Role of ß-Blocker Therapy in the Post-Myocardial Infarction Patient With and Without Left Ventricular Dysfunction

The Post-Myocardial Infarction Guideline Committee

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Patients with acute myocardial infarction are at early and long-term risk for recurrent infarction, heart failure, arrhythmias, and mortality. ß-blockers have been demonstrated to reduce morbidity and mortality in the initial hours and days of evolving infarction and the weeks, months, and years after myocardial infarction. Guidelines from the American Heart Association and American College of Cardiology recommend the use of ß-blockers in patients early and long-term after myocardial infarction in the absence of contraindications.[1,2]

Despite clinical trial evidence and national guidelines supporting the long-term use of ß-blockers in patients after myocardial infarction, less than half of myocardial infarction patients are prescribed ß-blockers in the outpatient setting. Patients with left ventricular dysfunction with or without heart failure symptoms are even less likely to be treated. Physician reluctance to use ß-blockers after acute myocardial infarction may involve physician concerns regarding the safety and benefits of ß-blockers in post-myocardial infarction patients with left ventricular dysfunction with or without heart failure symptoms. Misunderstandings may persist regarding the safety and benefits in patients with diabetes, chronic obstructive pulmonary disease, and older age. Other issues may also include a perception of diminished benefits in the setting of reperfusion/revascularization, ACE inhibitors, and statins.[3-8]

A recent clinical trial demonstrates the significant mortality reduction with ß-blocker therapy in post-myocardial infarction patients with left ventricular dysfunction compared to the benefits of contemporary myocardial infarction care, including reperfusion therapy, antiplatelet therapy, ACE inhibitors, and lipid-lowering therapy. A substantial number of post-myocardial infarction patients, especially those with left ventricular dysfunction, remain untreated with ß-blockers; there is an important opportunity to improve the use of this evidence-based therapy. This document provides guidance regarding the initiation and long-term use of ß-blocker therapy for post-myocardial infarction patients.

ß-Blocker Therapy in Acute Myocardial Infarction: Initial Hours

ß-blocker therapy is recommended to reduce morbidity and mortality during the initial hours of acute myocardial infarction. During the first few hours of infarction, ß-blocker agents may diminish myocardial oxygen demand by reducing heart rate, systemic arterial pressure, and myocardial contractility. In addition, ß-blockers have cardioprotective effects that appear to limit damage to the injured/reperfused myocardium. As a result, immediate ß-blocker therapy reduces the magnitude of myocardial infarction and incidence of associated complications in subjects not receiving concomitant reperfusion therapy and the rate of reinfarction in patients receiving thrombolytic therapy.[1,2]

In subjects not receiving thrombolytic therapy, intravenously administered ß-blocker therapy exerts a modest effect on decreasing short-term mortality. In the First

International Study of Infarct Survival in which more than 16,000 patients with suspected acute myocardial infarction were enrolled within 12 hours of onset of symptoms, immediate intravenous atenolol, 5 to 10 mg, followed by oral atenolol, 100 mg daily, reduced 7-day mortality from 4.3% to 3.7% ($P < .02$; 6 lives saved per 1000 treated). The mortality difference between those receiving and not receiving atenolol was evident by the end of day one. In subjects receiving concomitant thrombolytic therapy, intravenously administered ß-blocker drugs diminished the incidence of subsequent nonfatal reinfarction and recurrent ischemia. In the Thrombin Inhibition in Myocardial Infarction II trial in which all patients received intravenous alteplase, those randomly assigned to receive intravenous metoprolol, 15 mg, followed by oral metoprolol, 50 mg twice a day for 1 day and then 100 mg twice a day thereafter, had a diminished incidence of subsequent nonfatal reinfarction and recurrent ischemia when compared with those begun on oral metoprolol 6 days after the acute event.[9-11]

The AHA/ACC guidelines for acute myocardial infarction give a Class I recommendation to the early use of ß-blockers in acute myocardial infarction patients without contraindications who can be treated within 12 hours of onset of infarction, irrespective of administration of concomitant thrombolytic therapy or performance of primary angioplasty and including non-ST segment elevation myocardial infarction. The presence of moderate or severe left ventricular failure early in the course of acute myocardial infarction should preclude the use of early intravenous ß-blocker therapy but is a strong indication for the oral use of ß-blockade before discharge.[1,2]

ß-Blocker Therapy in Acute Myocardial Infarction: Days to Long-Term

Multiple placebo-controlled clinical trials, involving a total of more than 35,000 survivors of acute myocardial infarction not receiving thrombolytic therapy, have shown that chronic ß-blocker therapy reduces mortality. In the ß-Blocker Heart Attack Trial (BHAT) which enrolled 3837 post-MI patients for 27 months, propranolol significantly reduced overall mortality by 26% compared with placebo. In the Norwegian trial of timolol conducted in the late 1970s in survivors of infarction, mortality was reduced from 9.8% in those given placebo to 7.2% in those receiving timolol, 10 mg twice daily, over a follow-up of 25 months. In addition, meta-analysis of 31 long-term ß-blocker studies with follow-up lasting 1 to 4 years found significant benefits in reducing mortality and morbidity in post-myocardial infarction patients.[12,13]

The long-term benefits of ß-blocker therapy have been shown to be greatest in high-risk patients, those with evidence of large or anterior infarction. There has been debate about whether low-risk subjects (i.e., those without the following: previous infarction, anterior infarction, advanced age, complex ventricular ectopy, or evidence of left ventricular systolic dysfunction) should be treated with ß-blockers because their long-term prognosis is extremely favorable irrespective of such therapy. There has also been debate as to whether long-term ß-blocker therapy should be administered to survivors of acute myocardial infarction who subsequently have successfully undergone revascularization.[u]

While the AHA/ACC acute myocardial infarction guidelines gave a Class I indication for all but low-risk acute myocardial infarction patients without contraindications, patients at low risk were considered a Class IIa indication. However, patients with moderate or severe left ventricular failure were given only a Class IIb indication.[1,2] This latter recommendation, made in 1996, is currently being revised, since many trials have since shown benefit of ß-blockade in patients with left ventricular dysfunction.

ß-Blocker Therapy in Acute Myocardial Infarction Patient with Left Ventricular Dysfunction: Days to Long-Term

Although the results of ß-blocker studies represented a major advance in post-myocardial infarction management, they did not include patients with heart failure. Thus, substantial concerns existed regarding the risk and benefits of ß-blocker therapy in post myocardial infarction patients with left ventricular dysfunction, with or without heart failure symptoms. In addition, since most of the ß-blocker trials occurred before the demonstration of benefit of reperfusion therapy, ACE inhibitors, and lipid-lowering therapy, many questioned whether the benefits of ß-blockers would be diminished or eliminated in the presence of these therapies.

The Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) trial evaluated the effects of adding carvedilol (a nonselective ß-blocker with alpha-1 blocking) to standard therapy in patients with acute myocardial infarction and left ventricular systolic dysfunction (ejection fraction < 0.40), with or without heart failure symptoms. Almost all patients in CAPRICORN were given ACE inhibitors, > 85% were on aspirin, and 45% received reperfusion therapy. In this study, all-cause mortality was significantly reduced by carvedilol. In addition there was a reduction in non-fatal myocardial infarction, atrial fibrillation, and ventricular arrhythmias. This study thus demonstrates there are long-term benefits of carvedilol therapy in patients with left ventricular

dysfunction with or without heart failure symptoms that is additive to other cardiovascular protective therapies.[14]

Choice of Therapy

Acute Therapy

For intravenous ß-blocker therapy, propranolol, metoprolol, and atenolol have each been shown to be efficacious. There have been no head-to-head comparisons with regard to outcomes.[15-20]

Intermediate and Long-Term Therapy: Absence of Left Ventricular Dysfunction

For intermediate and long-term oral ß-blocker therapy, propranolol and timolol have each been shown to be efficacious. There have been no head-to- head comparisons with regard to outcomes.[15,20]

Intermediate and Long-Term Therapy: Presence of Left Ventricular Dysfunction

For intermediate and long-term oral ß-blocker therapy, only carvedilol has been shown to be efficacious. In chronic heart failure clinical trials, bisoprolol, metoprolol CR/XL, and carvedilol were shown to improve survival. In the Carvedilol or Metoprolol European Trial (COMET) in patients with mild, moderate, or severe chronic heart failure, carvedilol was shown to be superior to the ß-1 selective ß-blocker metoprolol.[20] COMET enrolled 3029 patients with LVEF < 0.35 and chronic heart failure. Patients were randomized to carvedilol (target dose 25 mg twice daily) or metoprolol tartrate (target dose 50 mg twice daily). The average daily dose of carvedilol received in the trial was 42 mg and the average daily dose of metoprolol was 85 mg. There were similar reductions in resting heart rates and blood pressure compared to baseline over the duration of the trial, except for very mild differences in the first few months. The co-primary endpoint of the trial, all cause mortality, showed a 17% relative risk reduction with carvedilol relative to metoprolol. Mortality was reduced from 39.5% with metoprolol to 33.9% with carvedilol (HR 0.83, 95% CI 0.74-0.93, $P < 0.0017$). The survival advantage with carvedilol translated to a prolongation of median survival by an extra 1.4 years of life.[21-23]

Patient Selection Criteria[1,2]

Indications

All patients with acute myocardial infarction, in the absence of absolute contraindications, should be treated with ß-blocker therapy indefinitely.

Benefits extend to patients with left ventricular dysfunction with or without heart failure symptoms. The benefits are additive to reperfusion/revascularization, antiplatelet, ACE inhibitor, and statin therapy.

Contraindications

The following are absolute contraindications to ß-blocker therapy.

- Symptomatic bradycardia
- Systolic arterial pressure < 80 mm Hg
- Signs of peripheral hypoperfusion and/or cardiogenic shock
- Second- or third-degree AV block, without pacemaker
- Severe reactive airway disease

Indicated with Precautions

A number of co-morbidities have been referred to as "relative contraindications" to ß-blocker therapy in the post-myocardial infarction patients. However, patients with acute myocardial infarction with these comorbidities have been shown to derive major benefits from ß-blocker therapy. Thus patients with these conditions should be treated with ß-blockers, unless absolute contraindications develop.

- Asymptomatic bradycardia, heart rate 50-60 bpm
- First degree atrio-ventricular block
- Diabetes mellitus
- Peripheral vascular disease
- Mild or moderate chronic obstructive pulmonary disease
- Mild, moderate, or severe heart failure

Side Effects

Although adverse effects of ß-blockers, such as fatigue, depression, sexual dysfunction, nightmares, and difficulty with recognition of hypoglycemia in diabetics are known to occur, the frequency and severity of these effects are sufficiently low to warrant their use even in low-risk patients.

Dosage/Administration[1,2,11,13]

Initiation

For acute myocardial infarction patients without left ventricular dysfunction or heart failure, recommended starting doses are timolol 5 mg twice daily or propranolol 20 mg four times daily. The recommended initiation dose for patients with left ventricular dysfunction (LVEF < 0.40) with or without heart failure symptoms is carvedilol 6.25 mg PO twice daily.

Titration

In patients without left ventricular dysfunction or heart failure, the dose can be advanced rapidly to achieve target dose. In the setting of left ventricular dysfunction with or without heart failure symptoms, the dose of ß-blocker

Table 1
Recommended Doses in the Absence of Left Ventricular Dysfunction

Agent	Initiation Dose	Target Dose
Timolol	5 mg bid	10 mg bid
Propanolol	20 mg qid	60 mg qid
Atenolol*	50 mg qd	100 mg qd
Metoprolol*	50 mg bid	100 mg bid
Carvedilol*	12.5 mg bid	25 mg bid

*No large scale positive randomized clinical trials with these agents in this patient population. Agents and doses shown for reference purposes.

Table 2
Recommended Doses with the Presence of Left Ventricular Dysfunction

Agent	Initiation Dose	Titration Steps	Target Dose
Carvedilol	6.25 mg bid	12.5 mg bid	25 mg bid

therapy is generally increased at two-week intervals until the target dose is achieved. In patients with mild heart failure who are hypertensive, the titration steps may occur more rapidly. In patients who cannot achieve target doses of the ß-blocker, the highest dose tolerated should be maintained.

For post-myocardial infarction patients that do not tolerate in-hospital initiation of ß-blocker therapy, initiation should be re-attempted on an outpatient basis after 1-2 weeks of clinical stability. In post-myocardial infarction heart failure patients discharged without initiation of ß-blocker therapy, treatment should be initiated as soon as patient is clinically stable, in the absence of contraindications.

Monitoring—Blood Pressure and Heart Rate

- Blood pressure and heart rate should be monitored per standard routine
- Notify physician if patient develops symptomatic hypotension or SBP < 80 mm Hg
- The ß-blocker dose should be held for SBP < 80 mm Hg (recheck in one hour, notify physician)
- The ß-blocker dose should be held for symptomatic bradycardia (recheck in one hour, notify physician for dosing decision)

Monitoring—Symptoms

Most post-myocardial infarction patients will notice no worsening in symptoms with ß-blockers. The occasional patient may note increased fatigue or slight dizziness. These symptoms usually resolve.

Concomitant Drug Therapy[1,2]

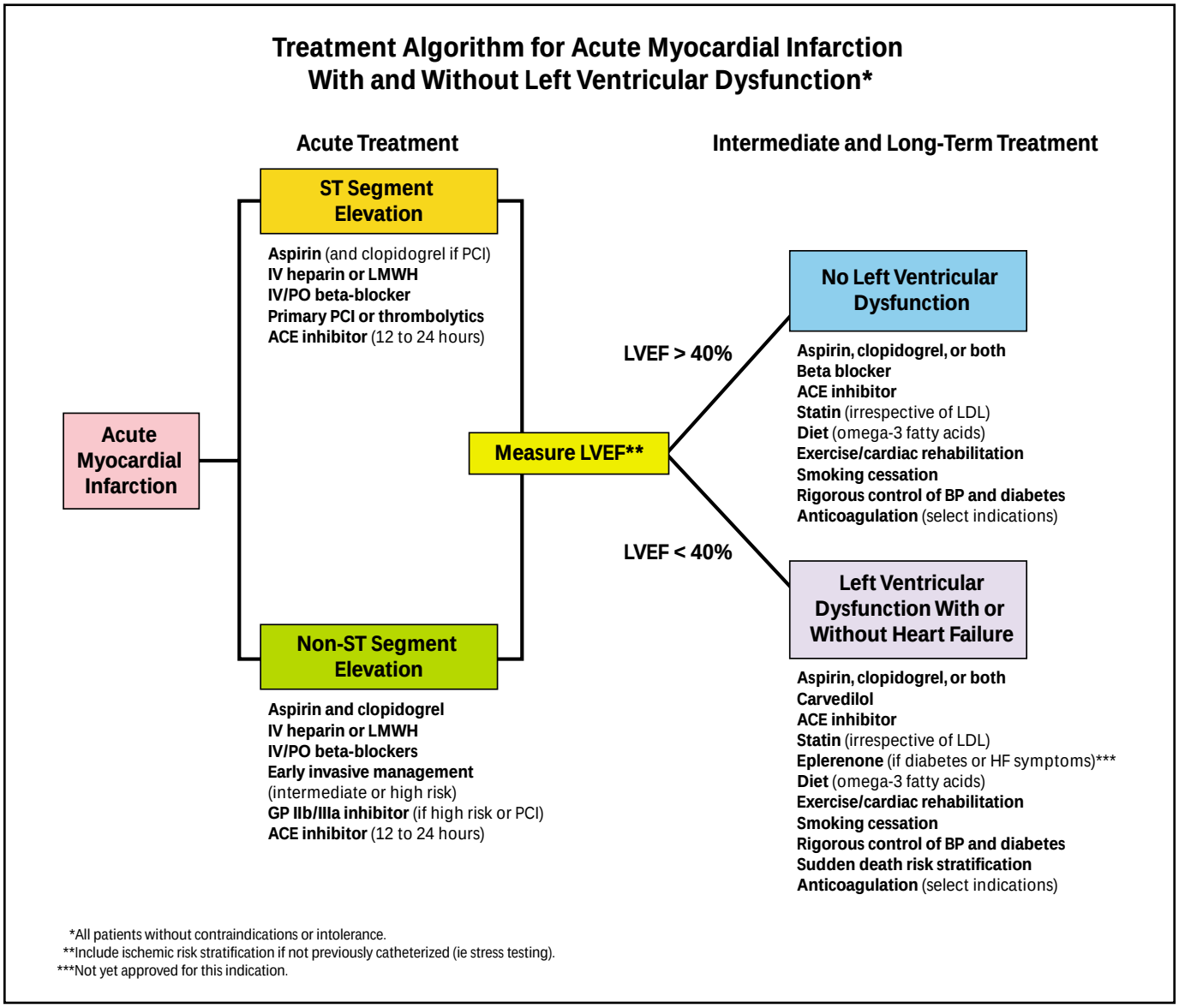
Patients with acute myocardial infarction should be treated with ACE inhibitors and ß-blockers in the absence of contraindications. ACE inhibitors are recommended for initiation 12 to 24 hours after admission for acute myocardial infarction. Patients may thus be started on ß-blockers before, during, or after initiation of ACE inhibitors. ACE inhibitors do not need to be at target doses prior to the initiation of a ß-blocker. Subsequent uptitration of the ACE inhibitor can be done after ß-blocker dose has been optimized. Both agents may be titrated up to target doses over time. Aldosterone antagonists can be initiated, continued, or dose adjusted before or during ß-blocker treatment. ß-blocker therapy should not be initiated while the patient is receiving dopamine, dobutamine, or milrinone infusions.

Staggering of ACE inhibitor, ß-blocker, and other vasoactive medication doses may be helpful in patients with dizziness or orthostatic symptoms. Monitor for adverse drug interactions. If excessive bradycardia occurs in digitalis-treated patients, exclude digitalis toxicity.

Quality Care Alert

The data supporting the beneficial effect of the long-term use of ß-blocker therapy after acute myocardial infarction is considered so compelling that the Department of Clinical Quality Improvement of the American Medical Association has circulated a document endorsed by the American College of Cardiology, the American Heart Association, the American College of Physicians, the American Academy of Family Practice, and numerous other societies. The document provides a consensus for the long-term use of ß-blockers after acute myocardial infarction. An expert review panel agreed that the totality of evidence demonstrates the following: use of ß-blockers after acute myocardial infarction decreases cardiovascular mortality, decreases reinfarctions, and increases the probability of long-term survival by up to 40%.

Although relative contraindications once may have been thought to preclude the use of ß-blockers in some patients, new evidence suggests that the benefits of ß-blockers in reducing reinfarctions and mortality actually outweigh its risks, even in patients with insulin-dependent diabetes mellitus; chronic obstructive pulmonary disease; severe peripheral vascular disease; PR interval > 0.24 second; and moderate LV failure. It is also emphasized that the use of ß-blockers in such patients requires careful monitoring of the patient to be certain that adverse events do not occur. ■



Role of ß-Blocker Therapy in the Post Myocardial Infarction Patient With and Without Left Ventricular Dysfunction Consensus Guideline

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