Reappraisal of ß-Blocker Therapy in the Acute and Chronic Post–Myocardial Infarction Period

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In patients presenting with acute myocardial infarction (MI), the early use of intravenous ß-blockade followed by short-term oral administration in the absence of reperfusion therapy has shown a modest reduction in mortality. In contrast, major reductions in mortality and reinfarction have been shown when ß-blockers have been used soon after an acute MI and continued long-term. These benefits were observed in trials conducted in the 1970s and 1980s, prior to the widespread use of reperfusion therapies, antiplatelet agents, and angiotensin-converting enzyme inhibitors; those trials excluded patients with postischemic heart failure. Recently, the CAPRICORN trial has shown a significant reduction in all-cause mortality and reinfarction in post-MI patients with systolic dysfunction, in response to carvedilol. In spite of compelling evidence supporting the use of ß-blockers in the post-MI setting, data published by the National Cooperative Cardiovascular Project have shown that fewer than half of all post-MI patients receive ß-blockers as long-term therapy. It appears that post-MI patients with perceived contraindications, such as advanced age, diabetes, heart failure, peripheral vascular disease, and/or chronic pulmonary obstructive disease, may derive a substantial benefit from the use of ß-blockers. Given the considerable evidence from randomized clinical trials, the use of ß-blockers is recommended in all post-MI patients without a contraindication, particularly in those with left ventricular systolic dysfunction.
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In the United States, it is estimated that 12.9 million people have a history of myocardial infarction (MI), angina pectoris, or both; yearly, 650,000 patients will have a new MI, 450,000 will present with a recurrent MI, and nearly 200,000 will die as the result of an MI.[1] Approximately 40% of all MIs are accompanied by left ventricular (LV) systolic dysfunction with or without clinical

heart failure.[2] Thus, the risk of major coronary events progressing toward heart failure and its poor prognosis remain an alarming public health concern. However, there have been major advances in the management of acute MI, with reperfusion therapy, antiplatelets, angiotensin-converting enzyme (ACE) inhibitors, ß-blockers, and lipid-lowering agents, providing life-saving benefits.

Acute coronary syndrome (ACS) is a term referring to any constellation of clinical symptoms that are compatible with acute myocardial ischemia. It encompasses acute MI (ST-segment elevation and non–ST-segment elevation) as well as unstable angina (UA). According to the updated American College of Cardiology (ACC)/European Society of Cardiology definition, acute, evolving, or recent myocardial infarction is diagnosed by:

1. A typical rise and gradual fall (troponin) or more rapid rise and fall (creatine kinase MB) of biochemical markers of myocardial necrosis with at least one of the following:
   a. ischemic symptoms
   b. development of pathologic Q waves on electrocardiogram
   c. electrocardiographic changes indicative of myocardial ischemia (ST-segment elevation or depression)
   d. coronary artery intervention, or
2. Pathologic findings of an acute MI[3]

In the revised 2001 Consensus Statement on secondary prevention for patients with coronary and other vascular disease, the American Heart Association (AHA) and ACC noted that aggressive risk factor management clearly improves patient survival, reduces recurrent events and the subsequent need for interventional procedures, and improves patient quality of life. These updated guidelines recommend the initiation of ß-blocker therapy in all post-MI patients without contraindication and its continuation indefinitely.[4]

Potential Mechanism for Clinical Benefits of ß-Blockers

Many studies have confirmed the cardioprotective role of ß-blockers in patients who have survived an acute MI and have demonstrated that their use in these patients can provide considerable reductions in all-cause mortality, including sudden death and nonfatal reinfarction. The precise mechanisms by which ß-blockers affect these outcomes remain speculative. These agents are thought to interfere with pathologic pathways involving a variety of post-MI processes, such as arrhythmias, ischemia, and atherosclerosis.[5]

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Anti-ischemic/ Antiatherosclerotic Effects

The anti-ischemic effects of ß-blockers are supported by evidence that these agents can decrease the heart rate and blood pressure, prolong diastole, increase coronary blood flow through the myocardium, and reduce oxygen consumption. The inhibitory effect on atherosclerosis may be due to mechanisms that help mitigate the disease process as well as other factors that reduce arterial wall stress, modify the structure of low-density lipoproteins in a manner that reduces their potential to bind to the arterial wall, and increase the synthesis of prostacyclins.[5] ß-blockers may provide an antiarrhythmic effect by reducing sympathetic activity.

Improvement in LV Ejection Fraction

A considerable number of patients with reduced systolic function due to primary or ischemic cardiomyopathy have viable but noncontractile myocardium. This state may be related to neurohormonal abnormalities, metabolic imbalances, or chronic ischemia (stunning/hibernation).[6]

The viable but noncontractile myocardium maintains, however, a contractile reserve that can be unmasked by inotropic stimulation, such as by the infusion of low-dose dobutamine. The contractility improvement generated by the use of ß-blockade appears to be particularly evident in the areas of myocardium where the contractile reserve is mostly preserved.[7]

To emphasize that the effects of ß-blocking agents on contractility are not directly related to their pharmacologic properties, Hall and colleagues[8] studied the effects of metoprolol in patients with low ejection fraction (EF). The study demonstrated that soon after metoprolol administration, the EF was mildly reduced within 24 hours, and then increased substantially at 3 months. Thus, the delayed improvement in the EF after treatment with ß-blockers appears to be related to a biologic,[9] rather than to their

pharmacologic, effect.

Underuse of ß-Blockers

Despite a strong and growing body of evidence in support of the use of ß-blockers for secondary prevention in the post-MI setting, fewer than half of all post-MI patients are prescribed ß-blockers as long-term therapy.[10] The reluctance of many physicians to prescribe these agents after an acute MI stems from several misconceptions and safety concerns. There seems to be a perceived decline of benefits since the advent of revascularization procedures, antiplatelet agents, ACE inhibitors, and statins. There are concerns regarding safety in patients with advanced age, heart failure, chronic obstructive pulmonary disease (COPD), and diabetes mellitus, and regarding the side effect profile of these agents. In addition, many physicians do not believe that there is a benefit for patients who have had a non–ST-elevation MI.[11] Implementation programs, rather than education, are needed to address many of these misperceptions, so that patients may gain the life-saving benefits these agents provide.[12]

Implementation programs, rather than education, are needed to address many of the misperceptions about ß-blockers, so that patients may gain the life-saving benefits these agents provide.

Use of ß-Blockers in the Acute Setting of MI

Early studies have suggested that ß-blockers should be administered intravenously in the acute post-MI period. The Göteborg Metoprolol Trial was a randomized, double-blinded, placebo-controlled trial of 1395 patients with suspected acute MI with the primary objective to determine whether metoprolol would reduce 3-month mortality. Patients received either intravenous (IV) metoprolol or placebo on entry to hospital. Placebo or oral metoprolol titrated to 100 mg twice daily was continued for 3 months. Exclusion criteria were hypotension, bradycardia, or heart failure. By intention-to-treat analysis, a 36% reduction in mortality at 3 months was observed with metoprolol compared with placebo. Nineteen percent of patients were withdrawn in both groups. In these patients, no differences in mortality were observed between the placebo and metoprolol group. The reinfarction rate was not reported. Metoprolol also resulted in a 15% reduction in enzyme-estimated infarct size among patients treated within 12 hours after onset of pain (69% of all patients).[13]

The Metoprolol in Acute Myocardial Infarction (MIAMI) Study randomized 5778 patients with suspected MI to receive IV metoprolol (three 5-mg doses) or placebo on entry to the coronary care unit. The agents were titrated to 100 mg twice daily and continued for 15 days. Exclusion criteria were current ß-blocker or calcium channel blocker treatment, heart rate <65 beats per minute (bpm), and systolic blood pressure <105 mm Hg. Treatment with metoprolol was associated with a nonsignificant 13% reduction in all-cause mortality at 15 days, the primary end point (4.9% vs 4.3% in placebo and metoprolol group, respectively). The reinfarction rate was not assessed. In retrospect, patients with more than three of the following risk factors—age >60 years, abnormal electrocardiogram, history of MI, hypertension, chronic heart failure, diabetes, use of diuretics or cardiac glycosides (a high-risk group representing 23% of the population)—had a 39% reduction in all-cause mortality.[14]

In the first International Study of Infarct Survival (ISIS-1) trial, 16,027 patients with suspected acute MI were randomized to either the 5–10 mg IV atenolol or a control group immediately on hospital admission, followed by oral dosing of 100 mg daily for 7 days or until the patient was discharged, if earlier. Atenolol reduced vascular mortality by 15% during the treatment period, an effect primarily observed during the first 24 hours. Reinfarction rate was not reduced in the atenolol group (2.5% vs 2.8% in the atenolol and control groups, respectively). The study concluded that one would have to treat 200 consecutive patients with suspected MI to prevent one death, one cardiac arrest, and one reinfarction.[15] When the ISIS-1 data was analyzed together with all prior available data of early IV ß-blockade in acute MI (more than 20,000 patients) there was a 22% reduction in all-cause mortality and a 27% reduction in nonfatal reinfarction at 7 days.[15]

The Thrombolysis in Myocardial Infarction (TIMI) IIB trial treated 3262 patients with suspected MI with IV recombinant tissue plasminogen activator (rt-PA); subjects were further randomized to an aggressive or conservative strategy. Within this study, 1434 eligible patients were randomized to one of two groups: One group received immediate administration of 5 mg IV metoprolol (at 2 minute intervals over a course of six minutes, total dose 15 mg) followed by oral metoprolol 50 mg twice a day, titrated to 100 mg twice daily the day after, if tolerated (720 patients). The

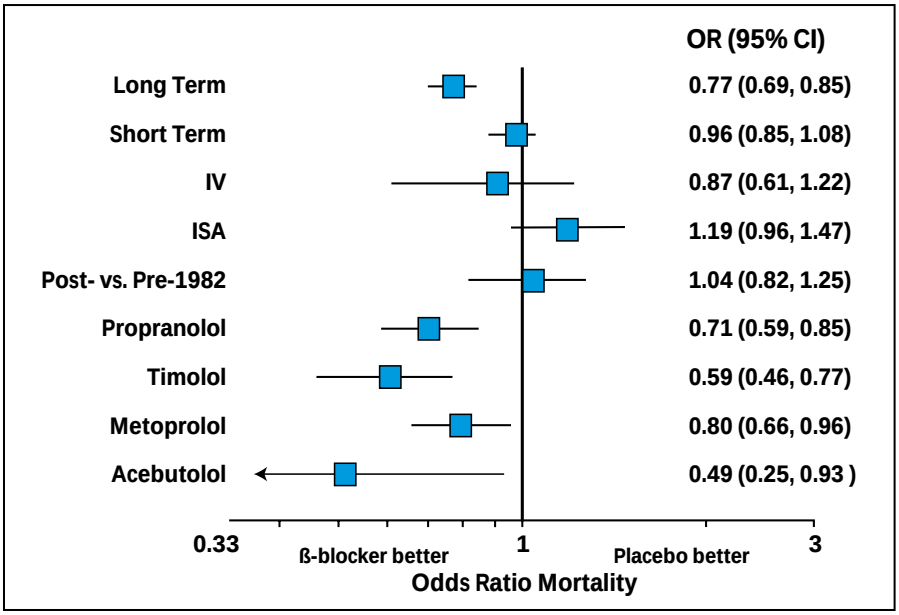

Figure 1. *ß-blockade after myocardial infarction. CI, confidence interval; ISA, intrinsic sympathomimetic activity; OR, odds ratio. Data from Freemantle et al.*[17]

other group was started on oral metoprolol 50 mg twice daily, titrated to 100 mg twice daily, if tolerated, on day 6 after MI (714 patients). The primary end point of this embedded study was assessment of the resting EF at hospital discharge. Secondary end points were EF after 6 weeks, EF after exercise, EF both at hospital discharge and at 6 weeks, mortality, fatal and nonfatal reinfarction, and recurrent ischemia. There were no differences in EF in the immediate versus delayed-treatment groups. Also, there were no differences in mortality between the two groups at either time point. However, by early administration of ß-blockers, the reinfarction rate at 6 days was reduced from 5.1% to 2.7%. A trend in decreased reinfarction rate was noted at 6 weeks: 3.9% in the immediate versus 6.1% in the deferred group. Recurrent ischemia was reduced by early administration of IV metoprolol (18.8%) compared with delayed administration (24.1%) during the first 6 days. Patients treated 2–4 hours after the onset of symptoms experienced the most benefits from the early treatment. The results of this study are still applicable to current treatment strategies.[16]

These results have led to the suggestion that intravenous ß-blockers should be used routinely in patients with suspected acute MI. However, in a meta-analysis of 51 short-term trials (up to 6 weeks) in which patients were randomized to receive a ß-blocker or placebo, administration of ß-blockers in the acute post-MI period was associated with only a slight (4%) reduction in all-cause mortality (Figure 1); nevertheless, the early benefits of IV dosing may consist of an improvement of ischemic symptoms and a decrease in the rate of reinfarction.[17]

These beneficial effects may be more evident in patients who have undergone thrombolysis, because in spite of a reduction in all-cause mortality, the use of thrombolytics is associated with a higher reinfarction rate.[18] The early use of ß-blockers in the TIMI IIB trial was associated with decreased rates of reinfarction and recurrent angina.[16]

In addition, a potential benefit of using ß-blockers in the early phase of treatment is an increase in the long-term utilization rate.[15]

Use of ß-Blockers in the Chronic Post-MI Period

A meta-analysis of 31 randomized trials that enrolled a total of 24,974 patients was designed to evaluate the efficacy of long-term ß-blockade post MI (Figure 1). The analysis revealed that ß-blockers provided a 23% reduction in mortality.[17]

Norwegian Multicenter Study Group (timolol), ß-Blocker Heart Attack Trial (BHAT; propranolol), and Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) are the major ß-blocker trials conducted on chronic post-MI patients (design and baseline data are shown in Table 1).

The Norwegian trial compared the effects of timolol (10 mg twice daily), a nonselective ß-blocker, to placebo. The treatment was started 7 to 28 days after the onset of MI in 1884 patients (945 patients randomized to timolol, 939 to placebo). The follow-up time was 12 to 33 months. In an intention-to-treat analysis, timolol reduced all-cause mortality by 39% at 33 months (17.5% vs 10.6% in the placebo and treatment group, respectively). Timolol decreased the reinfarction rate by 28% at 33 months (20.1% vs 14.4% in the placebo and timolol group, respectively) and the sudden death rate by 44.6% (13.9% in the placebo group vs 7.7% in the timolol group, respectively). The number of patients withdrawn from treatment was higher in the timolol group, especially in the first month of follow-up. The excessive withdrawal in the treatment group was mainly due to bradycardia and hypotension, when compared to

Table 1
Comparison of Major ß-Blocker Trials in the Chronic Post–Myocardial Infarction (MI) Period

	Trial					
	CAPRICORN		BHAT		Norwegian	
	Carvedilol (n=975)	Placebo (n=984)	Propranolol (n=1916)	Placebo (n=1921)	Timolol (n=945)	Placebo (n=939)
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	
Mean no. days after entry from MI (range)	10 (3-21)		13.8 (5-21)		11.5 (7-28)	
Inclusion criteria	Documented MI, Left ventricular ejection fraction < 40% or wall motion score <1.3		Documented MI		Documented MI	
Exclusion criteria	Continued requirement for IV inotropic therapy or uncontrolled heart failure, Blood pressure <90 mm Hg, heart rate <60 bpm, uncontrolled hypertension		Marked brachycardia, History of HF or asthma		Uncontrolled HF, heart rate <50 bpm, 2º or 3º atrioventricular block, blood pressure <100 mg Hg, Unstable diabetes mellitus, COPD, intermittent claudication	
Mean age, y (range)	63 (29-88)	63 (25-90)	54.7 (30-69)	54.9 (30-69)	60.3 (20-75)	61.4 (20-75)
Men/women, %	73/27	74/26	84/16	85/15	80/20	78/22
Mean left ventricular ejection fraction, % (SD)	33 (6.4)	33 (6.4)	NP	NP	NP	NP
Previous MI, %	31	29	14	13	19	19
Previous angina, %	57	54	36	36	38	38
Previous hypertension, %	55	52	41	40	18	22
Previous diabetes mellitus, %	21	23	12	11	N/A	N/A
Revascularization, %	12	11	N/A	N/A	N/A	N/A
Thrombolysis/percutaneous coronary intervention, %	45	47	N/A	N/A	N/A	N/A
ACE inhibitor, %	98	97	N/A	N/A	N/A	N/A
Aspirin, %	86	86	N/A	N/A	N/A	N/A
Anticoagulant, %	63	65	14	15	N/A	N/A
Nitrates, %	73	73	N/A	N/A	N/A	N/A
IV diuretics, %	35	33	N/A	N/A	N/A	N/A

Adapted with permission from Gheorghiade and Goldstein.[11]
ACE, angiotensin-converting enzyme; BHAT, ß-Blocker Heart Attack Trial; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; COPD, chronic obstructive pulmonary disease; HF, heart failure; N/A, not available; NP, not performed; SD, standard deviation.

Table 2
Clinical Outcomes in Major ß-Blocker Trials in the Chronic Post–Myocardial Infarction Period

	Trial											
	CAPRICORN				BHAT				Norwegian			
	Carvedilol, %	Placebo, %	Reduction, %	*P*	Propanolol, %	Placebo, %	Reduction, %	*P*	Timolol, %	Placebo, %	Reduction, %	*P*
All-cause mortality	11.9	15.3	23	0.031	7.2	9.8	26	<0.005	10.6	17.5	39	0.0005
Sudden death	5	7	28	0.098	3.3	4.6	28	<0.05	7.7	13.9	45	0.0001
Nonfatal reinfarction	3	7.5	40	0.014	4.4	5.3	16	NS	14.4	20	28	0.0006
All-cause mortality and reinfarction	14	20	30	0.002	10*	13*	23	<0.01	N/A	N/A	N/A	N/A

*Coronary heart disease mortality and reinfarction.
Adapted with permission from Gheorghiade and Goldstein.[11]
BHAT, ß-Blocker Heart Attack Trial; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; N/A, not available; NP, not performed.

placebo. Treatment with timolol resulted in a significant reduction in overall and cardiac mortality and reinfarction rates in patients with both Q and non–Q wave MI.[19]

The BHAT, a multicenter randomized, double-blinded, placebo-controlled trial, was designed to test whether the administration of propranolol (a nonselective ß-blocker without intrinsic sympathomimetic activity) in post-MI patients would lead to a significant reduction in all-cause mortality over placebo during a 2- to 4-year follow-up period. Secondary end points of the study were cardiovascular mortality, sudden death, and combined end point cardiovascular mortality plus definite nonfatal MI. During a 27-month period, 3837 patients were randomized to propranolol (1916 patients) or placebo (1921 patients). After an average follow-up period of 25 months, propranolol (60 or 80 mg tid) demonstrated a significant reduction in all-cause mortality (26%), sudden death (23%), and cardiovascular mortality plus nonfatal MI (23%), without affecting the reinfarction rate, when compared with placebo. Because of the positive mortality results, the trial was stopped 9 months ahead of schedule. Study medication was withdrawn in more patients in the propranolol group (12.7% vs 9.7%, compared with placebo), largely because of hypotension, reduced sexual activity, and gastrointestinal problems.[20]

Almost 20 years later, the CAPRICORN trial enrolled 1959 patients with a proven acute MI and LV systolic dysfunction (EF ≤ 40%), with or without symptoms of heart failure. This trial was designed to examine the effects of adding carvedilol (a nonselective ß-blocker with α-blocking capability) to standard therapy that included antiplatelets (85%), ACE inhibitors (98%), statins (27%), and reperfusion therapy (46%). Patients were randomly assigned 6.25 mg carvedilol (975 patients) or placebo (984 patients). Study medication was progressively increased to a maximum of 25 mg twice daily during the next 4–6 weeks. Patients were followed up for a mean of 1.3 years. Carvedilol showed a 23% relative risk reduction in the co-primary end point of all-cause mortality, a benefit similar to that found in the previous trials. Carvedilol also led to a reduction in cardiovascular mortality and nonfatal reinfarction.[21]

As shown in Table 2, all three trials demonstrated that ß-blocker therapy provides significant reduction in all-cause mortality, sudden death and/or nonfatal reinfarction.[11] However, BHAT, the Norwegian trial, and other early studies that established the efficacy of ß-blockers in reducing major coronary events and improving outcomes after acute MI were conducted before the introduction of thrombolysis or primary percutaneous intervention for reperfusion and before ACE inhibitors became standard as post-MI maintenance

therapy. CAPRICORN is the only long-term trial that demonstrated an additional therapeutic benefit of ß-blocker treatment to standard, modern management (eg, reperfusion therapy, aspirin, and ACE inhibitors) in post-MI patients with LV systolic dysfunction.[21] The public health implications of this finding are dramatic, as the number of patients needed to treat with carvedilol in the studied population (43) compares favorably with other life-saving medications recently studied in cardiovascular disease (Table 3).

The importance of ß-blockers post MI when other life-saving therapies are being used was highlighted in the recent Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS) trial. The reduction in all-cause mortality with eplerenone, an aldosterone-blocking agent, was particularly evident in patients receiving ß-blockade.[22]

Table 3
Numbers Needed to Treat Based on Results from Recent Trials

Trial (Drug)	Number Needed to Treat for 1 Year to Save One Life
HOPE (ramipril)[49]	221
4S (simvastatin)[50]	159
SAVE (captopril)[51]	86
CAPRICORN (carvedilol)[21]	43
MERIT-HF (metoprolol succinate)[52]	26
COPERNICUS (carvedilol)[53]	14

4S, Scandinavian Simvastatin Survival Study; HOPE, Heart Outcomes Prevention Evaluation; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; MERIT-HF, Metoprolol Controlled-Release Randomized Intervention Trial in Heart Failure.

Precautions for Chronic Use of ß-Blockers in the Post–MI Patient

ß-blockers have been considered relatively contraindicated in post-MI patients with specific associated comorbidities, such as heart failure, COPD, and diabetes, and/or in advanced age. However, the available data show that ß-blockers, when added to standard therapies for MI, produce benefits that outweigh the risks.

To determine which patients are most likely to benefit from the use of ß-blockers in the post-MI setting, the National Cooperative Cardiovascular Project examined the medical records of 201,752 patients for 2 years following MI. Only 34% of these patients received a ß-blocker post MI. High-risk patients (African Americans, advanced age, low EF, HF, COPD, elevated serum creatinine concentration, or type I diabetes) were less likely to be treated with ß-blockers. Nonetheless, mortality rates were reduced in every subgroup of patients treated with ß-blockers compared to untreated patients. In patients with uncomplicated MI, non–Q wave infarction, and COPD, ß-blocker treatment was associated with a 40% reduction in mortality. A lower-percentage reduction in mortality was observed in African Americans, patients ≥80 years of age, and diabetics; however, these patients present higher mortality rates than other subgroups, so the absolute reduction in mortality was similar to or greater than that found in patients with no other risk factors.[23] A treatment algorithm for the administration of ß-blockers in the post-MI period is shown in Figure 2.

CAPRICORN is the only long-term trial that demonstrated an additional therapeutic benefit of ß-blocker treatment to standard, modern management (eg, reperfusion therapy, aspirin, and ACE inhibitors) in post-MI patients with LV dysfunction.

ß-Blockers in the Elderly

The National Cooperative Cardiovascular Project also assessed the relationship between ß-blockers and mortality in 115,015 patients 65 years of age or older. Among the patients without contraindications to ß-blockers, only 50% who survived an acute MI actually received ß-blockers as a discharge medication. However, 1 year after discharge from hospital, the elderly patients who had been prescribed ß-blockers had a 14% lower risk of mortality compared with those not on ß-blocker therapy.[10] An observational study of 58,165 patients aged 65 years or older revealed that ß-blockers were not prescribed for 51% of elderly patients who were hospitalized with an acute MI and had no contraindications to this therapy.[24] The Cooperative Cardiovascular Project reported that patients ≥80 years of age had a 32% reduction in mortality when given ß-blocker therapy following an MI.[23]

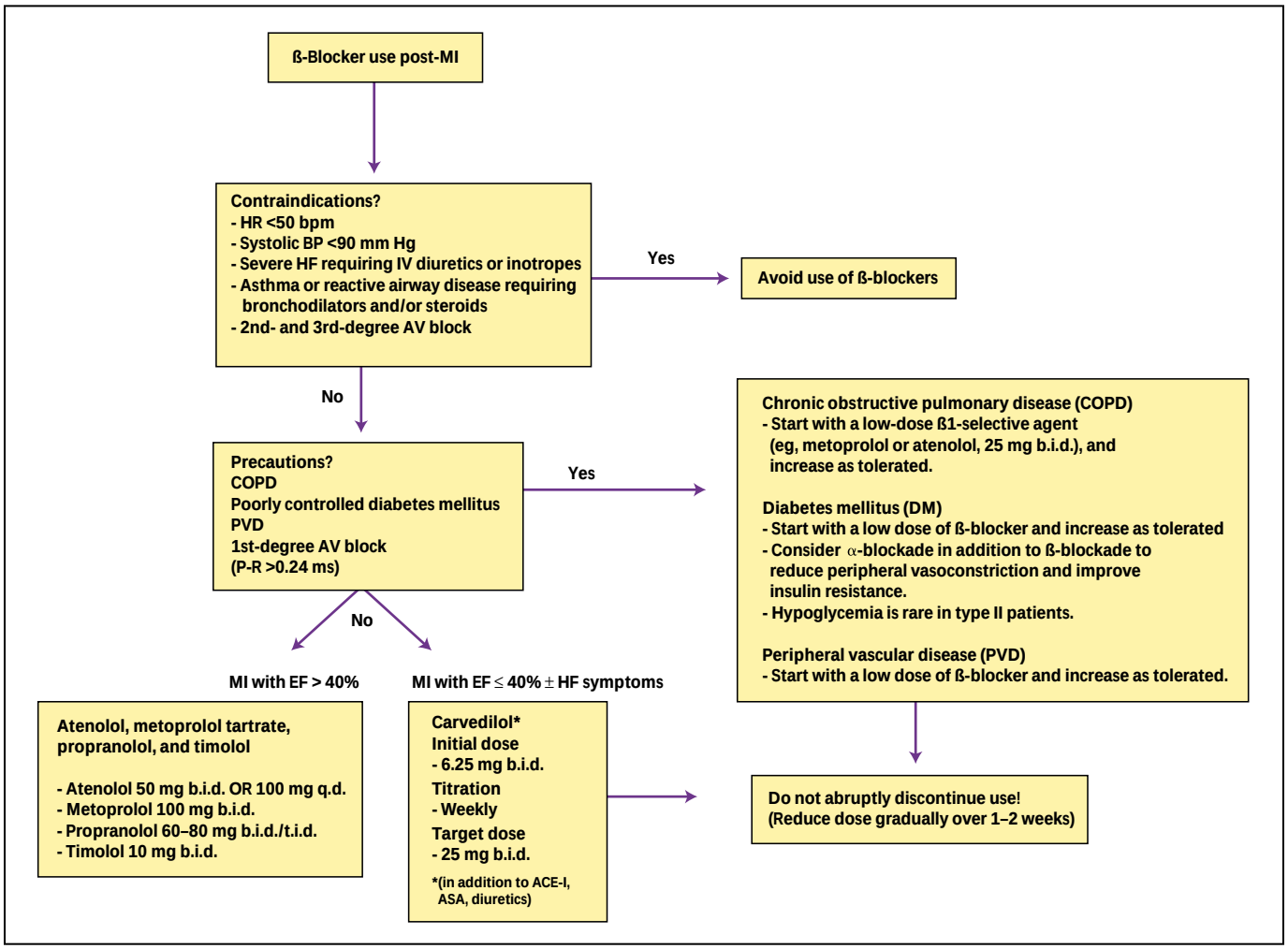

Figure 2. *Suggested algorithm for the use of ß-blockers in the chronic post–myocardial infarction period. ACE-I, angiotensin-converting enzyme inhibitor; ASA, aspirin; AV, atrioventricular; BP, blood pressure; bpm, beats per minute; EF, ejection fraction; HF, heart failure; HR, heart rate; MI, myocardial infarction; P-R, P-R interval. Adapted with permission from Gheorghiade and Goldstein.*[11]

ß-Blockers in Patients with Heart Failure

ß-blockers have been considered contraindicated in patients with heart failure because of the initial transient negative inotropic effects of these agents.[25] Several clinical trials conclusively demonstrated reductions in mortality in mild, moderate, and severe heart failure.[26] Although BHAT excluded patients with heart failure at randomization, a subset analysis of patients with a history of heart failure prior to randomization revealed that propranolol reduced total mortality by 27% compared with 25% in patients without a history of heart failure and the incidence of sudden death by 47% compared with 13% in those without a history of heart failure.[25] In the CAPRICORN trial, about 50% of patients had symptomatic LV systolic dysfunction; the derived mortality benefits were similar with or without symptoms of heart failure.[21] Abrupt discontinuation of ß-blocker therapy in heart failure patients should be avoided because it may be associated with rebound effects resulting in increased morbidity and mortality. In patients presenting with worsening heart failure while taking ß-blockers, the first consideration should be to achieve compensation by adjusting other medications, including diuretics, digoxin, and ACE inhibitors, before decreasing the dose of or discontinuing the ß-blocker.[26]

ß-Blockers in Patients with COPD

COPD is not a contraindication to ß-blocker therapy unless significant

reactive airway disease is present.[10] The Cooperative Cardiovascular Project found that patients with COPD who received ß-blockers post MI experienced a 40% reduction in mortality.[23] Some evidence indicates that even patients who are prescribed ß-agonists may benefit from ß-blocker therapy.[27] If ß-blockers are considered essential treatment for a patient post MI with reactive airway disease, initiating a cardioselective agent, such as metoprolol or atenolol, at the lowest possible dosage may represent the safest choice.[28]

ß-Blockers in Patients with Diabetes or Dyslipidemia

The use of ß-blockers in patients with diabetes has been questioned because these agents may mask hypoglycemic symptoms and may interfere with insulin release. Nevertheless, patients with diabetes who were prescribed ß-blockers had significantly lower mortality rates at 1 year than those not receiving ß-blockers, regardless of the type and severity of diabetes.[23,29–31] Some ß-blockers have been shown to reduce high-density lipoprotein (HDL) and increase serum triglyceride levels.[32] Despite the changes in plasma lipids, ß-blockers exert marked antiischemic properties by decreasing myocardial oxygen requirements and have been shown to result in a 30% reduction in mortality following a myocardial infarction.[33] In a recent study, the administration of low-dose metoprolol CR/XL (25 mg once daily), alone or in combination with fluvastatin (40 mg once daily) significantly reduced the progression of carotid artery intima-media thickness over 36 months of treatment.[34] Carvedilol was shown to exert neutral or positive effects on lipid profiles[35,36] and insulin sensitivity.[35,37] Favorable effects on increasing insulin sensitivity have been observed in other vasodilating ß-blockers, such as celiprolol,[38] suggesting that the addition of α1-blockade confers some metabolic effects, not observed with ß1-selective or ß-nonselective agents, that may be particularly beneficial in patients with insulin resistance or dyslipidemia.

ß-Blockers in African Americans with Heart Failure

The effects of bucindolol were investigated in the ß-Blocker Evaluation of Survival Trial. The results of this study have suggested that African American patients with heart failure may not respond as well to treatment with ß-blockers.[39] In the Cooperative Cardiovascular Project, however, the relative risk of death was reduced by 40% in African American patients who were prescribed ß-blockers when discharged from hospital.[23] In the U.S. Carvedilol Heart Failure Trials Program, carvedilol reduced the all-cause mortality and the all-cause hospitalization by 48% and lowered the risk of progression of heart failure by 54%, in African American patients.[40]

ß-Blockers in Patients with Peripheral Vascular Disease

It is not uncommon for patients receiving ß-blocker therapy to experience side effects such as cold extremities, even in the absence of hypertension or peripheral arterial disease. In patients with peripheral vascular disease, ß-blockers are not generally contraindicated. These agents should be administered with caution when disease is severe, but in less severe forms of occlusive disease, ß-blockers are well tolerated and may even improve flow to the diseased area.[40,41] Carvedilol, with its vasodilating properties, has shown improvement in both peripheral hemodynamics and hemorheologic parameters such as erythrocyte aggregation and plasma viscosity, suggesting possible benefit in this population.[42,43]

ß-Blockers in Patients with Non–ST-Elevation MI

The effect of ß-blocker therapy on the cardiac event rate in patients recovering from a non–Q wave MI was questioned in a post hoc analysis of the BHAT, which showed that propranolol provided no benefit in reducing the cardiac event rate in this subgroup of patients.[44] However, analysis of the Cooperative Cardiovascular Project data revealed that ß-blocker therapy reduced mortality rates in patients with non–ST-elevation MI by 9.5%.[23] Similar data were obtained in the Norwegian trial, showing that timolol was also effective in reducing the mortality in patients with non–Q wave MI.[45] Although improvement in survival rates is not as strong in patients with non–ST-elevation MI, current evidence suggests that ß-blockers should be used in these patients as well as in patients with an ST-elevation MI.[10] Patients with non–ST-elevation MI may be at higher risk for reinfarction in the infarct-related artery compared with patients with an ST-elevation MI.[46]

Side Effects of ß-Blockers

Many physicians are reluctant to prescribe ß-blockers because of the anticipated side effects of these agents (eg, fatigue, decreased heart rate, hypotension, diminished libido). However, in the BHAT, 43.2% of patients in the propranolol group reported reduced sexual activity compared with 42% of those in the placebo group, and this difference was not statistically significant. Fatigue was reported by 66.8% of patients in the propranolol group compared with 62.1% in the place-

bo group. Propranolol treatment had to be discontinued in only 0.7% of patients because of sinus bradycardia, 1.2% of patients because of hypotension, 1.5% of patients because of fatigue, 0.4% of patients because of depression, and 0.2% of patients because of reduced sexual activity.[47]

Conclusion

The life-saving benefits of ß-blocker therapy in the chronic post-MI setting are supported by a convincing body of evidence. Based on this evidence, the American Medical Association and five other medical organizations recently issued a Quality Care Alert: "ß-Blocker Prophylaxis After Acute Myocardial Infarction." This alert notes that the benefits of ß-blockers in reducing mortality and reinfarction may outweigh their risks, even in patients with asthma, diabetes mellitus, COPD, a P-R interval >0.24 seconds, or moderate to severe LV failure.[48] ß-blockers should not be withdrawn abruptly in post-MI patients, particularly if they have LV systolic dysfunction.

Overall, the available evidence supports the administration of ß-blockers to all post-MI patients who do not have a contraindication to these agents, and treatment should be continued indefinitely, as specified in the revised 2001 Consensus Statement on secondary prevention for patients with coronary and other vascular disease.[4] ■

References

1. American Heart Association. *Heart Disease and Stroke Statistics—2003 Update*. Dallas, TX: American Heart Association; 2002. Available at http://www.americanheart.org.
2. Kober L, Torp-Pedersen C, Jorgensen S, et al. Changes in absolute and relative importance in the prognostic value of left ventricular systolic function and congestive heart failure after acute myocardial infarction. TRACE Study Group. Trandolapril Cardiac Evaluation. *Am J Cardiol*. 1998;81:1292–1297.
3. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959–969.
4. Smith SC Jr, Blair SN, Bonow RO, et al. AHA/ACC Scientific Statement: AHA/ACC

Main Points

- In the revised 2001 Consensus Statement on secondary prevention for patients with coronary and other vascular disease, the American Heart Association and the American College of Cardiology noted that aggressive risk factor management clearly improves patient survival, reduces recurrent events and the subsequent need for interventional procedures, and improves patient quality of life. These updated guidelines recommend the initiation of ß-blocker therapy in all post–myocardial infarction (MI) patients without contraindication and the continuation of this therapy indefinitely.
- Despite a strong and growing body of evidence in support of the use of ß-blockers for secondary prevention in the post-MI setting, fewer than half of all post-MI patients are prescribed ß-blockers as long-term therapy.
- Early studies have suggested that ß-blockers should be administered intravenously early in the acute post-MI period.
- A meta-analysis of 31 randomized trials was designed to evaluate the efficacy of long-term ß-blockade post MI. The analysis revealed that ß-blockers provided a 23% reduction in mortality. These findings suggest that ß-blockers are effective in long-term secondary prevention post MI.
- BHAT, the Norwegian trial, and other early studies that established the efficacy of ß-blockers in reducing major coronary events and improving outcomes after acute MI were conducted before the introduction of thrombolysis or primary angioplasty for reperfusion and before angiotensin-converting enzyme (ACE) inhibitors became standard as post-MI maintenance therapy. CAPRICORN is the only long-term trial that demonstrated an additional therapeutic benefit of ß-blocker treatment to standard, modern management (eg, reperfusion therapy, aspirin, and ACE inhibitors) in post-MI patients with left ventricular (LV) dysfunction.
- ß-blockers have been considered absolutely or relatively contraindicated in post-MI patients with specific associated comorbidities, such as heart failure, chronic obstructive pulmonary disease (COPD), and diabetes, and/or in advanced age. However, decisive evidence shows that ß-blockers, when added to standard therapies for MI (eg, aspirin, ACE inhibitors, statins), produce benefits that outweigh the risks.
- The life-saving benefits of ß-blocker therapy in the chronic post-MI setting are supported by a convincing body of evidence. Based on this evidence, the American Medical Association and five other medical organizations recently issued a Quality Care Alert: "ß-Blocker Prophylaxis After Acute Myocardial Infarction." This alert notes that the benefits of ß-blockers in reducing mortality and reinfarction may outweigh their risks, even in patients with asthma, diabetes mellitus, COPD, a P-R interval >0.24 seconds, or moderate to severe LV failure.[48]

guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation*. 2001;104:1577–1579.
5. Tse WY, Kendall M. Is there a role for beta-blockers in hypertensive diabetic patients? *Diabet Med*. 1994;11:137–144.
6. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation of coronary artery disease. *Circulation*. 1998; 97:282–289.
7. Shah DJ, Diluzio S, Bello D, et al. Dobutamine echocardiography for predicting functional recovery of myocardium in heart failure patients treated with beta blocker therapy. *Circulation*. 2001;104(Suppl II):A518.
8. Hall SA, Cigarroa CG, Marcoux L, et al. Time course of improvement in left ventricular function, mass, and geometry in patients with congestive heart failure treated with ß-adrenergic blockade. *J Am Coll Cardiol*. 1995; 25:1154–1161.
9. Bristow MR, Gilbert EM. Improvement in cardiac myocyte function by biological effects of medical therapy: a new concept in the treatment of heart failure. *Eur Heart J*. 1995;16(Suppl F):20–31.
10. Krumholz HM, Radford MJ, Wang Y, et al. National use and effectiveness of beta-blockers for the treatment of elderly patients after acute myocardial infarction: National Cooperative Cardiovascular Project. *JAMA*. 1998;280:623–629.
11. Gheorghiade M, Goldstein S. Beta-blockers in the post-myocardial infarction patient. *Circulation*. 2002;106:394–398.
12. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med*. 2000;160:459–467.
13. Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomized trial. *Lancet*. 1981;2:823–827.
14. MIAMI Trial Research Group. Metoprolol in acute myocardial infarction (MIAMI). A randomized placebo-controlled international trial. The MIAMI Trial Research Group. *Eur Heart J*. 1985;6:199–226.
15. ISIS-1 Collaborative Group. Randomized trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. *Lancet*. 1986;2:57–66.
16. Roberts R, Rogers WJ, Mueller HS, et al. Immediate versus deferred beta-blockade following thrombolytic therapy in patients with acute myocardial infarction. *Circulation*. 1991;83:422–437.
17. Freemantle N, Cleland J, Young P, et al. Beta-blockade after myocardial infarction: systematic review and meta-regression analysis. *BMJ*. 1999;318:1730–1737.
18. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. *Lancet*. 1987;2:871–874.
19. Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med*. 1981;304:801–807.
20. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA*. 1982;247:1707–1714.
21. CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomized trial. *Lancet*. 2001;357:1385–1390.
22. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med*. 2003;348:1309–1321.
23. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med*. 1998;339:489–497.
24. Krumholz HM, Radford MJ, Wang Y, et al. Early beta-blocker therapy for acute myocardial infarction in elderly patients. *Ann Intern Med*. 1999;131:648–654.
25. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation*. 1986;73:503–510.
26. Gheorghiade M, Colucci WS, Swedberg K. ß-Blockers in chronic heart failure. *Circulation*. 2003;107:1570–1575.
27. Chen J, Radford MJ, Wang Y, et al. Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol*. 2001;37:1950–1956.
28. Tafreshi MJ, Weinacker AB. Beta-adrenergic-blocking agents in bronchospastic diseases: a therapeutic dilemma. *Pharmacotherapy*. 1999;19:974–978.
29. Chen J, Marciniak TA, Radford MJ, et al. Beta-blocker therapy for secondary prevention of myocardial infarction in elderly diabetic patients. Results from the National Cooperative Cardiovascular Project. *J Am Coll Cardiol*. 1999;34:1388–1394.
30. Kjekshus J, Gilpin E, Cali G, et al. Diabetic patients and beta-blockers after acute myocardial infarction. *Eur Heart J*. 1990;11:43–50.
31. Malmberg K, Ryden L, Hamsten A, et al. Mortality prediction in diabetic patients with myocardial infarction: experiences from the DIGAMI study. *Cardiovasc Res*. 1997;34:248–253.
32. Byington RP, Worthy J, Craven T, Furberg CD. Propranolol-induced lipid changes and their prognostic significance after a myocardial infarction: the Beta-Blocker Heart Attack Trial experience. *Am J Cardiol*. 1990;65:1287–1291.
33. Cruickshank JM. Beta-blockers, plasma lipids, and coronary heart disease. *Circulation*. 1990;82(Suppl 3):II60–II65.
34. Hedblad B, Wikstrand J, Janzon L, et al. Low-dose metoprolol CR/XL and fluvastatin slow progression of carotid intima-media thickness: main results from the Beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study (BCAPS). *Circulation*. 2001;103:1721–1726.
35. Giugliano D, Acampora R, Marfella R, et al. Metabolic and cardiovascular effects of carvedilol and atenolol in non–insulin-dependent diabetes mellitus and hypertension. A randomized, controlled trial. *Ann Intern Med*. 1997;126:955–959.
36. Hauf-Zachariou U, Widmann L, Zulsdorf B, et al. A double-blind comparison of the effects of carvedilol and captopril on serum lipid concentrations in patients with mild to moderate essential hypertension and dyslipidemia. *Eur J Clin Pharmacol*. 1993;45:95–100.
37. Jacob S, Rett K, Wicklmayr M, et al. Differential effect of chronic treatment with two beta-blocking agents on insulin sensitivity: the carvedilol-metoprolol study. *J Hypertens*. 1996;14:489–494.
38. Jacob S, Balletshofer B, Henriksen EJ, et al. Beta-blocking agents in patients with insulin resistance: effects of vasodilating beta-blockers. *Blood Press*. 1999;8:261–268.
39. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344:1659–1667.
40. Yancy CW, Fowler MB, Colucci WS, et al. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N Engl J Med*. 2001;344:1358–1365.
41. Heintzen MP, Strauer BE. Peripheral vascular effects of beta-blockers. *Eur Heart J*. 1994;15:2–7.
42. Nagakawa Y, Akedo Y, Kaku S, Orimo H. Effects of carvedilol on common carotid arterial flow, peripheral hemodynamics, and hemorheologic variables in hypertension. *Eur J Clin Pharmacol*. 1990;38(Suppl 2):S115–S119.
43. Bauriedel G, Skowasch D, Hofling B. [Carvedilol as vasodilating beta-blocker for the treatment of hypertensive patients with peripheral vascular disease-a pilot study]. *Herz/Kreisl*. 2000;32:69–73.
44. Gheorghiade M, Schultz L, Tilley B, et al. Effects of propranolol in non-Q wave acute myocardial infarction in the beta-blocker heart attack trial. *Am J Cardiol*. 1990;66:129–133.
45. Pedersen TR for the Norwegian Study Group. The Norwegian multicenter study of timolol after myocardial infarction. *Circulation*. 1983;67(Suppl I):I49–I53.
46. Gibson RS, Beller GA, Gheorghiade M, et al. The prevalence and clinical significance of residual myocardial ischemia 2 weeks after uncomplicated non-Q wave infarction: a prospective natural history study. *Circulation*. 1986;73:1186–1198.
47. Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. II. Morbidity results. *JAMA*. 1983;250:2814–2819.
48. American Medical Association. Beta-blocker prophylaxis after acute myocardial infarction. Quality care alert. Available at www.ama-assn.org. Accessed June 24, 2003.

49. Otterstad JE, Sleight P. The HOPE study: comparison with other trials of secondary prevention. *Eur Heart J.* 2001;22:1307–1310.
50. Otterstad JE, Ford I. The effect of carvedilol in patients with impaired left ventricular systolic function following an acute myocardial infarction. How do the treatment effects on total mortality and recurrent myocardial infarction in CAPRICORN compare with previous beta-blocker trials? *Eur J Heart Fail.* 2002;4:501–506.
51. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med.* 1992;327:669–677.
52. Merit-HF Investigators Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet.* 1999;353:2001–2007.
53. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart