New Evidence from the CAPRICORN Trial: The Role of Carvedilol in High-Risk, Post–Myocardial Infarction Patients

Jonathan D. Sackner-Bernstein, MD, FACC

Heart Failure and Cardiomyopathy Center, Division of Cardiology, North Shore University Hospital, Manhasset, NY

The CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) trial established that the ß-blocker carvedilol reduces the risk of death in patients with left ventricular dysfunction post myocardial infarction, whether or not the infarct is complicated by clinical heart failure. Thus, the utility of the ß-blocker carvedilol is confirmed in the modern era as an adjunct to revascularization, angiotensin-converting enzyme inhibitors, aspirin, and statins. In addition, the results prompt us to review the prior studies of ß-blockers postinfarction. Critical review of CAPRICORN and earlier ß-blocker studies suggests that specific ß-blockers should be matched to specific clinical scenarios. The COMET (Carvedilol or Metoprolol European Trial) study reinforces this view by establishing that ß-blockers are not simply interchangeable agents.
[Rev Cardiovasc Med. *2003;4(suppl 3):S25–S29*]

Key words: ß-Blockers • Heart failure • Myocardial infarction • Class effects

ß-blockers are standard treatment for the management of patients post–myocardial infarction (MI), primarily based on the reduction in the risk of death and reinfarction.[1] The guidelines recommend long-term, ß-blocker therapy for most patients postinfarction but express reservations about their use in higher-risk patients with left ventricular (LV) dysfunction,

particularly those who have symptoms of heart failure. These patients, at the highest risk of reinfarction and death,[2] would seem to be the most likely to benefit,[3] but no study has directly assessed the effect of a ß-blocker in this population.

Prior investigators suggested that the ß-blockers propranolol[3] and timolol[4] are effective in high-risk subsets, but these were retrospective analyses from studies that excluded patients with significant LV dysfunction. Further, the randomized trials that support the utility of long-term ß-blocker therapy post MI have not focused on patients with LV dysfunction or heart failure, and none has been performed in the modern era of treatment.[5–7]

CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) was designed to address these issues. Specifically, the trial evaluated the clinical impact of carvedilol in high-risk postinfarction patients with LV dysfunction, with or without symptoms of heart failure, providing the only evidence for the utility of a ß-blocker in the modern era of treatment. This article reviews CAPRICORN in the context of prior ß-blocker trials[8] and the COMET (Carvedilol or Metoprolol European Trial) results.[9]

CAPRICORN: Methods and Results

The CAPRICORN investigators randomized 1959 patients to carvedilol or placebo in addition to standard background therapies within 3–21 days of a myocardial infarction. Patient characteristics are summarized in Table 1.[10,11] In contrast to all prior studies of ß-blockers postinfarction, patients were only enrolled in the trial if their LV ejection fraction (LVEF) was 40% or less. Patients were enrolled with (47%) and without clinical heart failure but were stabilized prior to the initiation of study medication. More than one-third of the patients enrolled had received open-label ß-blocker therapy for their infarction (which was stopped by their primary physician prior to enrollment). Investigators were strongly encouraged to initiate therapy with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker.[12]

The trial was designed as a mortality trial,[13] but the protocol was amended in midstream when the

Table 1
Baseline Characteristics of the Patients in the CAPRICORN Trial

	Placebo (n = 984)	Carvedilol (n = 975)
Age (yr)	63	63
Sex (% men)	74	73
Systolic blood pressure (mm Hg)	121	122
Heart rate (beats/min)	77	77
Left ventricular ejection fraction (%)	33	33
Days from index MI to randomization (range)	10.0 (1–30)	10.0 (1–28)
History of hypertension before index MI (%)	52	55
History of angina before index MI (%)	54	57
History of MI before index MI (%)	29	31
ACE inhibitor use before index MI (%)	7	9
Diabetes mellitus (%)	23	21
Hyperlipidemia (%)	33	32
ß-Blocker use before index MI (%)	3	3
Site of index MI (% anterior)	55	59
Typical cardiac pain during index MI (%)	94	95
Pulmonary edema during index MI (%)	18	19
Increased cardiac enzymes during index MI (%)	85	84
Thrombolytic therapy for index MI (%)	37	36
Primary coronary angioplasty for index MI (%)	13	12
IV heparin for index MI (%)	65	63
IV or other nitrate for index MI (%)	73	73
IV diuretics for index MI (%)	33	35
IV ß-blocker for index MI (%)	10	11
Oral ß-blocker for index MI (%)	32	31
ACE inhibitor use before randomization (%)	97	98
ß-Blocker use before randomization (%)	35	33
Aspirin use before randomization (%)	85	85
Use of lipid-lowering drugs before randomization (%)	24	22
Heart failure prior to randomization (%)	47	48

ACE, angiotensin-converting enzyme; MI, myocardial infarction.

MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) and CIBIS-II (Cardiac Insufficiency Bisoprolol Study) reported significantly reduced risk of death with metoprolol succinate[14] and bisoprolol.[15] The steering committee believed in an ethical mandate to treat all enrolled patients with open-label ß-blocker therapy who had experienced heart failure, which would reduce the statistical power of the study. Therefore, the first secondary endpoint was elevated to co-primary status with appropriate statistical adjustments.[16]

When the final study results showed a 23% reduction in the risk of death,[12] many were concerned about its statistical significance. The Food and Drug Administration (FDA) shared this concern, but after extensive review of all relevant data, the administration and its advisory panel concluded that the mortality reduction was a real effect of carvedilol, and not a result of statistical chance.[10,17–19] The FDA approved carvedilol for the reduction of cardiovascular mortality in postinfarction patients with LV dysfunction with or without clinical heart failure.

Table 2
Trials Studying Long-Term Effects of ß-Blockers Postinfarction

Trial	BHAT[6]	Norwegian Timolol[5]	Lopressor Intervention Trial[7]
Agent	Propranolol	Timolol	Metoprolol tartrate
Daily dosage (mg)	240	20	100
Subjects in trial (n)	3887	1884	2395
Deaths (n; active/control)	138/188	98/152	65/62
Mean observation (mo)	25	17	12
Effect on mortality (%)	↓26*	↓39*	↑4
Effect on reinfarction (%)	↓16	↓28*	N/A

*$P < .05$.
↓, decrease; ↑, increase.

Reinfarction was significantly reduced by 41%. Sudden death tended to be less frequent with carvedilol (P = .09), in parallel with marked decreases in clinical incidence of atrial fibrillation/flutter and ventricular tachycardia/fibrillation.

Carvedilol did not affect the co-primary end point of the combined risk of death and all-cause cardiovascular hospitalizations. Of the secondary end points, reinfarction was significantly reduced by 41%. Sudden death tended to be less frequent with carvedilol ($P = .09$), in parallel with marked decreases in clinical incidence of atrial fibrillation/flutter and ventricular tachycardia/fibrillation.[11,16]

The lack of effect on the combined risk of death and cardiovascular hospitalizations was based on the definition used to designate a hospitalization as cardiovascular. None of the pivotal trials of ß-blockers for postinfarction or chronic heart failure patients used an all-inclusive definition for cardiovascular hospitalizations, as did CAPRICORN. Instead, prior studies focused on major cardiovascular hospitalizations, not considering atypical chest pain as the equivalent of a reinfarction, for example. When the CAPRICORN database was analyzed retrospectively but in a blinded fashion, using these definitions for major cardiovascular hospitalizations, carvedilol was associated with statistically significant and clinically relevant reductions in risk.[20]

Carvedilol initiated at 6.25 mg twice daily with up-titration every 3–10 days was well tolerated in CAPRICORN, with 86% of the patients on a minimum of 12.5 mg twice daily. Equal numbers of patients withdrew from therapy in the placebo and active treatment groups. Dizziness was a more frequent serious adverse experience (1.3% vs 0.2%) and nonserious cardiovascular event. Otherwise, the side effects were similar to placebo.[10,11]

Prior to CAPRICORN, the last randomized, controlled postinfarction trial of a ß-blocker was published in 1987.[7] These trials were conducted prior to the use of thrombolytics, ACE inhibitors, and aspirin, and in fact, only three trials evaluated the effects of therapy for longer than 3 months (Table 2). Although propranolol[6,21] and timolol[5] significantly reduced the risk of death and timolol the risk of reinfarction, the only long-term trial that evaluated the effects of metoprolol tartrate did not detect a difference between metoprolol and placebo.[7]

Implications of CAPRICORN in the COMET Era

The COMET study demonstrated that carvedilol reduces the risk of

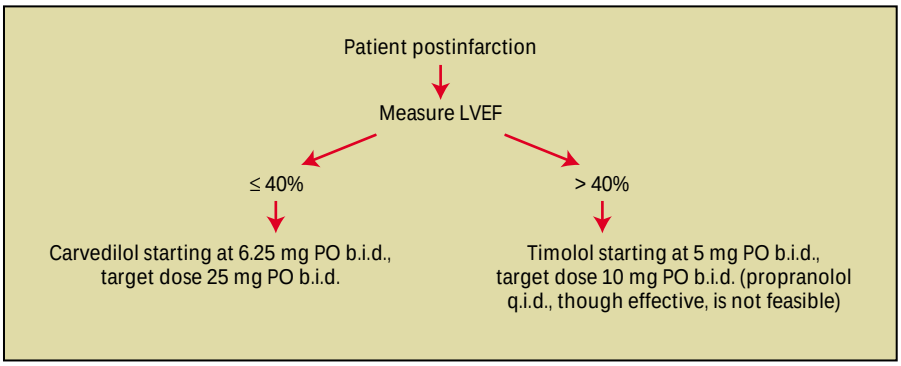

Figure 1. *Selection of ß-blocking agent for patients postinfarction based on clinical trial data. Logistics dictate that timolol is preferred over propranolol, given the dosing frequency of twice daily versus four times a day. LVEF, left ventricular ejection fraction.*

death compared with metoprolol tartrate in patients with chronic heart failure (hazard ratio = .83, P = .0017).[9] A clinical trial comparing two agents in the same class in a head-to-head comparison is quite unusual; therefore, the results should be considered in the specific population but also could be evaluated for their applicability outside of the population studied.

COMET established that carvedilol is superior to metoprolol tartrate in patients with heart failure.[9] Because CAPRICORN proved the effectiveness of carvedilol postinfarct[12] and metoprolol has not been proven effective long-term postinfarct,[7] carvedilol also appears superior to metoprolol in postinfarction patients with LV dysfunction. Although metoprolol is approved by the FDA for the postinfarction patient, this is based on intermediate-term data from the Goteborg Metoprolol Trial,[22] and neither metoprolol tartrate nor metoprolol succinate have been proven effective in long-term controlled trials.[7] Therefore, direct evidence from a randomized comparative trial proves that carvedilol is superior to metoprolol in heart failure, and indirect evidence supports its superiority in the postinfarction patient with LV dysfunction.

The COMET study demonstrated that carvedilol reduces the risk of death compared with metoprolol tartrate in patients with chronic heart failure.

The trials provide specific guidance for ß-blocker selection in the postinfarction patient with preserved LV, with both propranolol[6,21] and timolol[5] having proven effective. In the ß-Blocker Heart Attack Trial (BHAT), patients took propranolol four times daily, a dosage that prevents its use in clinical practice. Timolol can be used instead, and is proven to reduce the risk of death and reinfarction.[5] Based on these data, metoprolol appears inferior to propranolol and timolol in the postinfarction patient with preserved ventricular function.

Conclusion

Based on the pharmacology of ß-blockers and the pathophysiology of cardiovascular disease, it seems rational to assume that the benefits of ß-blockers are a class effect. The American Heart Association/American College of Cardiology guidelines for acute MI are written with this perspective, as are FDA decisions regarding drug approval and product labeling. Together, such perspectives encourage clinicians to consider ß-blockers as interchangeable.

But the data are the ultimate arbiter, and two lines of evidence suggest that this reasoning may be flawed. First, the ß-blocker bucindolol is ineffective[23] and the centrally acting sympathoinhibitor moxonidine increases the risk of death.[24] Second, the COMET trial establishes that there are clinically meaningful

Main Points

- CAPRICORN evaluated the clinical impact of carvedilol in high-risk postinfarction patients with left ventricular (LV) dysfunction, with or without symptoms of heart failure, providing the only evidence for the utility of a ß-blocker in the modern era of treatment.
- None of the pivotal trials of ß-blockers for postinfarction or chronic heart failure patients used an all-inclusive definition for cardiovascular hospitalizations as did CAPRICORN
- COMET established that carvedilol is superior to metoprolol tartrate in patients with heart failure.
- In the presence of data supporting the use of specific ß-blockers for particular indications, physicians should select proven agents instead of choosing based on familiarity.

differences between ß-blockers that do not seem to relate to the dosages used in the study.[9] The heterogeneity among ß-blockers is proven, and drug selection must be based on the results of randomized clinical trials whenever available (Figure 1). In the presence of data supporting the use of specific ß-blockers for particular indications, physicians should select proven agents instead of choosing based on familiarity. ■

References

1. 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.
2. St John Sutton M, Pfeffer MA, Moye L, et al. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. *Circulation*. 1997;96:3294–3299.
3. 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.
4. Hansteen V. Beta blockade after myocardial infarction: the Norwegian propranolol study in high-risk patients. *Circulation*. 1983;67(6 Pt 2):I57–60.
5. Timolol Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. *N Engl J Med*. 1981;304:801–807.
6. Propranolol Study Group. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA*. 1982;247:1707–1714.
7. 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.
8. Borrello F, Beahan M, Klein L, Gheorghiade M. Reappraisal of ß-Blocker Therapy in the Acute and Chronic Post-Myocardiol Infarction Period. *Rev Cardiovasc Med*. 2003;4(suppl 3):S13-S24.
9. Poole-Wilson PA, Swedberg K, Cleland, 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 controlled trial. *Lancet*. 2003;362:7–13.
10. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Joint clinical review. Available at: www.fda.gov/ohrms/dockets/ac/03/briefing/3920B2_02_A-FDA-Coreg.pdf. Accessed July 16, 2003.
11. GlaxoSmithKline. The efficacy of carvedilol in patients with left ventricular dysfunction following a recent myocardial infarction. Available at: www.fda.gov/ohrms/dockets/ac/03/briefing/3920B2_01_GSK-Briefing-Document.ppt. Accessed July 19, 2003.
12. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357:1385–1390.
13. Dargie HJ. Design and methodology of the CAPRICORN trial—a randomised double blind placebo controlled study of the impact of carvedilol on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction. *Eur J Heart Fail*. 2000;2:325–332.
14. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) [see comments]. *Lancet*. 1999;353:2001–2007.
15. CIBIS-II Investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9–13.
16. GlaxoSmithKline. Sponsor presentation to FDA Cardiovascular and Renal Advisory Panel. Available at: www.fda.gov/ohrms/dockets/ac/03/slides/3920S2_01_GlaxoSmithKline.ppt. Accessed July 19, 2003.
17. Center for Drug Evaluation and Research, U.S Food and Drug Administration. Joint clinical review. Available at: www.fda.gov/ohrms/dockets/ac/03/briefing/3920B2_02_B-FDA-Coreg-Amend.pdf. Accessed July 19, 2003.
18. Center for Drug Evaluation and Research, U.S Food and Drug Administration. Statistical review and evaluation (amendment of clinical/statistical review of 12/04/02). Available at: www.fda.gov/ohrms/dockets/ac/03/briefing/3920B2_02_C-FDA-Coreg-Errata.pdf. Accessed July 19, 2003.
19. Center for Drug Evaluation and Research, U.S Food and Drug Administration. Transcript of the 98th meeting of the Cardiovascular and Renal Advisory Committee, January 7, 2003. Available at: www.fda.gov/ohrms/dockets/ac/03/transcripts/3920T2.htm. Accessed July 19, 2003.
20. Sackner-Bernstein J, et al., Effect of carvedilol on major cardiovascular events in post-infarction patients treated with ACE inhibitors: further analysis of the CAPRICORN trial [abstract]. *J Am Coll Cardiol*. 2003.
21. Propranolol Study Group. A randomized trial of propranolol in patients with acute myocardial infarction. II. Morbidity results. *JAMA*. 1983;250:2814–2819.
22. Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction. A double-blind randomised trial. *Lancet*. 1981;2:823–827.
23. The 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.
24. Jones CG, Cleland JG. Meeting report—the LIDO, HOPE, MOXCON and WASH studies. Heart Outcomes Prevention Evaluation. The Warfarin/Aspirin Study of Heart Failure. *Eur J Heart Fail*. 1999;1:425–431.