or atenolol 100 to 200 mg daily, and 6.25 mg bid for those taking 50 mg daily. Patients in either dose group should have carvedilol titrated by doubling the dose stepwise to 25 mg bid every 3 to 10 days. The measurement of LVD is the key to this management strategy and should be considered vital in all post-MI patients before an evidence-based approach to care can be chosen.

**Conclusions**

A convincing body of evidence supports the lifesaving benefits of beta-blocker therapy in the post-MI patients. Based on this evidence, the latest ACC/AHA guidelines for MI indicate that all patients without contraindication should be started on beta-blocker therapy, irrespective of concomitant fibrinolytic therapy or performance of primary percutaneous coronary intervention. There is little evidence that a class effect exists, however, and every effort should be made to utilize those specific agents and doses demonstrated to be effective in randomized clinical trials. It is critical to initiate and maintain long...
term this evidence-based, guideline-recommended, life-prolonging therapy. JCMC

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