

# Addressing the Gap in the Management of Patients After Acute Myocardial Infarction: How Good Is the Evidence Supporting Current Treatment Guidelines?

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**B**eta-adrenergic blocking drugs were the first agents shown in large clinical trials to improve the outcomes of survivors of acute myocardial infarction (MI). Lower mortality was observed in the group randomized to active therapy, with a beta-adrenergic blocking drug in most, but not all, of the trials.

## Evidence Supporting Post-MI Use of Beta-adrenergic Blockers

**Table 1** shows the results in individual trial groups according to the properties of the specific beta-adrenergic blocking drug under evaluation. The Beta-Blocker Heart Attack Trial (BHAT),<sup>1</sup> which randomized 3837 patients to propranolol or placebo, and the Norwegian Multicenter Timolol Study,<sup>2</sup> with 1884 randomized patients convincingly demonstrated that therapy with a nonselective beta-adrenergic blocking agent improved survival.

Conversely, trials with agents with significant intrinsic sympathomimetic activity (ISA) did not generally report positive results, with the exception of a small trial with acebutolol, an agent with a low level of ISA. Similarly, results with agents with specificity for the beta<sub>1</sub> adrenoceptor have not consistently shown an improvement in mortality. Metoprolol, the shorter-acting tartrate salt, did not improve survival in the 2395 patients included in the Lopressor Intervention Trial (LIT).<sup>3</sup> However, practolol, also a beta<sub>1</sub>-selective agent, did improve survival

in a trial of 3038 survivors of acute MI, although the agent was subsequently withdrawn because of toxicity.<sup>4</sup>

All the original randomized clinical trials that provide support for the long-standing recommendation for routine use of beta-blocking drugs following acute MI were performed in the 1970s and 1980s, which was a very different era in the routine management of patients during and after acute MI and also in our appreciation of the safety and benefit of beta-adrenergic blocking drugs in patients with heart failure (HF). The patients recruited into these trials had not had the benefit of early acute thrombolysis or direct mechanical intervention to the infarct-related coronary occlusion by angioplasty. Aspirin use was not widespread or was actually contraindicated in the trial population to prevent a confounding impact on survival. Angiotensin-converting enzyme (ACE) inhibitors had not yet been developed, and other therapies, such as heparin, were not routinely used. On the other hand, some other probably harmful therapies, such as lidocaine infusions, which are no longer routinely used, were commonly used at that time.

Although not every individual trial showed a survival benefit, the capability, demonstrated for the first time, to improve long-time survival following acute MI resulted in a widespread and general recommendation to use a beta-adrenergic blocking drug routinely in all patients without a contraindication. Because at that time beta-adrenergic blocking drugs were

**Table 1.** Findings from Major Long-term Beta-blocking Agent Trials Post-MI: Pre-1999\*

	<b>Propranolol</b> <b>BHAT<sup>1,2</sup></b> <b>(1978-1981)</b>	<b>Timolol</b> <b>Norwegian<sup>3</sup></b> <b>Multicenter Study</b> <b>(1978-1981)</b>	<b>Metoprolol</b> <b>tartrate</b> <b>Lopressor Inter-</b> <b>vention Trial<sup>4</sup></b> <b>(1979-1982)</b>	<b>Atenolol</b> <b>No major</b> <b>trials</b>	<b>Metoprolol-XL</b> <b>No major</b> <b>trials</b>
Type of agent	Nonselective	Nonselective	Selective	Selective	Selective
Daily target dosage	180-240 mg	20 mg	200 mg	NA	NA
Number of patients	3837	1884	2395	NA	NA
Effect on mortality	-26% at	-39% at	+4% at	NA	NA
mean duration of trial	25 months <i>P</i> < .005	17 months <i>P</i> < .0005	12 months <i>P</i> = NS		
Effect on reinfarction	-16% at	-28% at	Not studied	NA	NA
mean duration of trial	25 months <i>P</i> < NS	17 months <i>P</i> < .0006			

\*Trials longer than 3 months in duration with >1000 patients.

MI indicates myocardial infarction; NA, not applicable; NS, nonsignificant.

<sup>1</sup>Beta-Blocker Heart Attack Trial Research Group. *JAMA*. 1982;247:1707-1714.

<sup>2</sup>Beta-Blocker Heart Attack Trial Research Group. *JAMA*. 1983;250:2814-2819.

<sup>3</sup>Norwegian Multicenter Study Group. *N Engl J Med*. 1981;304:801-807.

<sup>4</sup>Lopressor Intervention Trial Research Group. *Eur Heart J*. 1987;8:1056-1064.

considered to be contraindicated in HF and perhaps because it was thought that low-risk patients did not require additional long-term therapy, adoption of beta-adrenergic blocking drugs fell short of expectations.

Guidelines on post-MI management<sup>5</sup> also advocated widespread use of beta-adrenergic blocking agents based on their beneficial effects on the risk of reinfarction. This effect was demonstrated in the Norwegian trial, in which the nonselective beta-adrenergic blocker timolol reduced the risk of infarction by 28% (*P* < .0006). Similarly, in the BHAT study, the nonselective beta-adrenergic blocker propranolol reduced the risk of reinfarction by 16% (*P* = NS).

Although all the trials of beta-adrenergic blocking drugs from this era excluded patients with advanced HF, evidence from subgroup analyses provided a tantalizing prediction, which was confirmed more than a decade later, that beta-adrenergic blockade would be especially beneficial in patients with HF. In the BHAT study, a subgroup of patients with mild HF following the index MI

had a higher subsequent mortality rate and the greatest benefit from randomization to propranolol. Similarly, in the Norwegian study, a subgroup of patients with cardiomegaly on chest radiograph was especially likely to benefit from timolol. Although atenolol and metoprolol (tartrate or succinate salt) are currently the beta-adrenergic blockers most commonly prescribed following acute MI, neither of these agents has been demonstrated in a large-scale randomized trial to improve either survival or the risk of reinfarction.

## How Effective Are Other Post-MI Therapies?

Not all agents that have been evaluated for post-MI therapy are effective. Drugs, such as diuretics, nitrates, and calcium channel blockers, that do not directly counter the abnormal neurohormonal environment in this patient population have not been shown to be effective.<sup>6,7</sup> Despite lowering blood

pressure and reducing myocardial ischemia, calcium channel blocking drugs do not improve survival and are actually detrimental in patients with HF.

Only neurohormonal antagonists have been shown to attenuate or reverse the progressive left ventricular (LV) remodeling that occurs after MI, especially in patients whose LV ejection fraction is reduced to  $\leq 40\%$ . For example, in the Survival and Ventricular Enlargement (SAVE) trial, ACE inhibitors improved survival and attenuated the LV remodeling process in patients with LV dysfunction after acute MI.<sup>8</sup>

## CAPRICORN Trial of Beta Blockers Post-MI

The Carvedilol Post Infarct Survival Control in LV Dysfunction (CAPRICORN) study<sup>9</sup> is the only trial to date to evaluate the role of beta-adrenergic blocking drugs in patients with significant post-MI LV dysfunction as an entry criterion. Patients also had to have been treated with ACE inhibitors for at least 48 hours prior to randomization (unless there were contraindications). The trial compared carvedilol with placebo in patients who had had an acute MI within the previous 21 days and who had an LV ejection fraction of  $\leq 40\%$ . HF was present in approximately half of the patients studied.

CAPRICORN is also the only study of beta-adrenergic blocking drugs undertaken in patients who had the benefit of contemporary management of acute MI. Therapies routinely applied to the study population that are known to improve survival included thrombolytic therapy or direct angioplasty when indicated, ACE inhibition (use of which was an actual inclusion criteria), aspirin, and statins. **Table 2** shows the percentage of patients in the CAPRICORN study who received these agents.

The CAPRICORN trial enrolled 1959 patients, 975 randomized to carvedilol and 984 to placebo, who were followed for an average of 1.3 years. The dose of the study medication was uptitrated from 6.25 mg twice daily to a

**Table 2.** Therapies Routinely Used in CAPRICORN Population

	Carvedilol group (n = 975)	Placebo group (n = 984)
<i>Treatment for index myocardial infarction</i>		
Nitrates	715 (73%)	717 (73%)
IV beta blockers	112 (11%)	100 (10%)
IV heparin	617 (63%)	635 (65%)
SC heparin	460 (47%)	481 (49%)
IV diuretics	338 (35%)	320 (33%)
Thrombolysis/ primary angioplasty	442 (45%)	465 (47%)
<i>Medications at time of randomization</i>		
ACE inhibitor	953 (98%)	955 (97%)
Aspirin	838 (86%)	847 (86%)

CAPRICORN indicates Carvedilol Post Infarct Survival Control in LV Dysfunction; IV, intravenous; SC, subcutaneous; ACE, angiotensin-converting enzyme.

Source: Adapted, with permission, from reference 9.

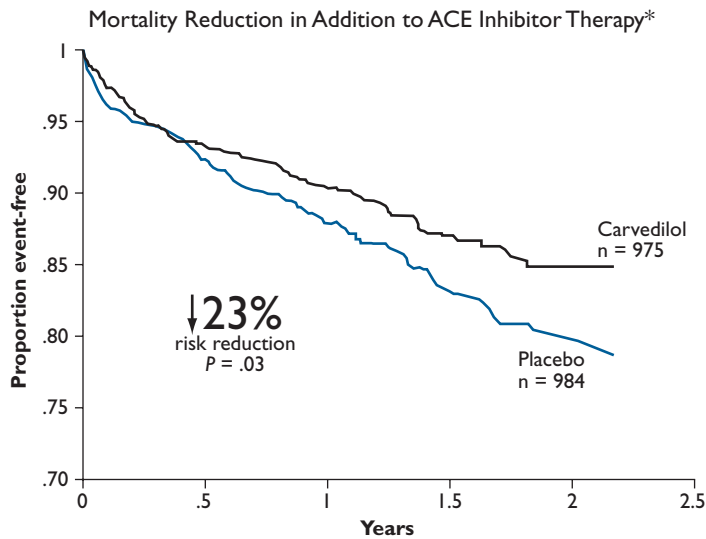
maximum of 25 mg twice daily.

The trial was initially designed and powered to detect a favorable impact of carvedilol on survival. Subsequently, on the advice of an independent end points committee, the primary end point was altered to an analysis of death from any cause or hospitalization for a cardiovascular cause. When the results were analyzed, it was found that carvedilol had improved survival by 23% (**Figure**), whereas there was no statistically significant difference between the carvedilol and placebo groups in the combined end point of death or cardiovascular hospitalization.

The impact of carvedilol on reinfarction was substantial and was the greatest reduction in reinfarction reported in any large trial of beta blockers following acute MI. Carvedilol also had a favorable influence on the risk of supraventricular or ventricular arrhythmias.<sup>10</sup>

Carvedilol was well tolerated, and the results are especially remarkable because

**Figure.** CAPRICORN: All-cause Mortality



\*97% of patients were receiving ACE inhibitors.  
CAPRICORN indicates Carvedilol Post Infarct Survival Control in LV Dysfunction;  
ACE, angiotensin-converting enzyme.  
Source: Reference 9.

“drop-in” patients—given open-label beta-adrenergic blocking drugs—would have tended to reduce the observed favorable influence of carvedilol. Patients who received optimal therapy for acute MI, including revascularization by angioplasty or thrombolysis, were no less likely to benefit than the other patients. Approximately half the patients in the trial did not have HF, but they obtained a similar benefit to the group with HF.

### Class Effect or Drug-specific Effect?

Meta-analyses suggest that all beta-adrenergic blocking drugs that do not have ISA improve survival following MI. Most meta-analyses and the latest study that included the current data with carvedilol suggest that important and clinically relevant differences may exist between the benefit obtained from beta<sub>1</sub> selective agents and nonselective drugs, such as carvedilol. Meta-analyses of the 26 580 patients in placebo-controlled trials following acute MI and the 15 905 patients evaluated in HF trials do show an average ≥

13% reduction in mortality with the nonselective agents in both clinical scenarios.<sup>11</sup>

The suggestion that nonselective beta-adrenergic blocker agents may produce a greater clinical benefit after acute MI is well supported on a mechanistic basis, although most of the studies, including the Carvedilol or Metoprolol European Trial (COMET),<sup>12</sup> that confirmed the superiority of a nonselective agent (carvedilol) over a selective agent (short-acting metoprolol), were conducted in patients with HF.

Following acute MI, many of the pathophysiological features that influence disease progression and outcomes are the same as those in HF. Norepinephrine exerts an important influence on the risk of reinfarction, the risk of supraventricular and ventricular arrhythmias, and the adverse remodeling process that develops, particularly in survivors of MI.

## Conclusion

Beta-adrenergic blocking drugs have been convincingly demonstrated in large clinical trials to improve the natural history following acute MI. Improved survival and reduced risk of reinfarction have been shown in large-scale randomized trials. Much of the evidence supporting the routine use of beta-adrenergic blocking drugs for the long-term therapy of patients without contraindications comes from trials of nonselective agents. In the modern era of acute MI management, when many successful therapies are combined to improve post-MI outcomes, only carvedilol has been shown not only to improve survival and reduce reinfarction but also to attenuate the remodeling process.

Moreover, carvedilol has been shown to benefit a patient population selected on the basis of high risk and treated because of this high risk with concomitant ACE inhibitors. The CAPRICORN study found that far from being surpassed by more modern agents and approaches to the management of acute MI, beta-adrenergic blocking drugs, specifically carvedilol, are highly effective and important therapy for post-MI patients.

## References

1. 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.
2. 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.
3. Lopressor Intervention Trial Research Group. The Lopressor Intervention Trial: multicentre study of metoprolol in survivors of acute myocardial infarction. *Eur Heart J*. 1987;8:1056-1064.
4. Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. A multicentre international study. *Br Med J*. 1975;3:735-740.
5. **Ryan TJ, Antman EM, Brooks NH, et al.** 1999 update: ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction: Executive Summary and Recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation*. 1999;100:1016-1030.
6. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-I. *Lancet*. 1986;2:57-66.
7. Multicenter Diltiazem Post Infarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med*. 1988;319:385-392.
8. **Pfeffer MA, Braunwald E, Moyer 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. *N Engl J Med*. 1992;327:669-677.
9. The CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357:1385-1390.
10. **McMurray JJ, Dargie HJ, Ford I, et al.** Carvedilol reduces supraventricular and ventricular arrhythmia after myocardial infarction. Evidence from the CAPRICORN study. *Circulation*. 2001;104: Abstract 3303.
11. **Packer M.** Do beta-blockers prolong survival in heart failure only by inhibiting the beta 1-receptor? A perspective on the results of the COMET trial. *J Card Fail*. 2003;9:429-443.
12. **Poole-Wilson PA, Swedberg K, Cleland JGF, et al.** Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised clinical trial. *Lancet*. 2003;362:7-13.