

Briefing Document

The Efficacy of Carvedilol in Patients with Left Ventricular Dysfunction Following a Recent Myocardial Infarction

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1. EXECUTIVE SUMMARY

Carvedilol, a nonselective β -blocker with vasodilating properties, is currently approved by the FDA (1) for the treatment of essential hypertension, alone or in combination with other drugs and (2) for the treatment of mild to severe heart failure due to an ischemic or nonischemic cardiomyopathy, usually in addition to diuretics, ACE inhibitor and digitalis, to increase survival and also to reduce the risk of hospitalization.

GlaxoSmithKline is seeking a revision of current labeling for carvedilol with the intent of providing information about its use in survivors of an acute myocardial infarction. This request is based on the findings of the CAPRICORN trial, which evaluated the efficacy of carvedilol in patients with left ventricular dysfunction and a recent myocardial infarction (< 21 days), who were at high risk and were receiving all appropriate treatments for the immediate and long-term management of the post-infarction patients, including ACE inhibitors in all patients. In this trial, carvedilol reduced all-cause mortality by 23% ($P=0.03$). Although this effect did not reach levels of statistical significance specified in an amendment to the study protocol, the trial did demonstrate an effect on the primary endpoint as defined in the original protocol and at the magnitude ($\geq 20\%$) and the significance level ($P \leq 0.05$) specified in the original protocol.

In addition to the finding of a nominally significant mortality reduction, the strength of evidence supporting a benefit of carvedilol in post-infarction patients includes the following:

- The CAPRICORN trial was designed to evaluate the effect of carvedilol on survival; the study was carried out as a survival trial; and the number of deaths recorded in the study was comparable to that seen in other mortality trials in post-infarction patients. The study failed to achieve its primary endpoint at the prespecified α because of a strong recommendation by the Data and Safety Monitoring Board to change the primary endpoint — a recommendation that would have been difficult for the Steering Committee and the sponsor to ignore.
- The mortality finding in CAPRICORN has been replicated in other trials that evaluated the effect of β -blockers in post-infarction patients. The magnitude of the reduction in mortality risk with carvedilol was very similar to that seen in these earlier trials. The effects of treatment with carvedilol on non-fatal events in the CAPRICORN study was also similar (both in direction and magnitude) to those seen in these earlier studies.

- Data from other trials with carvedilol in patients with chronic heart failure indicate that treatment with the drug reduces mortality in a disorder which is closely related to that seen in the post-infarction patient. The magnitude of the benefit in chronic heart failure is almost identical to that seen with other β -blockers. These findings indicate that carvedilol does not exert effects that may detract from the ability of its β -blocking actions to reduce mortality in patients with left ventricular dysfunction.

Currently, β -blockers are used infrequently in the management of post-infarction patients with left ventricular dysfunction, even though treatment with a β -blocker is very likely to be indicated in these patients once the acute phase of the infarction has passed and symptoms of heart failure have developed. The totality of available evidence indicates that such patients would benefit from early treatment with carvedilol and that it would be reasonable to allow information regarding such use to be incorporated into the drug's prescribing information.

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2. INTRODUCTION

2.1. Efficacy of Beta-Adrenergic Blockade in Post-Infarction Patients

There is widespread recognition that long-term treatment with a beta-blocker in patients who have recently experienced an acute myocardial infarction has favorable effects in reducing the subsequent risk of death and recurrent myocardial infarction.[1,2] Three beta-blockers are presently approved by the FDA for such use: timolol, metoprolol and propranolol.

The main features of the large-scale trials that have been carried out with these three drugs in post-infarction patients are summarized below. The Division of Cardio-Renal Drug Products suggested that inclusion of such a review into the current document might be informative and provide a useful perspective from which to judge the efficacy of carvedilol in post-infarction patients.

2.1.1. Norwegian Timolol Trial (1981)

In the Norwegian Timolol Trial,[3] 1884 patients who had experienced an acute myocardial infarction 7-28 days prior to entry were randomized to treatment with either placebo or timolol for a mean of 17 months. Cardiac function was not assessed as an entry criterion. Patients were excluded if they had uncontrolled heart failure or had a systolic blood pressure < 100 mm Hg. None of the patients were reported to have received treatment with an ACE inhibitor, a thrombolytic drug, or intravenous heparin or nitroglycerin. Furthermore, patients who required long-term treatment with aspirin, an anticoagulant or a lipid lowering drug were not allowed to participate in the trial to minimize the likelihood that these concomitant treatments might diminish the ability to detect a benefit of beta-blockade. Patients initially received a dose of 10 mg of timolol daily (or matching placebo) which (if tolerated) was titrated to a target dose of 20 mg daily.

Four major endpoints were specified: total mortality, cardiovascular mortality, sudden death and reinfarction; none was specified as the primary endpoint. At the end of follow-up, when compared with the placebo group, patients in the timolol group had a 39% reduction in the risk of death ($P=0.0003$), a 23% reduction in cardiovascular mortality ($P=0.002$), and a 28% reduction in the risk of reinfarction ($P=0.0006$). [However, data on reinfarction were incomplete because patients who discontinued treatment with the study drug were followed for the occurrence of non-fatal events for only 28 additional days and not until the end of the trial.] The effect of timolol on the risk of cardiovascular hospitalization was not evaluated, but patients in the timolol group had a higher risk of several

adverse cardiovascular events (i.e., heart failure [including pulmonary edema], hypotension, dizziness, bradycardia and peripheral vascular symptoms), but a lower risk of cardiac arrhythmias.

2.1.2. Göteborg Metoprolol Trial (1981)

In the Göteborg Metoprolol Trial,[4,5] 1395 patients who had experienced an acute myocardial infarction within approximately 24 hours were randomized to treatment with either placebo or metoprolol for 3 months. Cardiac function was not assessed as an entry criterion. Patients were excluded if they had Killip class III or IV heart failure or had a systolic blood pressure < 100 mm Hg. None of the patients were reported to have received treatment with an ACE inhibitor, a thrombolytic drug, or intravenous heparin or nitroglycerin. Patients initially received a dose of 15 mg of metoprolol intravenously (or matching placebo) which (if tolerated) was followed by treatment with oral metoprolol titrated to a target dose of 200 mg daily.

According to FDA documents, no primary endpoint of the study was specified a priori; but the major prespecified objectives included the risk of reinfarction, the risk of arrhythmias, all-cause mortality and ventricular function. At the end of follow-up, when compared with the placebo group, patients in the metoprolol group had a 36% reduction in the risk of death ($P=0.03$), but metoprolol had no significant effect on the risk of reinfarction ($P=0.12$). The effect of metoprolol on the risk of cardiovascular hospitalization was not evaluated, but the investigators reported an increased frequency of specific cardiovascular events (i.e., hypotension, bradycardia, heart block and heart failure).[5]

2.1.3. Beta-Blocker Heart Attack Trial (1982)

In the Beta-Blocker Heart Attack Trial,[6-8] 3837 patients who had experienced an acute myocardial infarction 5-21 days prior to entry were randomized to treatment with either placebo or propranolol for a mean of 27 months. Cardiac function was not assessed as an entry criterion. Patients were excluded if they had evidence of overt heart failure. None of the patients were reported to have received treatment with an ACE inhibitor, a thrombolytic drug, or intravenous heparin or nitroglycerin; only 6-7% were receiving an antiplatelet drug before randomization and only 2-3% received a lipid lowering drug at any time during the trial. Patients initially received a dose of 20 mg of propranolol (or matching placebo) which (if tolerated) was titrated to a target dose of 180-240 mg daily.

The primary endpoint of the study was all-cause mortality; the secondary

endpoints were cardiovascular mortality, sudden cardiac death and non-fatal myocardial infarction. At the end of follow-up, when compared with the placebo group, patients in the propranolol group had a 26% reduction in the risk of death ($P=0.005$) and a significant reduction in cardiovascular mortality ($P < 0.01$) and sudden cardiac death ($P < 0.05$), but propranolol had no significant effect on the risk of reinfarction. The effect of propranolol on the risk of cardiovascular hospitalization was not evaluated, but the investigators reported an increased risk of adverse cardiovascular events (i.e., early heart failure, hypotension, peripheral vascular symptoms) in the propranolol group,[6] although there were fewer reports of ventricular arrhythmias in this group.

2.1.4. Lopressor Intervention Trial (1987)

In the Lopressor Intervention Trial,[9] 2395 patients who had experienced an acute myocardial infarction 6-16 days prior to entry were randomized to treatment with either placebo or metoprolol for a minimum of 12 months. Patients were excluded if they had heart failure or had a systolic blood pressure < 95 mm Hg. Cardiac function was not assessed as an entry criterion. None of the patients were reported to have received treatment with an ACE inhibitor, a thrombolytic drug, or intravenous heparin or nitroglycerin. Furthermore, patients who were receiving treatment with aspirin or a lipid lowering drug were not allowed to participate in the trial to minimize the likelihood that these concomitant treatments might diminish the ability to detect a benefit of beta-blockade. Patients initially received a dose of 25-50 mg of metoprolol (or matching placebo) which (if tolerated) was titrated to a target dose of 200 mg daily.

The primary endpoint of the study was all-cause mortality at 7 and 12 months of follow-up; secondary endpoints included cardiac mortality and sudden cardiac death. After 7 months, there were 54 and 42 deaths in the placebo and metoprolol groups, respectively; after 12 months, there were 62 and 65 deaths in the placebo and metoprolol groups, respectively. At the end of follow-up (up to 18 months in some patients), there were 93 and 86 deaths in the placebo and metoprolol groups, respectively. None of these differences were statistically significant. Metoprolol also did not significantly reduce the risk of cardiac death or sudden cardiac death. The effect of metoprolol on the risk of cardiovascular hospitalization was not evaluated, but the investigators reported an increased risk of cardiovascular events (i.e., hypotension and bradycardia) in the metoprolol group, although there were fewer reports of ventricular arrhythmias in this group.

2.1.5. Summary of Earlier Post-Infarction Trials with Beta-Blockers

The results of these trials led to the approval of timolol, metoprolol and propranolol for the long-term management of patients who had experienced a recent myocardial infarction.

- Timolol is approved to reduce cardiovascular mortality and to reduce the risk of reinfarction in survivors of an acute infarction.
- Propranolol is approved to reduce cardiovascular mortality in survivors of an acute infarction.
- Metoprolol is approved to reduce cardiovascular mortality in patients who are experiencing an acute myocardial infarction; labeling indicates that the drug should be given intravenously first followed by long-term oral treatment. [Metoprolol is approved for long-term oral treatment even though the benefits seen in the Goteborg Metoprolol Trial may have been primarily related to early treatment with intravenous beta-blocker.^{10,11} The only trial to evaluate the long-term effects of oral therapy with metoprolol (without preceding intravenous therapy) failed to show a mortality benefit.^[9] Nevertheless, metoprolol is currently the most commonly prescribed beta-blocker used for the management of post-infarction patients.]

The trials with timolol, propranolol and metoprolol were appropriately regarded as landmark studies when they were carried out 20 years ago. However, when considered from the perspective of modern-day clinical trial design and interpretation, these studies have important limitations.

- High risk patients were generally not enrolled in these studies, including those with heart failure prior to randomization or with a systolic blood pressure < 100 mm Hg.
- Many currently available treatments for the *immediate* management of the post-infarction patient (e.g., ACE inhibitors, intravenous nitroglycerin and intravenous heparin, and thrombolytics) were not available or were not generally used.
- Patients receiving appropriate treatments for the *long-term* management of the post-infarction patient (e.g., ACE inhibitors, aspirin, anticoagulants and lipid lowering drugs) were not allowed in the trials to minimize the likelihood that

these concomitant treatments might diminish the ability to detect a benefit of beta-blockade.

- The trials frequently did not have clearly defined primary endpoints or had multiple primary endpoints that were each evaluated at $\alpha=0.05$. In addition and perhaps more importantly, data on the occurrence of non-fatal events (and sometimes fatal events) were frequently not collected in patients who discontinued treatment with the study drug.

Hence, it is not clear how the results of these landmark trials should be applied to the modern era, especially in the management of high-risk patients.

2.2. Current Utilization of Beta-Blockers in Post-Infarction Patients

About half of eligible patients who have experienced an acute myocardial infarction do not receive long-term treatment with a beta-blocker.[12-14] Physicians are particularly reluctant to prescribe beta-blockers in patients who have depressed left ventricular systolic function or heart failure following their infarction,[15] even though in post hoc analyses such patients appear to benefit from long-term beta-blockade as well as (if not more than) patients with minimal hemodynamic or clinical impairment.[8]

Four factors may contribute to the low utilization of beta-blockers in these patients:

1. The benefits of beta-blockers in post-infarction patients were observed in trials that were conducted before the advent of ACE inhibitors, thrombolytics or intravenous nitroglycerin and heparin and largely without the use of aspirin, anticoagulants or lipid lowering drugs. Hence, it is unclear whether beta-blockers would be effective when added to other treatments that are known to attenuate the magnitude of cardiac necrosis, reduce the degree of cardiac remodeling, decrease the risk of reinfarction, and minimize the adverse effects of neurohormonal activation.

Indeed, ACE inhibitors have become the neurohormonal antagonist of choice in the post-infarction patient with left ventricular dysfunction, effectively replacing the use of beta-blockers. This is despite the fact that, in trials demonstrating the efficacy of ACE inhibitors in post-infarction patients, ACE inhibitors were added to beta-blockers in patients who were receiving them. Furthermore, post hoc analyses of these trials have indicated that beta-blockers added independently to the survival benefits seen in these studies.[16]

2. The benefits of beta-blockers in post-infarction patients with heart failure have been observed only in subgroup analyses of randomized controlled trials which recorded few events.[8] No trial has been prospectively designed to evaluate the effects of beta-blockers in patients with impaired left ventricular function following an acute myocardial infarction.
3. Physicians remain concerned about the cardiodepressant actions of beta-blockers, particularly in patients with impaired cardiac function. Post-infarction patients with a history of heart failure are at increased risk of worsening heart failure following initiation of beta-blocker therapy.⁸
4. Because of the lack of patent protection, no pharmaceutical company promotes the use of beta-blockers for the post-infarction patient, whereas physicians are educated widely and extensively about the use of ACE inhibitors (and angiotensin II antagonists) in these patients.

For all of these reasons, beta-blockers are used infrequently in the management of post-infarction patients with left ventricular dysfunction,[15] even though treatment with a beta-blocker is very likely to be indicated in these patients once the acute phase of the infarction has passed and symptoms of heart failure have developed.

The current clinical climate is further complicated by the fact that different beta-blockers are approved for use at different times during the course of illness in a single patient. A patient may receive propranolol, atenolol or timolol following an acute myocardial infarction, but it is not clear what should be done if the same patient subsequently develops symptoms of heart failure, since none of these drugs are approved for the treatment of patients with established heart failure, and all carry a contraindication about their use in such patients. The long-acting (but not the immediate-release) formulation of metoprolol is approved for the treatment of heart failure, but this formulation has not been evaluated in and is not approved for use in the post-infarction setting, and the only trial to evaluate the effects of long-term treatment with oral metoprolol in post-infarction patients (in the absence of early intravenous therapy with the drug) failed to show a mortality benefit.[9]

The CAPRICORN trial was carried out to address these issues. This large-scale study was specifically designed to evaluate the effects of beta-blockade with carvedilol in post-infarction patients who had left ventricular systolic dysfunction (ejection fraction $\leq 40\%$) and who were already receiving treatment with an ACE

inhibitor as well as other effective modern-day treatments for post-infarction patients. The original intent of the study was to evaluate the effects of carvedilol on all-cause mortality with the intent of detecting a $\geq 20\%$ reduction in the risk of death. It was hoped that a favorable result would lead to the approval of carvedilol for the management of the post-infarction patient, which would allow patients who were likely to require and receive the drug in the future the ability to receive it in the post-infarction period.

2.3. Effects of Carvedilol in Experimental Myocardial Infarction

Carvedilol is a nonselective β -blocker, with vasodilating properties attributable to antagonism of α 1-adrenoceptors. Carvedilol is more potent in blocking β 1- or β 2-adrenoceptors than α 1-adrenoceptors, and the drug is devoid of intrinsic sympathomimetic activity or any inhibitory action on α 2-adrenoceptors. The pharmacologic effects of carvedilol have been studied extensively in a variety of test systems (molecular, cellular and organ) *in vitro*, as well as in intact animal models *in vivo*.

Carvedilol has been shown to both reduce infarct size and mortality in a large number of studies of experimental myocardial infarction across several different species (Table 1). The observed effect is similar to that reported for other beta-blockers.

Table 1. Effect of Carvedilol in Experimental Myocardial Infarction

Reference	Experimental model	Species	Timing of therapy	Results with carvedilol
Smith <i>et al.</i> [17]	Ischemia (15 min) & reperfusion (4 hr)	Rat	Pre+post	47% ↓ in infarct size
	Permanent occlusion (24 hr)		Pre+Post	55% ↓ in mortality
Ma <i>et al.</i> [18]	Ischemia (60 min) & reperfusion (60 min)	Rabbit	Pre	65% ↓ in infarct size
Yue <i>et al.</i> [19]	Ischemia (30 min) & reperfusion (4 hr)	Rabbit	Post	72% ↓ in infarct size
Gao <i>et al.</i> [20]	Ischemia (60 min) & reperfusion (3 hr)	Rabbit	Post	54% ↓ in infarct size
Feuerstein <i>et al.</i> [21]	Ischemia (60 min) & reperfusion (3 hr)	Rabbit	Post	63% ↓ in infarct size
Brunvand <i>et al.</i> [22]	Ischemia (40 min) & reperfusion (3 hr)	Cat	Pre	98% ↓ in infarct size
			Pre+Post	79% ↓ in infarct size

Brunvand <i>et al.</i> [23]	Ischemia (40 min) & reperfusion (3 hr)	Cat	Post	88% ↓ in infarct size
Hamburger <i>et al.</i> [24]	Ischemia (1hr) & reperfusion (24 hr)	Dog	Pre	78% ↓ in infarct size
Feuerstein <i>et al.</i> [25]	Permanent occlusion (6 hr)	Dog	Post	63% ↓ in infarct size
Bril <i>et al.</i> [26]	Ischemia (45 min) & reperfusion (4 hr)	Pig	Pre	90% ↓ in infarct size

Pre=drug given before occlusion; Post=drug given after occlusion

In addition, carvedilol has been shown in the experimental setting to:

- Reduce blood pressure in hypertensive animals[27]
- Suppress ventricular arrhythmias in ischemic hearts[22,23]
- Diminish cardiac work and myocardial oxygen demand in experimental infarction[21]
- Prevent cardiac hypertrophy in hypertensive rats[27]
- Retard cardiac remodeling after experimental infarction[28]
- Reduce the degree of post-ischemic myocardial contracture[29]
- Restore endothelium-dependent vascular relaxation in rabbits with myocardial ischemia[18]
- Inhibit the expression of adhesion molecules in experimental ischemia[30,31]
- Prevent apoptosis in the ischemic heart[19]
- Reduce the accumulation of leukocytes into ischemic myocardium[18]
- Prevent vascular medial hypertrophy in hypertensive rats[27]
- Inhibit vascular smooth muscle cell proliferation and migration *in vitro*[32]
- Retard neointimal formation following vascular injury[32]
- Prevent atherosclerosis in rabbits fed high cholesterol diet[33]
- Inhibit oxidation of LDL cholesterol,[30]
- Retard progression of renal disease in animals with renal impairment[34]
- Reduce mortality in experimental myocardial infarction and renal insufficiency[17,35]

The clinical significance of these experimental findings is unknown, but these effects are consistent with a benefit of carvedilol in patients with a recent myocardial infarction.

2.4. Prior Experience with Carvedilol in Patients With Left Ventricular Dysfunction Following an Acute Myocardial Infarction

Before the evaluation of carvedilol in the post-infarction setting, one trial (the ANZ trial [Australia-New Zealand Heart Failure study]) had specifically evaluated the effects of carvedilol in post-infarction patients with left ventricular dysfunction. In addition, two trials had evaluated the effects of carvedilol in a broad range of patients with left ventricular dysfunction, which included many patients who had a history of an acute myocardial infarction.

2.4.1. Australia-New Zealand Carvedilol Trial (ANZ)

This trial³⁶ enrolled 415 patients who had an ischemic cardiomyopathy (90% had experienced an acute myocardial infarction more than one month before entry) and were randomized to treatment with either placebo or carvedilol for 18-24 months. Participating patients had a left ventricular ejection fraction < 45% and included those with and without symptoms of heart failure; 85% were receiving concomitant therapy with an ACE inhibitor. Patients initially received carvedilol 3.125 BID and then were randomized to 6.25 mg BID or placebo with a gradual increase in dose to a target dose of 25 mg BID. At the end of follow-up, when compared with the placebo group, patients in the carvedilol group had a 29% lower risk of death (P=0.229) and a 28% lower combined risk of death and cardiovascular hospitalization (P=0.034). The reduction in mortality rate observed in carvedilol-treated patients became statistically significant when the actual time on trial medication was entered into the Cox model as an explanatory variable.^[37]

2.4.2. US Carvedilol Trial Program

This program^[38] of four concurrently run trials enrolled 1094 patients who had an ischemic or nonischemic cardiomyopathy (39% had experienced an acute myocardial infarction more than 3 months before entry) and were randomized to treatment with either placebo or carvedilol for an average of 7.5 months. Participating patients had a left ventricular ejection fraction < 35% and had primarily mild or moderate symptoms of heart failure; 95% were receiving concomitant therapy with an ACE inhibitor. Patients initially received carvedilol 6.25 mg BID or placebo with a gradual increase in dose to a target dose of 25-50 mg BID. At the end of follow-up, when compared with the placebo group, patients in the carvedilol group had a 65% lower risk of death (P=0.0001) and a 38% lower combined risk of death or cardiovascular hospitalization (P<0.001).

These effects were apparent and remained nominally significant even when the analysis was confined to patients with a history of an acute myocardial infarction (who had a 67% decrease in risk of death [P=0.004] and 36% decrease in risk of death or cardiovascular hospitalization [P=0.01] when treated with carvedilol).

2.4.3. COPERNICUS Trial

This trial[39] enrolled 2289 patients who had an ischemic or nonischemic cardiomyopathy (55% had experienced an acute myocardial infarction more than 2 months before entry) and were randomized to treatment with either placebo or carvedilol for an average of 10.5 months. Participating patients had a left ventricular ejection fraction < 25% and had severe symptoms of heart failure; 97% were receiving concomitant therapy with an ACE inhibitor. Patients initially received carvedilol 3.125 mg BID or placebo with a gradual increase in dose to a target dose of 25 mg BID. At the end of follow-up, when compared with the placebo group, patients in the carvedilol group had a 35% lower risk of death (P=0.00013) and a 27% lower combined risk of death or cardiovascular hospitalization (P=0.000023). These effects were apparent and remained nominally significant even when the analysis was confined to patients with a history of an acute myocardial infarction (who had a 34% lower risk of death [P=0.001] and 19% lower risk of death or cardiovascular hospitalization [P=0.006] when treated with carvedilol).

2.5. Current Labeling for Carvedilol

Based on the results of these and other trials, carvedilol is currently approved by the FDA for:

- For the treatment of essential hypertension, alone or in combination with other drugs.
- For the treatment of patients with mild, moderate or severe heart failure due to an ischemic or nonischemic cardiomyopathy, usually in addition to diuretics, ACE inhibitor and digitalis, to increase survival and also to reduce the risk of hospitalization.

Current labeling does not specifically mention how long following an acute myocardial infarction physicians should wait before being able to prescribe carvedilol effectively and safely for the treatment of heart failure.

2.6. Rationale for Carvedilol Post-Infarction Development

The combined data from the major clinical trials with carvedilol (section 1.4.) indicates that the administration of carvedilol to patients with left ventricular systolic dysfunction and a prior (> 1-3 month) history of myocardial infarction is associated with a reduction in the risk of death and cardiovascular events. However, the question remains as to whether carvedilol (like other beta-blockers) would be beneficial if administered at an earlier point in time in such patients.

Two trials were designed to specifically address this issue: (1) the CHAPS trial,[40] a single-center pilot study of carvedilol in patients who had experienced an acute myocardial infarction within 24 hours; and (2) the CAPRICORN trial,[41] a large-scale, multicenter trial of carvedilol in patients with left ventricular dysfunction who had experienced an acute myocardial infarction within 21 days.

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3. THE CHAPS TRIAL

3.1. Study Design

The CHAPS trial[40] was a single-center, randomized, double-blind, placebo-controlled study of carvedilol in patients with a recent acute myocardial infarction. This trial was intended to be a pilot study.

Patients with an acute myocardial infarction within 24 hours were enrolled at a single center (Northwick Park Hospital in the UK). All patients were to have experienced an acute myocardial infarction as evidenced by typical chest pain, electrocardiographic changes and an elevation of CK or CK-MB. Patients who had a history of cardiomyopathy or who had heart failure or cardiogenic shock complicating their acute infarction were not enrolled. Patients were allowed to have any other appropriate therapy for their acute infarction, including thrombolytic drugs and aspirin.

Patients were excluded from participation in the study if they had one of the following contraindication to long-term treatment with a beta-blocker: bradycardia (heart rate < 45 bpm), second or third degree block, systolic blood pressure < 90 mm Hg, peripheral vascular disease, obstructive airways disease, or insulin dependent diabetes mellitus. Patients were also not enrolled if they were being treated with a beta-blocker prior to randomization.

Patients fulfilling all entry criteria were randomly assigned in a double-blind manner to treatment with either placebo or carvedilol (in a 1:1 ratio) for 24 weeks. Randomization was stratified based on the site of infarction and the use/nonuse of thrombolytic drugs. The initial dose of the study medication was 2.5 mg of carvedilol or matching placebo infused intravenously over 15 minutes. Four hours later, patients received 6.25 mg BID, and the dose was increased 2 days later to 12.5 mg BID, and then 12 days later to 25 mg BID. Increments in dose were carried out only if the study medication was deemed to be well tolerated, but patients were increased to 25 mg BID only if their systolic blood pressure was > 120 mm Hg, their diastolic blood pressure was > 95 mm Hg and their heart rate was > 55 bpm (all three criteria needed to be fulfilled) while receiving 12.5 mg BID of the study drug. Once the dose of the study medication was determined (2 weeks following randomization), patients were to be maintained on placebo or carvedilol for an additional 22 weeks, at which time the study medication was discontinued. During this time, any cardiovascular drugs taken at the time of randomization could be continued, and patients were allowed to received any appropriate treatments, but the use of any new cardiovascular drug was deemed

an endpoint for the study and the study medication was discontinued following such use.

The primary endpoint of the study was the occurrence of an adverse cardiovascular event, defined as one of the following: cardiac death, heart failure, recurrent myocardial reinfarction or unstable angina, cerebrovascular accident, ventricular arrhythmia requiring a medical intervention, emergency coronary bypass surgery or percutaneous angioplasty, or the use of a new cardiovascular drug. This was the definition specified in the original protocol. The protocol also stated that the need for intravenous or sublingual nitrates or diuretics within 72 hours after the onset of pain or for the treatment of hypertension was not to be considered as a cardiovascular endpoint. The protocol-specified secondary endpoints included all-cause mortality, left ventricular ejection fraction and exercise tolerance.

According to the study protocol, all patients were to be followed until the occurrence of a cardiovascular endpoint or to the end of the planned study period (24 weeks), whether or not they continued receiving the study medication. Vital status was continually assessed in all patients as long as the study was in progress.

The planned sample size was 150 patients (75 in each treatment group) based on the following assumptions: 30% of the patients in the placebo group but only 10% of the patients in the carvedilol group would experience a cardiovascular endpoint during the 24 weeks following randomization, and the study would have 80% power (2-tailed) to detect a significant difference between the treatment groups ($\alpha=0.05$). The primary analysis was an intention-to-treat analysis that included all patients who had been randomized, were shown to have experienced an acute myocardial infarction (the primary entry criterion), and had received at least one dose of the study medication. Cumulative survival curves for the primary endpoint were constructed by Kaplan-Meier survivorship methods, and differences between the curves were tested for significance by both the log-rank statistic and a Cox proportional hazard regression model (with treatment as the only covariate).

3.2. Results

3.2.1. Patient Characteristics

A total of 151 patients were randomized into the CHAPS trial, 74 to the placebo group and 77 to the carvedilol group. One patient who was randomized to the placebo group was withdrawn from the trial before receiving any study

medication, because the patient was found to have a serum creatinine higher than the protocol-specified upper limit. Four patients (2 placebo, 2 carvedilol) were found not to have experienced a qualifying myocardial infarction and were withdrawn from the study (after having received ≤ 4 days of the study drugs). The remaining 146 patients (71 placebo and 75 carvedilol) comprised the intention-to-treat population for purposes of the primary analysis.

The baseline characteristics of these 146 patients are shown in Table 2. Patients presented with a typical acute myocardial infarction with preserved left ventricular function and were almost uniformly treated with thrombolytics, aspirin and heparin but not with ACE inhibitors or beta-blockers. The two treatment groups were generally similar with respect to their baseline characteristics, except that patients in the placebo group were more likely to have a history of hypertension whereas patients in the carvedilol group were more likely to be current smokers and have received diuretics for pulmonary congestion/heart failure during the index infarction, Table 2.

Table 2. CHAPS: Baseline Characteristics of Study Patients

	Placebo (n=71)	Carvedilol (n=75)
Age (years)	60	60
Sex (men/women)	60/11	63/12
History of hypertension	24%	9%
History of diabetes	18%	12%
History of hypercholesterolemia	1%	4%
Current smoker	34%	52%
History of MI before index MI	4%	3%
Site of index MI (% anterior)	51%	51%
Thrombolytic therapy for index MI	96%	99%
Aspirin therapy for index MI	100%	100%
IV heparin for index MI	96%	97%
Coronary vasodilators for index MI	78%	83%
ACE inhibitors for index MI	3%	4%
Thrombolytic therapy for index MI	96%	99%
Beta-blocker for index MI	3%	1%
Diuretics for heart failure post index MI	11%	25%
LV ejection fraction 48 hrs post randomization	51%	51%
Systolic BP (mm Hg)	130	130
Heart rate (beats/min)	82	80
Time from index MI to randomization (median)	17.0 hours	16.5 hours

All average values are medians. MI=myocardial infarction.

3.2.2. Conduct of the CHAPS Trial

Following randomization and uptitration, the most common dose of the study drug was 12.5 mg BID, which was received by 90% of the patients in the placebo group and 73% of the patients in the carvedilol group. This difference was likely related to the blood pressure lowering effects of carvedilol, which reduced the number of patients in this group who fulfilled criteria for uptitration to 25 mg BID (i.e., systolic blood pressure > 120 mm Hg, diastolic blood pressure > 95 mm Hg and heart rate > 55 bpm while receiving 12.5 mg BID; all three criteria needed to be fulfilled).

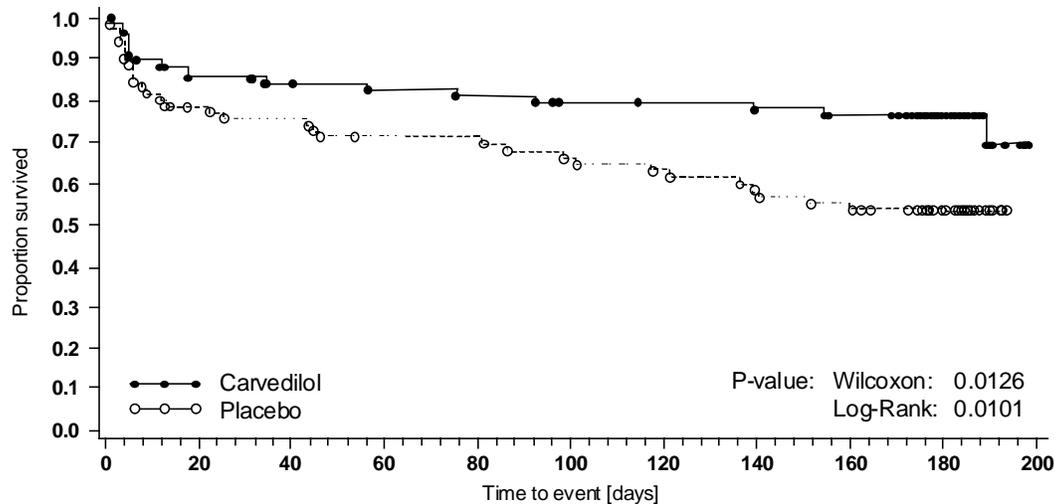
Of the 146 patients (71 placebo, 75 carvedilol) in the intention-to-treat analysis, only 87 patients (35 placebo and 52 carvedilol) continued to receive their study medication for 24 weeks. The most common reason for discontinuation of the study medication was the achievement of a primary endpoint. The designated reasons for withdrawal were death (3 placebo, 2 carvedilol); an adverse event (placebo 30, carvedilol 18); elective coronary bypass surgery (0 placebo, 1 carvedilol); or administrative reasons (3 placebo, 2 carvedilol).

The median duration of follow-up was 160 days in the placebo group and 178 days in the carvedilol group.

3.2.3. Primary Endpoint

The effect of carvedilol on the primary endpoint is shown in Figure 1. By the intention-to-treat analysis, a primary endpoint was achieved in 31 patients in the placebo group, but only 18 patients in the carvedilol. The difference in favor of carvedilol was significant, $P=0.01$ by log-rank and $P=0.0148$ by Cox model. The treatment effect was apparent within the first 2 weeks after randomization and was maintained during the double-blind treatment phase.

Figure 1. CHAPS: Time-to-First-Event Analysis of the Effect of Carvedilol on the Primary Endpoint



The specific reasons for achieving the primary endpoint are shown in Table 3. Carvedilol appeared to have its greatest effect on the recurrence of myocardial ischemic events, as evidenced by a lower frequency of reinfarction, unstable angina or emergent revascularization in the carvedilol group than in the placebo group (16 events vs 7 events).

Table 3. CHAPS: Patients Achieving a Primary Endpoint

	Placebo (n=71)	Carvedilol (n=75)
Cardiac death	3	2
Heart failure	5	5
Recurrent myocardial infarction	8	4
Unstable angina	6	3
Stroke	1	0
Emergent CABG or PTCA	2	0
Ventricular arrhythmia requiring IV treatment	1	0
New cardiovascular therapy	5	4
Total number of patients	31	18

The new cardiovascular therapies used in the placebo group were an ACE inhibitor (for hypertension, n=1), diltiazem (for stable angina, n=3) and captopril (for a low ejection fraction, n=1). The new cardiovascular therapies used in the carvedilol group were diltiazem and atenolol (for stable angina, n=1), a calcium antagonist (for stable angina, n=1), captopril (for worsening heart failure, n=1), and elective coronary artery bypass (n=1).

Several observations provide additional support for a favorable effect of carvedilol in this study:

1. Although the intention-to-treat analysis conducted by the principal investigator was based on 146 patients, 151 patients were randomized into the study. Available follow-up information in the 5 randomized patients excluded from the intention-to-treat analysis indicates that one patient in the placebo group experienced a ventricular arrhythmia 152 days later, and one patient in the carvedilol group experienced unstable angina 146 days later. If these patients are included in the analysis (even though they received the study drugs for ≤ 4 days), a favorable effect of carvedilol on the primary endpoint was still apparent (Cox model $P = 0.0143$; log rank $P = 0.0103$).
2. The events that defined the primary endpoint included those of unquestionable clinical importance (e.g., death, myocardial infarction, unstable angina, stroke) and those whose clinical importance can be debated (e.g., use of a new cardiovascular drug or revascularization). If the observed between-group difference were related primarily to a difference in frequency of occurrence of these “soft” endpoints, the clinical importance of the primary finding would be greatly diminished. Yet, when the use of a new cardiovascular drug or revascularization were excluded as components of the primary endpoint, the effect of carvedilol remained significant, with 24 events on placebo compared with 14 events on carvedilol ($P < 0.03$).^[40]
3. The CHAPS study enrolled patients with or without left ventricular systolic dysfunction, but a patient cohort of interest (given the purpose of this Briefing Document) is the group with a left ventricular ejection fraction $< 45\%$ at baseline. Although this was not a predefined subgroup, it is noteworthy that serious cardiac events (death, reinfarction, unstable angina, heart failure and ventricular tachycardia) were less common in the carvedilol group than in the placebo group (5 vs 13 events), $P = 0.04$, in this cohort with depressed cardiac function.^[40]

3.2.4. Secondary Endpoints

Six patients (four in the placebo group, two in the carvedilol group) died during the intended 24-week follow-up period.

The causes of death in the placebo group were reinfarction (in 2 patients) and asystole (in 2 patients, one of which was probably related to ventricular rupture). The four deaths occurred 1, 3, 26 and 56 days after randomization.

The causes of death in the carvedilol group were electromechanical dissociation (in 1 patient) and asystole (in 1 patient). The two deaths occurred 2 and 78 days after randomization.

Overall, there was no difference in ejection fraction or exercise tolerance between the two treatment groups. However, in the patients with a depressed ejection fraction at baseline ($< 45\%$), the ejection fraction at 3 months increased from 35% to 39% in the carvedilol group but from 32% to 34% in the placebo group (between-group $P=0.06$). After 3 months, the left ventricular end-systolic and end-diastolic volumes had increased in the placebo group and had decreased in the carvedilol group, both between-group $P < 0.01$.^[40]

3.2.5. Changes in Physiological Variables

3.2.5.1. Vital Signs and Body Weight

As expected from the drug's β -blocking actions, heart rates were lower in the carvedilol group than in the placebo group at all visits ($P < 0.001$). At the end of the uptitration period, heart rate declined by 12 beats/min in the carvedilol group but increased by 7 beats/min in the placebo group. Both systolic and diastolic blood pressures were also lower in the carvedilol group than in the placebo group at all visits ($P = 0.005$). These between-group differences in heart rate and systolic blood pressure were also apparent during exercise.

3.2.5.2. Laboratory Values

There were no clinically significant effects of carvedilol on any of the routine hematological or biochemical variables measured in the study.

3.2.6. Safety

3.2.6.1. Adverse Events

Because withdrawals from study medication were more frequent and earlier in the placebo group than in the carvedilol group, patients were treated longer with carvedilol than placebo. This should have led to an increase in the risk of reported adverse events in the carvedilol group (since adverse reactions were

recorded only during drug treatment (± 14 days). However, the proportion of patients who reported at least one adverse event was somewhat lower in the carvedilol group than in the placebo group (57% vs 67%). A time to event analysis of the occurrence of any adverse event is shown in Figure 2. The proportion of patients who reported at least one cardiovascular event was also somewhat lower in the carvedilol group than in the placebo group (44% vs 62%). A time to event analysis of the occurrence of any adverse cardiovascular event is shown in Figure 3.

Figure 2. CHAPS: Time-to-First-Event Analysis of the Occurrence of Any Adverse Event During the First Six Months Following Randomization

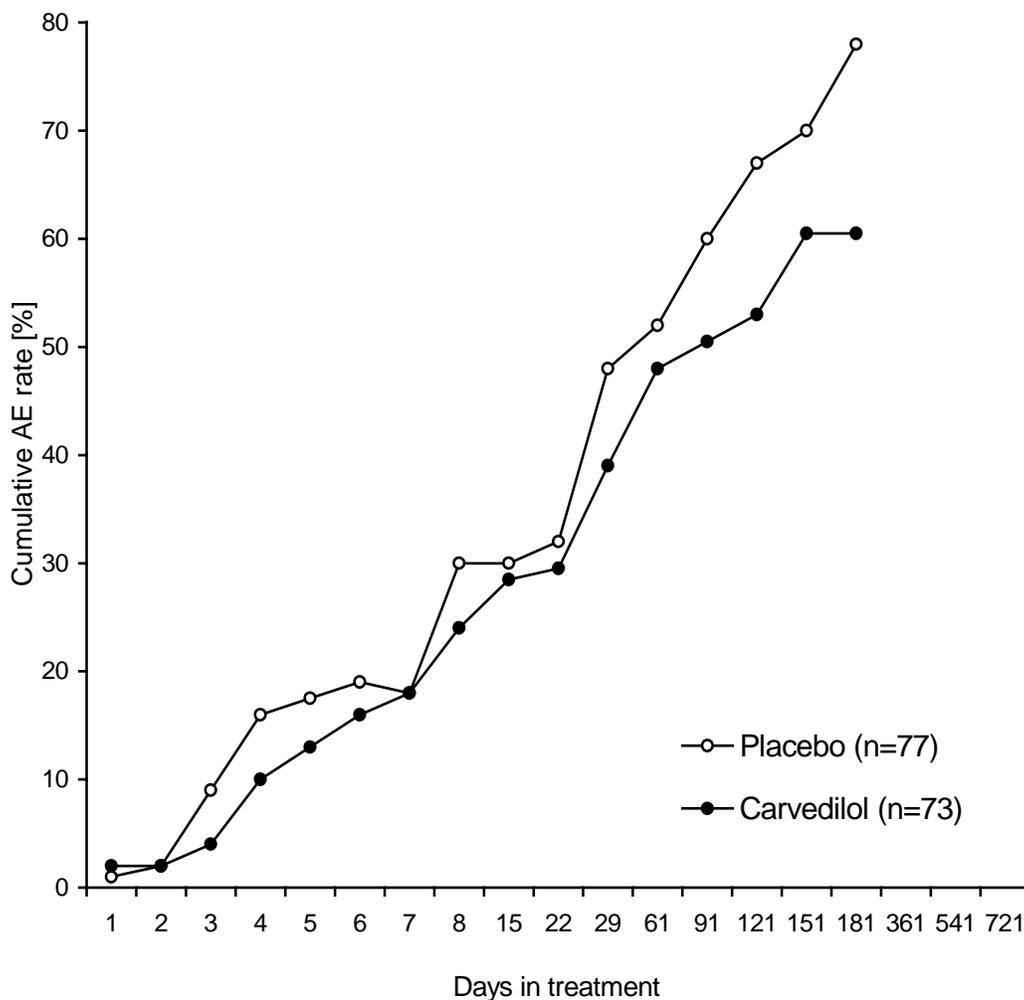
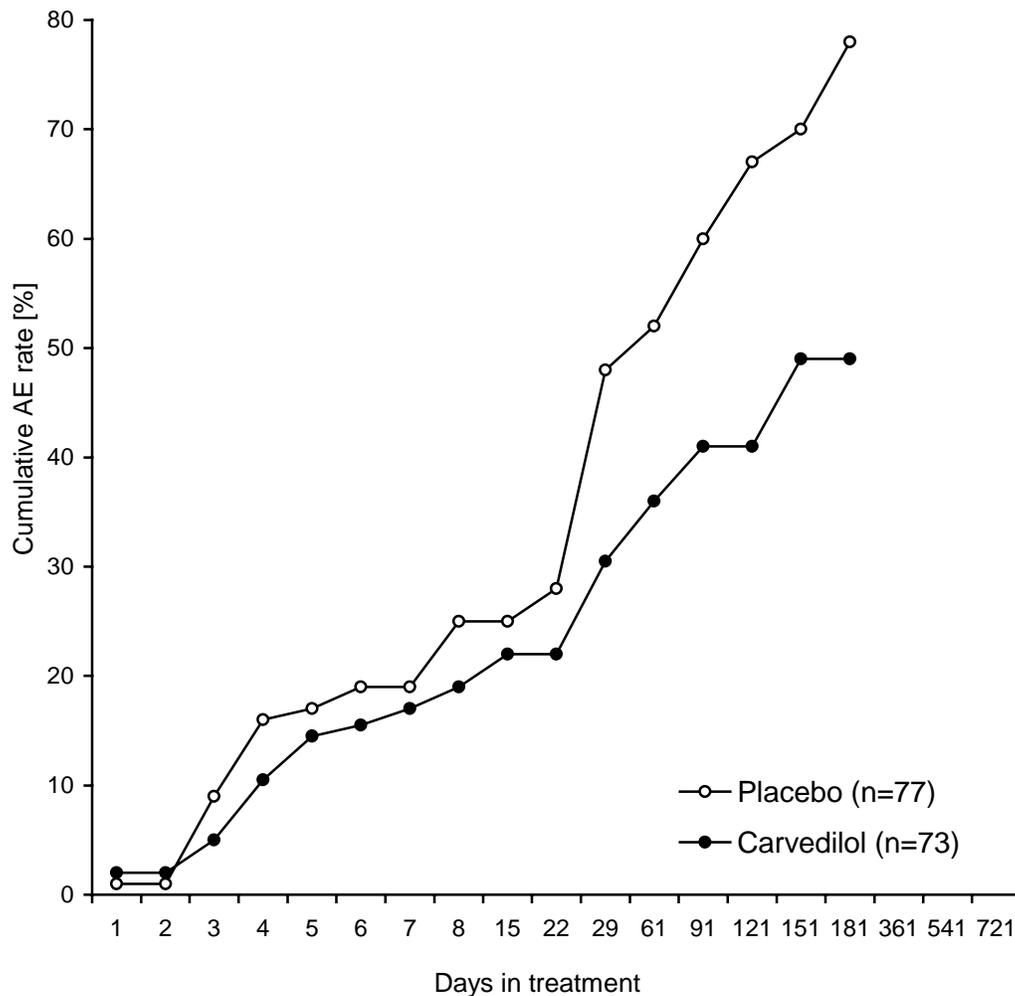


Figure 3. CHAPS: Time-to-First-Event Analysis of the Occurrence of Any Cardiovascular Adverse Event During the First Six Months Following Randomization



A listing of all cardiovascular adverse events is shown in Table 4. Patients in the carvedilol group were more likely to experience adverse events previously associated with drugs that block alpha or beta-adrenergic receptors (e.g., hypotension, dizziness, bradycardia and peripheral vascular disorder) and were less likely to experience adverse events reflecting worsening of the underlying disease (e.g., myocardial infarction or unstable angina, ventricular tachycardia and fibrillation). In addition, reports of hypertension as an adverse event were less frequent in the carvedilol group.

Table 4. CHAPS: Patients with Any Cardiovascular Adverse Event

	Placebo (n=73)	Carvedilol (n=77)
Angina pectoris/chest pain	10 (13.7%)	10 (13.0%)
Heart failure	6 (8.2%)	8 (10.4%)
Dizziness	1 (1.4%)	5 (6.5%)
Myocardial infarction	9 (12.3%)	4 (5.2%)
Unstable angina	6 (8.2%)	3 (3.9%)
Atrial fibrillation	1 (1.4%)	2 (2.6%)
Heart arrest	1 (1.4%)	2 (2.6%)
Ventricular arrhythmia	2 (2.7%)	2 (2.6%)
Headache	2 (2.7%)	2 (2.6%)
Asthenia	1 (1.4%)	2 (2.6%)
Bradycardia	--	2 (2.6%)
Hypotension	--	2 (2.6%)
Hypertension	6 (8.2%)	1 (1.3%)
Pericardial effusion	1 (1.4%)	1 (1.3%)
Peripheral vascular disorder	--	1 (1.3%)
Bigeminy	3 (4.1%)	--
ST depression	2 (2.7%)	--
Ventricular fibrillation	2 (2.7%)	--
Atrial flutter	1 (1.4%)	--
Bundle branch block	1 (1.4%)	--
Cerebrovascular accident	1 (1.4%)	--
Coronary artery disorder	1 (1.4%)	--
Thrombosis	1 (1.4%)	--
Ventricular tachycardia	1 (1.4%)	--

The number of patients in the analyses of safety include all patients who receive the study medication. Noncardiovascular adverse experiences occurring in only one patient each are not included in this table.

3.2.6.2. Adverse Events Leading to Withdrawal

A listing of all adverse events leading to withdrawal of the study drug is shown in Table 5. Patients in the placebo group were more likely to experience such an event than patients in the carvedilol group.

Table 5. CHAPS: Adverse Events Leading to Discontinuation of the Study Drug

	Placebo (n=71)	Carvedilol (n=75)
Heart failure	5	4
Both heart failure and angina	0	1
Angina	4	2
Recurrent myocardial infarction	6	4
Recurrent infarction and ventricular fibrillation	2	0
Unstable angina	5	3
Coronary revascularization	2	0
Stroke	1	0
Ventricular arrhythmia	1	0
Dizziness	1	1
Asthenia	0	1
Headache	1	0
Headache and dizziness	0	1
Postural hypotension	0	1
Hypertension	2	0
Total number of patients	30	18

3.3. Summary

The CHAPS Trial was a pilot trial to evaluate the efficacy and safety of early treatment with carvedilol in patients with an evolving acute myocardial infarction. The risk of a protocol-defined major cardiovascular event was lower in patients treated with carvedilol as compared to those treated with placebo. This difference in risk was primarily the result of a lower frequency of myocardial ischemic events (especially those leading to a lethal arrhythmia) in the carvedilol group. Carvedilol was well tolerated in the trial.

The results of the CHAPS Trial, although encouraging, need to be interpreted cautiously. The trial was small and observed relatively few major cardiovascular events. Furthermore, a large proportion of randomized patients did not continue double-blind treatment for the planned duration of the trial because of a protocol requirement that patients achieving a primary endpoint were to stop treatment with the study medication.

Therefore, the CHAPS trial should be primarily viewed as a study that (1) supports the ability of carvedilol to reduce the risk of death, reinfarction and life-

threatening arrhythmias in post-infarction patients, and (2) demonstrates the tolerability of carvedilol in the immediate post-infarction setting.

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4. THE CAPRICORN TRIAL

4.1. Study Design

The CAPRICORN trial[41] was a large multicenter randomized placebo-controlled study of carvedilol in patients with left ventricular systolic dysfunction following a recent acute myocardial infarction.

4.1.1. Original Trial Design

Patients with left ventricular systolic dysfunction within 21 days following an acute myocardial infarction were enrolled at 163 centers in 17 countries. All patients fulfilled two of the following three criteria for an acute myocardial infarction, i.e., ischemic chest pain or pulmonary edema; evolving pathological Q waves or ST segment elevation; or cardiac enzymes > 2 times the upper limit of normal. In addition, all patients had an ejection fraction $\leq 40\%$ (or a wall motion index ≤ 1.3) and were receiving an ACE inhibitor at the time of entry into the study. Patients who had had pulmonary edema or cardiogenic shock during their index infarction were not excluded from participation. Most patients (95%) had not been taking an ACE inhibitor prior to their index infarction and were initiated on an ACE inhibitor for the management of post-infarction left ventricular systolic dysfunction at least 48 hours before entry into the trial.

Patients were excluded from participation in the study if they had an indication or a contraindication to long-term treatment with a beta-blocker. Hence, patients were not enrolled if they had unstable angina; uncontrolled ventricular arrhythmias; a history of sick sinus syndrome (unless a pacemaker was in place); second or third degree heart block; systolic blood pressure < 90 mm Hg or uncontrolled hypertension; heart rate < 60 beats/min; were receiving intermittent or continuous intravenous inotropic therapy; had ongoing cardiogenic shock; or had unstable diabetes mellitus or chronic obstructive pulmonary disease requiring treatment with bronchodilators or steroids.

Patients fulfilling all entry criteria were randomly assigned in a double-blind manner to long-term treatment with either placebo or carvedilol (in a 1:1 ratio). The initial dose of the study medication was 6.25 mg BID, and the dose was increased rapidly every 3-10 days until a target dose of 25 mg BID was achieved (if tolerated). Patients were maintained on the highest tolerated dose of the study medication (in addition to other appropriate medications) for the duration of follow-up, which was to continue until a prespecified number of major clinical

events had occurred. During this time, patients were seen as an outpatient every 3-4 months. If side effects occurred that were thought to be drug-related, the dose of carvedilol or placebo could be reduced or temporarily discontinued, but investigators were encouraged to reinstitute partial or full doses of the study drug at a later time. Doses of all concomitant drugs could be adjusted at the discretion of the investigator. If the patient's condition deteriorated during the study, the investigator could utilize any interventions that were clinically indicated; however, investigators were instructed not to institute open-label treatment with a β -blocker.

Originally, the primary endpoint of the study was the evaluation of the effect of carvedilol on all-cause mortality. In addition, the original protocol specified three secondary endpoints: (1) the combined risk of all-cause mortality or cardiovascular hospitalization; (2) progression of heart failure, later clarified (by protocol amendment) to refer to hospitalization for heart failure; and (3) sudden death. Only adjudicated hospitalizations > 24 hours' duration which took place following discharge from the hospital for the qualifying myocardial infarction were included in these analyses. Hospitalizations were included whether or not they had occurred while patients were receiving the study medication or were fully in compliance with study procedures.

The sample size for the study was estimated based on the following assumptions: the 21-month mortality in the placebo group would be 29%; the risk of death would be altered by 20% as a result of treatment with carvedilol; and the study would have 90% power (two-tailed) to detect a significant difference between the treatment groups ($\alpha=0.05$). Because it was recognized that a priori estimates of the event rate might be too low, the study protocol specified that the trial would continue until 630 deaths had occurred with a minimum follow-up of 12 months (to allow for the effects of carvedilol to become apparent). However, this number of events did not allow for any dilutional effect created by patients who discontinued the study medication or were treated with open-label beta-blocker. All of the alpha ($\alpha=0.05$) was originally assigned to a single primary endpoint of all-cause mortality.

A comparison of time to event between the carvedilol and placebo treatment groups was performed using a log-rank test. Hazard ratios and associated 95% confidence intervals were computed from a Cox proportional hazard analysis with a model including an effect for treatment group. Cumulative survival estimates are displayed graphically using Kaplan-Meier estimates. These analyses were performed on all randomized patients and duration was defined as time from

randomization to time of the first event. Patients without an event were censored at the end of the trial. For the analysis of mortality, patients who underwent a cardiac transplant were censored from the date of transplantation.

4.1.2. Revision of Trial Following Recommendations of the DSMB

Enrollment in the CAPRICORN Trial began on June 10, 1997. In March 1999, the Data and Safety Monitoring Board (DSMB) notified the Executive Steering Committee that it was recommending a change in the protocol based primarily on considerations triggered by events *outside the conduct* of the CAPRICORN trial; the DSMB had not carried out any interim analysis of the data by treatment. The original protocol for the CAPRICORN trial had strongly discouraged the use of open-label therapy with a beta-blocker. However, public announcements in late 1998 and early 1999 that beta-blockers had been found to prolong life in two large-scale trials (CIBIS II[42] and MERIT-HF[43]) that enrolled patients with mild-to-moderate heart failure raised ethical concerns about the protocol-stated policy of withholding treatment with a beta-blocker until the completion of the study. The DSMB believed that patients who developed heart failure during the course of the CAPRICORN trial should be allowed to be treated with a beta-blocker (according to the judgment of the investigator), even though it fully recognized that implementation of such a liberalized policy would markedly impair the ability of the trial to find a favorable effect of carvedilol on the original prespecified primary endpoint.

The DSMB understood that, once the protocol was modified in accordance with its recommendations, the trial might be unlikely to achieve its primary objective. In March 1999, recruitment of patients into the study was behind schedule, and the mortality rate in the trial was lower than originally anticipated. These characteristics would not, in and of themselves, have jeopardized the trial; under normal circumstances, a lower recruitment rate and lower event rate would have simply meant that the trial would have continued for a longer time to have achieved the prespecified number of deaths. However, in the face of a DSMB recommendation to allow open-label therapy with beta-blockers, it was understood that the longer the trial, the higher the likelihood of open-label treatment with a beta-blocker. As a result, prolonging the trial might not result in an increase in statistical power, because any expected increase in power that might result from accruing a higher number of fatal events by prolonging the trial would be neutralized by a decrease in power related to progressive increase in open-label beta-blocker use in patients assigned to placebo and the resultant dilutional effect on any difference in mortality effect between the two groups.

Thus, it was felt that the best approach would be to complete the trial as rapidly as possible, but at the time of the DSMB deliberations, the number of deaths was deemed to be too small to allow for an adequate assessment of the effects of carvedilol on mortality in post-infarction patients. As a result, the DSMB recommended that the Executive Steering Committee change the primary endpoint to one that would allow for sufficient statistical power to detect some effect of active therapy. This recommendation was made prior to having carried out any analysis of any efficacy measures in the trial.

After considering the recommendations of the DSMB, the Executive Steering Committee made the following changes in the study, which were incorporated into a protocol amendment, dated July 27, 1999, which was submitted to FDA on August 16, 1999 (Serial No. 620) (Table 6):

- Patients who developed heart failure during the CAPRICORN trial were allowed (and the investigators were made aware of the ethical need for them) to receive open-label treatment with a beta-blocker. Before doing so, however, the amendment specified that patients had to be withdrawn from treatment with the study medication.
- A new primary endpoint (i.e., all-cause mortality or hospitalization for a cardiovascular reason) was added as a co-primary endpoint. Of the studywise alpha of 0.05, 0.045 would be allocated to this new endpoint and 0.005 would be allocated to the original (and retained) primary endpoint of all-cause mortality. The combined risk of all-cause mortality or cardiovascular hospitalization was added as a co-primary endpoint for two reasons: (1) All-cause mortality or hospitalization for a cardiovascular hospitalization had been the first-listed secondary endpoint in the original protocol; and (2) Statistical calculations indicated that about 630 events could be reached rather rapidly if either death or any cardiovascular hospitalization were to count as “events”.

[It should be noted that the Steering Committee considered the possibility of demoting all-cause mortality to the status of a secondary endpoint (with an $\alpha=0.05$) but rejected this option since doing so would have meant abandoning the original intent of the trial (i.e., to evaluate the effect of carvedilol on all-cause mortality).]

- The principles guiding the termination of the study were modified so that the trial would continue until a total of 633 deaths or cardiovascular

hospitalizations had occurred. This number would allow for the detection of a 23% reduction in the combined risk of death or cardiovascular hospitalization. This was done despite the fact that the effect of beta-blocker therapy on the combined endpoint of death or cardiovascular hospitalization had not been previously evaluated in earlier post-infarction trials and was therefore unknown. The potential for a dilutional effect due to the use of open-label beta-blockers was incorporated into the calculation of a revised sample size, but only to a limited degree, i.e., the projected total of 633 fatal non-fatal events would provide 90% power to evaluate a 23% reduction in risk only if $\leq 10\%$ of patients received open-label therapy with a beta-blocker. No consideration was given to the possible dilutional effect of study drug discontinuations. Given the revised target of 633 target events, it was recognized that it would not be necessary to recruit the 2600 patients specified in the original protocol, and instead, it was expected that 1850 patients would be recruited at the time that 633 events had occurred.

- To expedite closure of the study, the minimum duration of follow-up was reduced from 12 months to 3 months — even though it was understood that such a change might not allow for the full effects of carvedilol to be seen in patients recruited in the final months of the study.

Table 6. Comparison of Original and Revised CAPRICORN Statistical Plans Following Amendment of July 27, 1999

	Original Protocol	Amended Protocol
Projected number of patients	2600	1850
Use of open-label beta-blockers	Strongly discouraged	Allowed
Primary endpoint(s)	All-cause mortality	All-cause mortality; all-cause mortality or CV hospitalization
Assignment of alpha	0.05 to all-cause mortality	0.005 to all-cause mortality; 0.045 for death or CV hospitalization
Secondary endpoints	<ol style="list-style-type: none"> 1. All-cause mortality or CV hospitalization 2. Sudden death 3. Progression of heart failure 	<ol style="list-style-type: none"> 1. Sudden death 2. Hospitalization for heart failure
Target number of events	630 deaths	633 fatal or non-fatal events
Anticipated treatment effect	20%	23%
Minimum duration of follow-up	12 months	3 months
Anticipated frequency of use of open-label beta-blockers over duration of the study	0%	10%

CV=cardiovascular

Because of the changes made in the July 27, 1999 amendment, the CAPRICORN achieved its new target of 633 fatal and non-fatal events in February 2000, and patients began their final study visits for study close-out in March, 2000. Although the original protocol had specified the possibility of four interim analyses by the DSMB, only one interim analysis took place, and this occurred in August, 1999, one month following the protocol amendment that changed the primary endpoint. (There were no interim analyses before the protocol amendment.)

Before the end of the study and prior to the lock of the database, the Executive Steering Committee recognized that cardiovascular hospitalizations had now been used to define the co-primary endpoint even though there had been no pre-specified definition in the original protocol of what was meant by a “cardiovascular hospitalization”. For example, prior to the amendment, the Endpoint Committee had not adjudicated hospitalizations that were considered

“noncardiovascular”; yet, some hospitalizations classified as noncardiovascular were related to or complicated by worsening heart failure. To address this issue, the Endpoint Committee reviewed and reclassified all hospitalizations in a blinded manner. No further modifications of the definition of cardiovascular hospitalization were formally adopted before the lock of the database.

To elucidate specific reasons for a cardiovascular hospitalization due to a rhythm disturbance, further analyses of the cause of hospitalization were carried out in an exploratory manner after the lock of the database and the blind was broken. This was carried out only on definitive or presumed cardiovascular hospitalizations that qualified as events in the analysis of the primary endpoint. The case record forms of such patients were reviewed and an ascertainment of the cause of admission was carried out without knowledge of the treatment assignment.

In addition to the assessing the effect of treatment in all patients, the statistical plan (finalized before the code break) specified that the effect of carvedilol on the two co-primary endpoints was to be assessed in the following subgroups:

- Age (< 70 versus \geq 70 years)
- Gender
- Race
- Ejection fraction (< 20%, 20%-30%, 30%-40%, > 40%)
- History of heart failure (past/ongoing versus none)
- Killip class at screening (I/II/III/IV)
- Previous myocardial infarction (yes/no)
- History of diabetes (past/ongoing versus none)
- History of angina (past/ongoing versus none)
- History of hypertension (past/ongoing versus none)
- Use of diuretic prior to randomization (yes/no)
- Primary coronary angioplasty performed (yes/no)
- Country (US / non US; Russia / outside of Russia)
- Use of thrombolytic treatment during index infarction (yes/no)
- Diastolic blood pressure at baseline (\leq or > 90 mm Hg)
- Heart rate at baseline (\leq or > 70 beats/min)
- Site of index myocardial infarction (anterior/inferior/other)
- Dose level at start of maintenance (3.125/6.25/12.5/25 mg BID)

All of these proposed subgroups were based on characteristics of the patients at baseline, except for the analysis based on the dose level at the start of the maintenance period (which was based on a post-randomization event and thus is not summarized in this document).

4.2. Results

4.2.1. Patient Characteristics

A total of 1959 patients were randomized into the CAPRICORN trial, 984 to the placebo group and 975 to the carvedilol group. The two groups were similar with respect to their baseline characteristics, Table 7. Approximately 80% of the patients were still hospitalized at the time of randomization.

Table 7. CAPRICORN: Baseline Characteristics of Study Patients

	Placebo (n=984)	Carvedilol (n=975)
Age (years)	63	63
Sex (% men)	74%	73%
History of MI before index MI	29%	31%
ACE inhibitor use before index MI	7%	9%
β -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%
\uparrow Cardiac enzymes during index MI	85%	84%
IV β -blocker for index MI	10%	11%
Oral β -blocker for index MI	32%	31%
IV or other nitrate for index MI	73%	73%
IV heparin for index MI	65%	63%
Thrombolytic therapy for index MI	37%	36%
Primary coronary angioplasty for index MI	13%	12%
ACE inhibitor use before randomization	97%	98%
β -Blocker use before randomization	35%	33%
Aspirin use before randomization	85%	85%
Use of lipid lowering drugs before randomization	24%	22%
Use of heparins before randomization	21%	20%
Heart failure prior to randomization	47%	48%
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	10.0 (range 1-30)	10.0 (range 1-28)

MI=myocardial infarction; ACE=angiotensin converting enzyme inhibitor; IV=intravenous.

The baseline characteristics of the patients in this trial are distinguished from those in earlier beta-blocker trials in that the patients in the CAPRICORN trial were more likely to have heart failure (nearly half had heart failure prior to randomization and pulmonary edema was recorded as the primary presenting symptom for the index myocardial infarction in nearly 20%). In contrast, only 15-20% of patients in earlier beta-blocker trials had heart failure and none were Killip class III or IV at the time of entry into the trials. (Some of these earlier trials also excluded Killip class II patients.) Furthermore, a large number of patients in the current trial had received treatment with an intravenous or other nitrate, intravenous heparin, a thrombolytic agent, an ACE inhibitor, aspirin or a lipid lowering drug. None of these current treatments for the post-infarction patient was available or were allowed when earlier beta-blocker trials were performed.

Although 30% of the patients had experienced a prior myocardial infarction, it is of interest that only 3% had been taking a beta-blocker and only 7-9% had been taking an ACE inhibitor before their qualifying myocardial infarction. Both observations suggests that many patients — even those cared for at major medical centers — do not receive appropriate treatment following an acute myocardial infarction. In addition, the low pre-infarction utilization of ACE inhibitors suggests the heart failure condition (which was present in nearly half of the patients before randomization) had generally been of short duration and was related to the recent necrotic loss of myocardium.

It should be noted that — although some patients were randomized and received their study medication one day following their qualifying infarction — patients generally were initiated on treatment with placebo or carvedilol more than one week following their qualifying event. Hence, this trial was not an evaluation of carvedilol for the immediate treatment of an evolving myocardial infarction (as was CHAPS) but was an evaluation of the drug in the early management of post-infarction survivors who had heart failure or were at high risk of developing heart failure.

4.2.2. Conduct of the CAPRICORN Trial

Ten patients who were randomized (placebo 4, carvedilol 6) were withdrawn from the trial before receiving any study medication, but were nevertheless included in all analyses (according to the intention-to-treat principle).

Following randomization and uptitration, 84.4% of the patients had received target doses of placebo and 78.0% had received target doses of carvedilol within the first 12 weeks, and these doses were generally maintained until the end of the study. The duration of follow-up ranged from 3 to 33 months (mean 15 months).

Of the 1959 randomized patients, 468 patients [24%] (placebo 231, carvedilol 237) were reported to have permanently discontinued treatment with the study medication. Whether or not patients continued or stopped the study medication, the vital status and hospitalization status of all patients (except for 4 assigned to carvedilol and 2 assigned to placebo) were ascertained at the end of the trial.

A total of 236 patients (12%) received open-label treatment with a beta-blocker during the course of the study. This occurred more frequently in patients randomized to placebo than to carvedilol (145 vs 91 patients, respectively). In addition, when beta-blockers were used, they were used earlier in the placebo group (269 days vs 329 days post-randomization) and for a longer period of time (150 days vs 109 days).

At some point in the study, 12 patients in the placebo group were incorrectly dispensed bottles containing carvedilol for varying lengths of time. In this group of patients there were three cardiovascular hospitalizations and one death. In addition, 18 patients in the carvedilol group were incorrectly dispensed bottles containing placebo for varying lengths of time. In this group of patients there were five cardiovascular hospitalizations and two deaths.

The study blind was broken by the sponsor or investigator in 30 patients (15 in the placebo group and 15 in the carvedilol group). Of these, 12 patients (7 placebo, 5 carvedilol) did not die or experience a cardiovascular hospitalization, and 12 patients (5 placebo, 7 carvedilol) were hospitalized for a cardiovascular reason before the code break. Hence, only 6 patients (3 placebo, 3 carvedilol) experienced a primary endpoint event after the study blind was broken.

4.2.3. Primary Endpoints

The effects of carvedilol on the two co-primary endpoints are shown in Table 8 and Figures 4 and 5. The results in Table 8 are based on all randomized patients, analyzed according to the intention-to-treat principle, with all events that occurred until the end of the trial included whether or not patients remained on their assigned treatment.

By intention-to-treat, there were 367 patients who died or had a cardiovascular hospitalization in the placebo group and 340 such patients in the carvedilol group; this difference reflected an 8% lower risk of a primary event, $P = 0.297$ (amendment-specified $\alpha=0.045$), Figure 4.

In addition, by intention-to-treat, there were 151 deaths in the placebo group and 116 deaths in the carvedilol group; this difference reflected a 23% decrease in the risk of death, $P = 0.031$ (amendment-specified $\alpha=0.005$), Figure 5. The annual placebo mortality rate in the placebo group was 12.1%, which was reduced to 9.8% by treatment with carvedilol.

**Table 8. Results of the CAPRICORN Trial (Co-Primary Endpoints)
[Primary Prespecified Analysis]**

	Placebo (n=984)	Carvedilol (n=975)	Hazard Ratio (95% CI)	P value
Death or CV hospitalization	367	340	0.92 (0.80-1.07)	0.297
All-cause mortality	151	116	0.77 (0.60-0.98)	0.031

All randomized patients, analyzed according to the intention-to-treat principle, with all events that occurred until the end of the trial included whether or not patients remained on their assigned treatment. CV= cardiovascular. CV hospitalizations include all CV admissions (as adjudicated by Endpoint Committee) except for those for a cardiovascular procedure. This is the definition specified in the CAPRICORN statistical plan. All analyses reflect hazard ratio of carvedilol:placebo with 95% confidence intervals. P values were derived from the log rank test. The α allocated by protocol amendment was 0.045 for death or CV hospitalization and 0.005 for all-cause mortality.

Figure 4. CAPRICORN: Time to First Event Analysis of the Effect of Carvedilol on Death or Cardiovascular Hospitalization

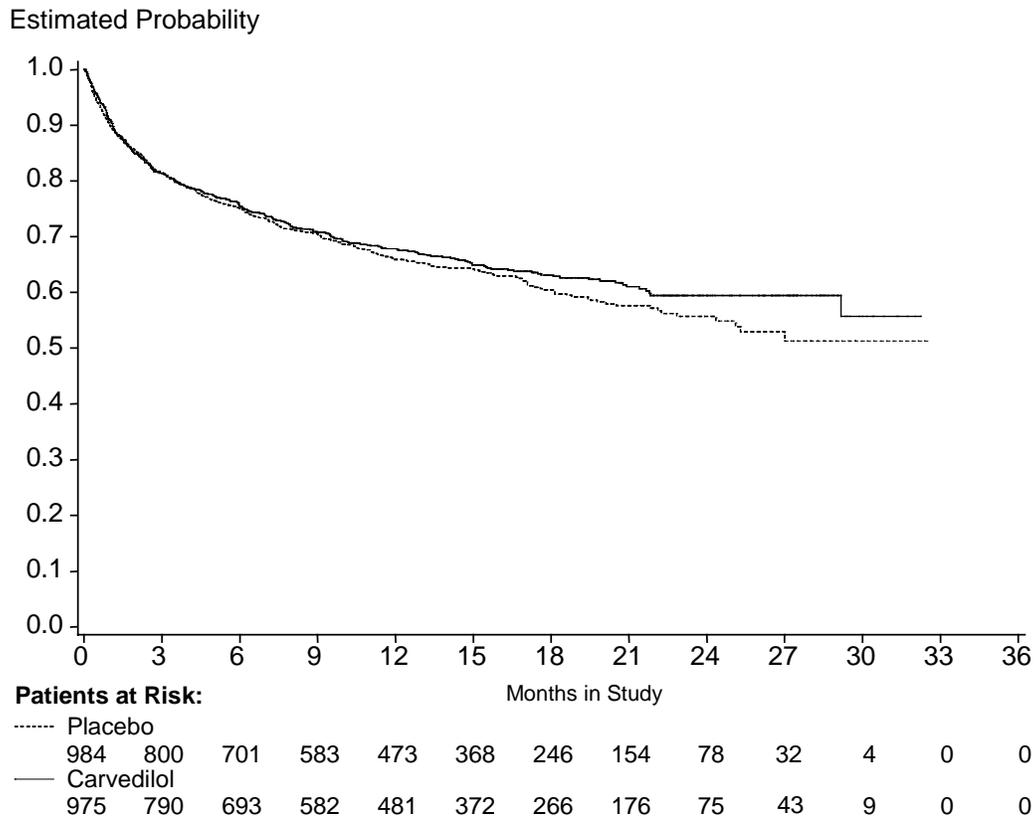
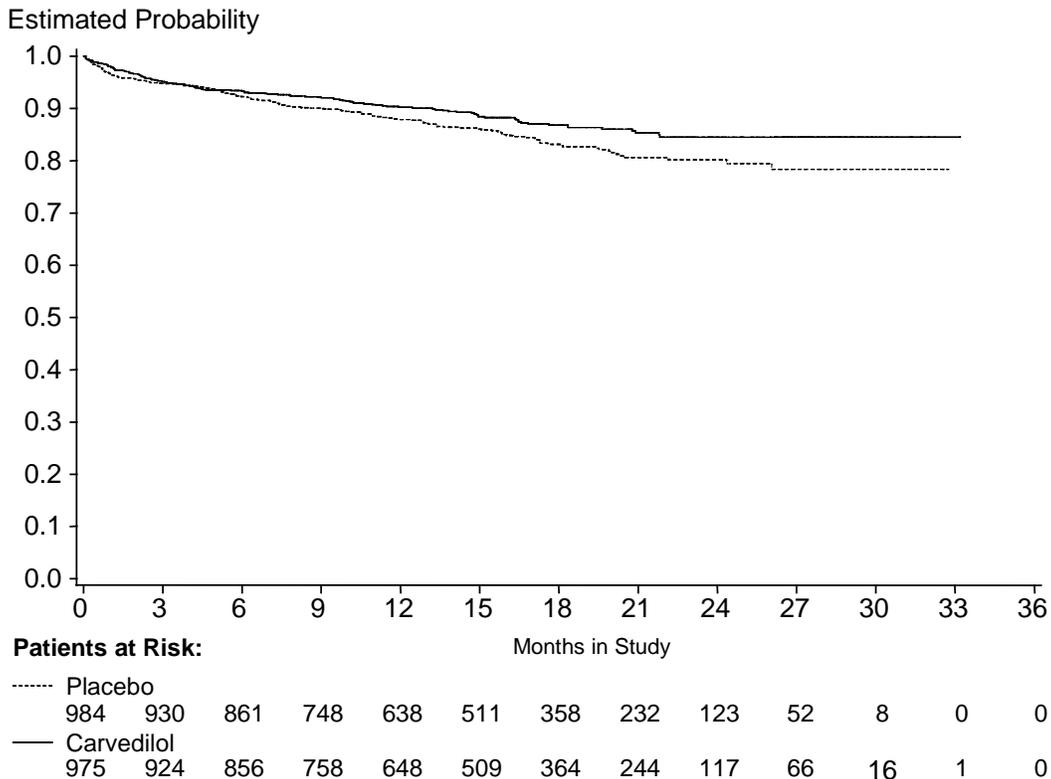


Figure 5. CAPRICORN: Time to Event Analysis of the Effect of Carvedilol on All-Cause Mortality



The effect of carvedilol on the two co-primary endpoints did not reach levels of statistical significance specified in the July 27, 1999 amendment, but the trial did demonstrate an effect on the original primary endpoint as defined in the original protocol and at P levels specified in the original protocol (before the July, 1999 amendment). The finding that the risk of death was 23% lower in the carvedilol group than in the placebo group (P=0.03) indicates that the trial achieved its original objective, both in terms of the magnitude of the expected treatment effect (i.e., $\geq 20\%$) and the level of statistical significance (i.e., < 0.05).

It is noteworthy that the observed magnitude of the mortality effect (23%) is identical to that observed in the most recent meta-analysis of post-infarction beta-blocker trials.[2] This is true despite the fact that the trials included in this meta-

analysis were carried out in lower-risk patients and before the widespread use of ACE inhibitors in post-infarction patients. It is also worth remembering that many of these early trials specified multiple primary endpoints, each of which was tested against an $\alpha=0.05$.

The mortality reduction associated with the use of carvedilol was observed during the first (and only) interim analysis carried out by the Data and Safety Monitoring Board — which took place (in August 1999) one month after the adoption of the protocol amendment that altered the α assigned to the mortality analysis. At that time, there were 76 deaths in the placebo group and 54 deaths in the carvedilol group (nominal $P=0.034$).

4.2.3.1 Subgroup Analyses of Primary Endpoints

The effects of carvedilol on the two co-primary endpoints in prespecified subgroups are shown in Tables 9 and 10. The magnitude of the treatment effect across subgroups based on baseline variables was similar to that seen in the analysis of all randomized patients. In most cases any trend toward a different response in a specific subgroup observed for the primary endpoint of death or cardiovascular hospitalization was not confirmed when that same subgroup was analyzed for the primary endpoint of all-cause mortality.

Of all the prespecified subgroups examined, only patients with Killip class III (those with pulmonary edema at the time of screening) appeared to have a response to carvedilol that differed from that seen in the overall trial. However, it should be noted that this subgroup was very small (only 65 patients were in Killip class III during screening).

Two post hoc analyses (presence or absence of elevated cardiac enzymes and level of baseline systolic blood pressure) are also shown.

- For both primary endpoints, patients with an index myocardial infarction confirmed by an elevation of cardiac enzymes showed a substantially better response to carvedilol to those without enzymatic confirmation of their qualifying infarction. The benefits of carvedilol on both all-cause mortality and the combined risk of death or cardiovascular hospitalization was largely

confined to those with enzymatic confirmation of their index infarction — a finding that was strikingly similar to that reported in an earlier post-infarction trial.[4]

- The higher the baseline systolic blood pressure, the better the response to carvedilol. [The interaction P value for systolic blood pressure and treatment was 0.089 for the combined endpoint of all-cause mortality and cardiovascular hospitalization and was 0.1879 for all-cause mortality.] This is noteworthy since (1) earlier post-infarction trials frequently excluded patients with a systolic blood pressure < 100 mm Hg[3,4,9] and enrolled very few (3-4%) patients with a systolic blood pressure < 110 mm Hg; and (2) a similar relationship between systolic blood pressure and treatment effect has been reported in an earlier post-infarction beta-blocker trial.[10,44]

**Table 9. CAPRICORN: Subgroup Analyses for Both Co-Primary Endpoints
[Based on Characteristics Present Prior to or During Index Infarction]**

	Death or CV Hospitalization		All-Cause Mortality	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Age				
< 70 years (n=1341)	0.93	0.77-1.12	0.78	0.56-1.10
≥ 70 years (n=618)	0.93	0.74-1.18	0.78	0.55-1.10
Gender				
Men (n=1440)	0.97	0.81-1.15	0.78	0.58-1.06
Women (n=519)	0.83	0.63-1.08	0.73	0.49-1.09
Location of study center				
Russia (n=600)	0.75	0.56-1.01	0.85	0.55-1.31
Outside Russia (n=1359)	1.00	0.84-1.18	0.73	0.55-0.98
Prior MI (before index MI)				
Yes (n=589)	0.98	0.78-1.24	0.87	0.62-1.22
No (n=1370)	0.87	0.72-1.05	0.64	0.45-0.91
Site of index MI				
Anterior (n=1108)	0.98	0.80-1.19	0.70	0.51-0.97
Inferior (n=410)	1.04	0.74-1.45	1.36	0.82-2.27
Other (n=441)	0.76	0.57-1.03	0.52	0.30-0.90
↑Cardiac enzymes (index MI)				
Yes (n=831)	0.88	0.75-1.03	0.71	0.54-0.92
No (n=153)	1.27	0.85-1.90	1.22	0.65-2.30
Thrombolytic during index MI				
Yes (n=718)	0.91	0.70-1.17	0.69	0.43-1.12
No (n=1241)	0.93	0.78-1.12	0.78	0.59-1.04
Angioplasty for index MI				
Yes (n=243)	1.11	0.73-1.69	0.76	0.36-1.62
No (n=1716)	0.90	0.77-1.05	0.77	0.59-0.99
Diuretic during index MI				
Yes (n=658)	0.84	0.70-1.11	0.68	0.49-0.96
No (n=1301)	0.94	0.77-1.13	0.83	0.59-1.17

Included are analyses based on baseline variables prespecified in the statistical plan that resulted in subgroups of meaningful size (i.e., at least 2 of the subgroups defined by baseline variables each included at least 10% of the randomized population]. Baseline variables that were specified in the protocol but did not fulfill this definition included: race, diastolic blood pressure, and US vs nonUS sites. All analyses reflect hazard ratio of carvedilol:placebo with 95% confidence intervals. Subgroups based on cardiac enzymes and systolic blood pressure are post hoc.

Table 10. CAPRICORN: Subgroup Analyses for Both Co-Primary Endpoints [Based on Characteristics Present Following Index Infarction]

	Death or CV Hospitalization		All-Cause Mortality	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Current or prior heart failure				
Yes (n=936)	0.87	0.72-1.07	0.80	0.59-1.08
No (n=1023)	0.97	0.77-1.21	0.69	0.47-1.03
Current or prior angina				
Yes (n=1090)	0.92	0.76-1.12	0.70	0.52-0.95
No (n=869)	0.91	0.72-1.15	0.86	0.58-1.28
Current or prior hypertension				
Yes (n=1055)	0.91	0.75-1.11	0.84	0.61-1.14
No (n=904)	0.92	0.73-1.15	0.65	0.44-0.95
Current or prior diabetes				
Yes (n=437)	0.88	0.80-1.13	0.93	0.61-1.44
No (n=1522)	0.95	0.66-1.16	0.71	0.53-0.96
Systolic BP at baseline				
< 110 mmHg (n=453)	1.04	0.76-1.41	0.85	0.52-1.40
110-130 mmHg (n=1039)	0.94	0.77-1.16	0.77	0.55-1.08
> 130 mmHg (n=464)	0.78	0.57-1.06	0.68	0.42-1.11
Heart rate at baseline				
< 70 bpm (n=590)	1.10	0.83-1.47	0.66	0.40-1.09
> 70 bpm (n=1365)	0.86	0.73-1.02	0.80	0.61-1.06
Killip Class at screening				
Class I (n=1289)	0.95	0.79-1.15	0.84	0.60-1.18
Class II (n=593)	0.84	0.65-1.09	0.67	0.46-0.98
Class III (n=65)	1.93	0.97-3.84	1.67	0.70-3.95

Included are analyses based on baseline variables prespecified in the statistical plan that resulted in subgroups of meaningful size (i.e., at least 2 of the subgroups defined by baseline variables each included at least 10% of the randomized population]. Baseline variables that were specified in the protocol but did not fulfill this definition included: race, diastolic blood pressure, and US vs nonUS sites. All analyses reflect hazard ratio of carvedilol:placebo with 95% confidence intervals. Subgroups based on cardiac enzymes and systolic blood pressure are post hoc.

4.2.4. Secondary Endpoints and Supplemental Efficacy Analyses

The two secondary endpoints in the CAPRICORN trial focused on the analysis of specific reasons for death and specific reasons for cardiovascular hospitalization.

4.2.4.1 Reasons for Death

The cause of death was classified without knowledge of the treatment assignment, and the summary of this classification effort is shown in Table 11. Most deaths were cardiovascular, and the two most common reasons for cardiovascular death were worsening heart failure and sudden death. Both occurred less commonly in the carvedilol group.

Table 11. CAPRICORN: Cause of Death in the Placebo and Carvedilol Groups

	Placebo (n=984)	Carvedilol (n=975)
Sudden death	69	51
Death due to worsening heart failure	30	18
Death due to recurrent myocardial infarction	16	12
Death due to cardiovascular surgery or procedure	5	8
Death due to stroke	5	6
Presumed cardiovascular death	12	8
Death due to other cardiovascular cause	2	1
Death due to non- cardiovascular cause	12	12

Results based on blinded adjudication of cause of death by the Endpoint Committee.

The analysis of sudden death (but not death due to worsening heart failure) was prespecified as a secondary endpoint in the study, even though the trial did not have adequate power to evaluate the effect of carvedilol on any specific cause of death. Carvedilol reduced the risk of sudden death by 26% (nominal $P=0.099$) and the risk of death due to worsening heart failure by 40% (nominal $P=0.083$), Table 12. In addition, the risk of a cardiovascular death was reduced by 25% in the carvedilol group (nominal $P=0.024$).

Table 12. CAPRICORN: Effect of Carvedilol on Cause of Death

	Placebo (n=984)	Carvedilol (n=975)	Hazard Ratio (95% CI)	P value
Cardiovascular death	139	104	0.75 (0.58-0.96)	0.024
Sudden death*	69	51	0.74 (0.51-1.06)	0.099
Death due to worsening heart failure	30	18	0.60 (0.33-1.07)	0.083

Asterisk identifies variable that was a prespecified secondary endpoint. All analyses reflect hazard ratio of carvedilol:placebo with 95% confidence intervals. P values were derived from the log rank test and are nominal. The analysis of death due to worsening heart failure is post hoc.

4.2.4.2. Reasons for the Occurrence of Death or Cardiovascular Hospitalization

The specific events responsible for the first occurrence of death or cardiovascular hospitalization are shown in Table 13. Patients in the carvedilol group had fewer deaths and fewer hospitalizations for worsening heart failure, nonfatal myocardial infarction and other cardiovascular reasons.

Table 13. CAPRICORN: Reasons for Occurrence of Co-Primary Endpoint of Death or Cardiovascular Hospitalization

	Placebo (n=984)	Carvedilol (n=975)
Death	78	65
Hospitalization due to non-fatal myocardial infarction	45	27
Hospitalization due to worsening heart failure	102	97
Hospitalization due to unstable angina	37	40
Hospitalization due to other angina or chest pain	42	57
Hospitalization due to stroke or TIA	12	12
Hospitalization for other cardiovascular reason	51	42
Total	367	340

Results based on blinded adjudication of cause of hospitalization by the Endpoint Committee. Hospitalizations with more than one cause identified by the Endpoint Committee were counted only once and attributed to the worst event listed as a reason for the admission (myocardial infarction > heart failure > unstable angina > stroke > TIA > other angina or chest pain > other). The Endpoint Committee generally assumed that patients hospitalized with chest pain that was not due to a myocardial infarction or unstable angina was "other angina", unless there was a good reason to suspect otherwise.

Only one cause of hospitalization (i.e., hospitalization for other angina or chest pain) occurred more frequently (> 10% excess) in the carvedilol group than in the placebo group. In interpreting this finding, it should be recognized that the Endpoint Committee generally assumed that patients hospitalized with chest pain that was not due to a myocardial infarction or unstable angina was “other angina”, unless there was a good reason to suspect otherwise. Hence, it is not clear how many of these hospitalizations for “other angina or chest pain” were cardiac or cardiovascular in origin.

This possibility is noteworthy given the fact that such hospitalizations have been prospectively excluded in most clinical trials that have designated the analysis of cardiovascular hospitalizations as an endpoint (or as a component of an endpoint). For example, in a recent controlled trial with carvedilol (COPERNICUS[39]) [which demonstrated highly favorable effects of carvedilol on survival and on the combined risk of death or cardiovascular hospitalization in patients with severe chronic heart failure], a cardiovascular hospitalization was defined as one due to a major cardiovascular event (heart failure, stroke or TIA, myocardial infarction or unstable angina, supraventricular or ventricular arrhythmia, bradycardia or heart block). Hospitalizations for a cardiovascular procedure were excluded as were hospitalizations for minor cardiovascular events (e.g., for other angina/chest pain). A similar approach has also been used in all other large-scale trials of post-infarction patients with left ventricular systolic dysfunction (the AIRE trial[45] with ramipril, the SAVE trial[46] with captopril, the TRACE trial[15] with trandolapril, and the EPHEBUS trial[47] with eplerenone). To our knowledge, *CAPRICORN is the only large-scale post-infarction trial of patients with left ventricular dysfunction and/or heart failure which defined cardiovascular hospitalization to include all hospitalizations for a cardiovascular reason (other than for a procedure).*

The decision to include all cardiovascular hospitalizations in the definition of a cardiovascular hospitalization had an important influence on the results of the CAPRICORN study. Reanalysis of the primary endpoints in the CAPRICORN trial (based on the COPERNICUS definition of a cardiovascular hospitalization) is shown in Table 14 and Figure 6, and specific reasons for the occurrence of death or cardiovascular hospitalization using this definition are tabulated in Table 15. Carvedilol reduced the risk of death or a major cardiovascular hospitalization

by 17% (nominal $P=0.019$). These post hoc evaluations indicate that — if the analysis were confined to the occurrence of major cardiovascular events — the effect of carvedilol would be nominally significant for both primary endpoints, Table 14. Examination of the specific reasons for fulfilling the primary endpoint indicates that — for nearly all categories — there were fewer major events in the carvedilol group than in the placebo group (Table 15). A favorable effect of carvedilol would also have been shown if alternative selective definitions for a cardiovascular hospitalization (e.g., those used in the AIRE, SAVE, TRACE or EPHEBUS trials) had been used to analyze the results of CAPRICORN (analyses not shown).

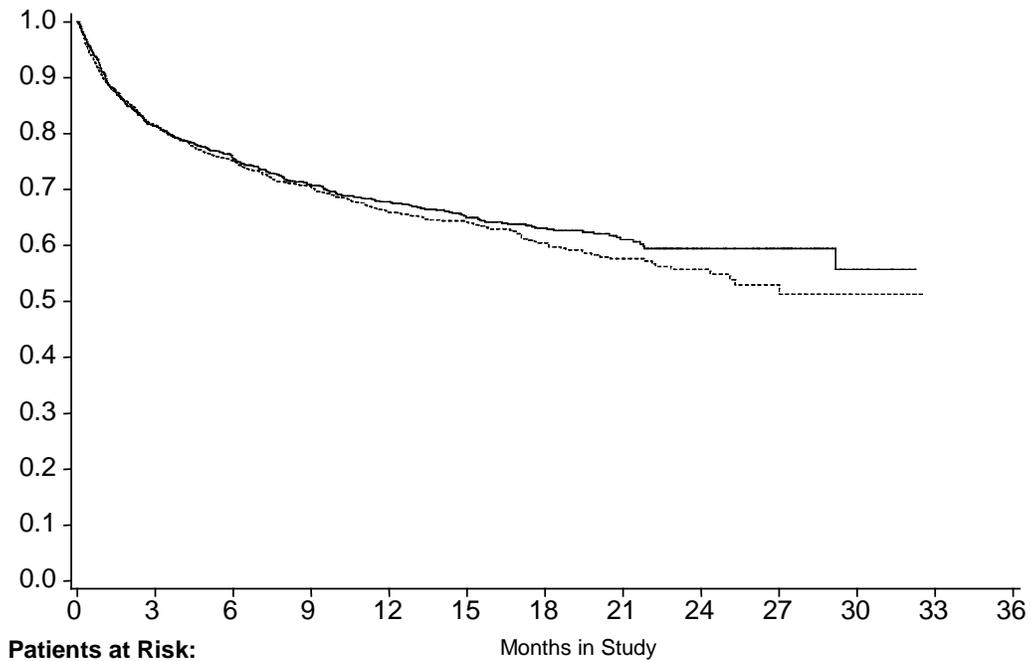
Table 14. CAPRICORN: Results of the CAPRICORN Trial (Co-Primary Endpoints) [Based on COPERNICUS Definition of CV Hospitalization]

	Placebo (n=984)	Carvedilol (n=975)	Hazard Ratio (95% CI)	P value
Death or CV hospitalization	327	275	0.83 (0.70-0.97)	0.019
All-cause mortality	151	116	0.77 (0.60-0.98)	0.031

All randomized patients, analyzed according to the intention-to-treat principle, with all events that occurred until the end of the trial included whether or not patients remained on their assigned treatment. CV hospitalizations include all CV admissions (as adjudicated by Endpoint Committee) for major CV events (heart failure, stroke or TIA, myocardial infarction or unstable angina, supraventricular or ventricular arrhythmia, heart block or bradycardia). This is the definition prespecified in the COPERNICUS statistical plan. The P value for this post hoc analysis was derived from the log rank test.

Figure 6. CAPRICORN: Kaplan-Meier Analysis of the Effect of Carvedilol on Death or Cardiovascular Hospitalization (COPERNICUS Definition)

Estimated Probability



Patients at Risk:

	Months in Study												
	0	3	6	9	12	15	18	21	24	27	30	33	36
----- Placebo	984	800	701	583	473	368	246	154	78	32	4	0	0
— Carvedilol	975	790	693	582	481	372	266	176	75	43	9	0	0

Table 15. CAPRICORN: Reasons for Occurrence of Co-Primary Endpoint of Death or CV Hospitalization [Based on COPERNICUS Definition of CV Hospitalization]

	Placebo (n=984)	Carvedilol (n=975)
Death	89	68
Hospitalization due to non-fatal myocardial infarction	48	31
Hospitalization due to worsening heart failure	108	104
Hospitalization due to unstable angina	40	49
Hospitalization due to supraventricular or ventricular arrhythmia	22	6
Hospitalization due to bradycardia or heart block	6	5
Hospitalization due to stroke or TIA	14	12
Total	327	275

The Endpoint Committee (EC) did not specifically identify hospitalizations due to a supraventricular or ventricular arrhythmia, bradycardia or heart block. These were identified post hoc by blindly reviewing all hospitalizations that the EC designated as “presumed” or “other” cardiovascular reasons and selecting those for which the primary cause of hospitalization could be identified as due to those causes. Hospitalizations with more than one cause identified by the EC were counted only once and attributed to the worst event listed as a reason for the admission (myocardial infarction > heart failure > unstable angina > stroke > TIA > supraventricular or ventricular arrhythmia).

4.2.4.3. Analysis of Risk of Worsening Heart Failure

The analysis of hospitalization due to worsening heart failure was prespecified as a secondary endpoint in the study. Carvedilol reduced the risk of a hospitalization for heart failure by 14% (P=0.207), Table 16. However, it should be noted that the efforts to validate the assumptions of the proportional hazards model used to carry this analysis cast doubt about the validity of this estimate, since the test for time-dependent covariates was nearly significant (P=0.0516). [Compared with the placebo group, the carvedilol group had more heart failure hospitalizations during the first 3-4 months but fewer such events thereafter.]

Furthermore, it should be noted that the protocol had originally specified this secondary endpoint to be “progression of heart failure” rather than “hospitalization for heart failure” (Table 6). Yet, an analysis of hospitalization for heart failure alone ignores the fact that the progression of heart failure in some patients is so severe that it results in death rather than in hospitalization. Furthermore, since death represents a competing risk (i.e. patients who die cannot

be hospitalized for heart failure), the most appropriate analysis of progression of heart failure would include all patients who died. Indeed, the combined risk of all-cause mortality or hospitalization for heart failure is the most commonly used definition of heart failure progression in major trials.

The effect of carvedilol on the combined risk of death or hospitalization for heart failure is shown in Table 16. Carvedilol reduced the combined risk of all-cause mortality or hospitalization for heart failure by 15% (nominal P=0.079).

Table 16. CAPRICORN: Effect of Carvedilol on Measures of Progression of Heart Failure

	Placebo (n=984)	Carvedilol (n=975)	Hazard Ratio (95% CI)	P value
Hospitalization for heart failure*	138	118	0.86 (0.67-1.09)	0.216
All-cause mortality or hospitalization for heart failure	240	203	0.85 (0.70-1.02)	0.079

Both analyses reflect hazard ratio of carvedilol:placebo with 95% confidence intervals. P values were derived from the log rank test. The analysis of all-cause mortality or hospitalization for heart failure is post hoc. Asterisk identifies variable that was a prespecified secondary endpoint.

4.2.4.4. Analysis of Risk of Recurrent Myocardial Infarction

The analysis of hospitalization due to a recurrent myocardial infarction was not a primary or secondary endpoint in the CAPRICORN trial, but the risk of non-fatal reinfarction was a primary or secondary endpoint in earlier post-infarction beta-blocker trials.[2-4,6,7] Hence, it is appropriate to examine the effects of carvedilol on this variable in the CAPRICORN trial. In doing so, it should be remembered that an analysis restricted to the occurrence of a non-fatal myocardial infarction ignores the fact that the occurrence of this event in some patients is so severe that it results in death rather than in hospitalization. Thus, it is appropriate to include fatal infarctions in any analysis of recurrent infarction. [Some would include all cardiovascular deaths, since sudden death can be the primary manifestation of an acute ischemic event in some patients.] Furthermore, since patients who die cannot be hospitalized for an acute unstable ischemic event (i.e., death represents a competing risk), some would argue that the most appropriate analysis would include all patients who died.

The effect of carvedilol on these outcome measures is summarized in Table 17 in a number of post hoc analyses. Carvedilol reduced the risk of a non-fatal

myocardial infarction by 41% (P=0.014); the combined risk of a fatal or non-fatal myocardial infarction by 40% (P=0.010); the combined risk of cardiovascular death or a non-fatal myocardial infarction by 30% (P=0.002); and the combined risk of all-cause mortality or non-fatal myocardial infarction by 29% (P=0.002).

Table 17. CAPRICORN: Effect of Carvedilol on Occurrence of Myocardial Infarction

	Placebo (n=984)	Carvedilol (n=975)	Hazard Ratio (95% CI)	P value
Hospitalization for non-fatal myocardial infarction	57	34	0.59 (0.39-0.90)	0.014
Fatal or non-fatal occurrence of myocardial infarction	66	40	0.60 (0.40-0.89)	0.010
CV death or non-fatal myocardial infarction	181	128	0.70 (0.56-0.87)	0.002
Any death or non-fatal myocardial infarction	192	139	0.71 (0.57-0.89)	0.002

All analyses reflect hazard ratio of carvedilol:placebo with 95% confidence intervals. P values for these post hoc analyses were derived from the log rank test. CV=cardiovascular.

4.2.4.5. Effect on Left Ventricular Function and Chamber Size

In a prospectively designed substudy, 129 patients were enrolled in the CAPRICORN trial at 12 centers in Australia, New Zealand and Spain underwent quantitative 2-dimensional echocardiography at baseline and after 1, 3 and 6 months of treatment with the study drug. Preliminary analyses of the data from this substudy have been published and are presented in Tables 18 and 19 but have not been reviewed by the sponsor or the FDA.[48,49] During the 6 months of follow-up, patients in the placebo group experienced an increase in left ventricular endsystolic and end-diastolic volumes without a change in left ventricular ejection fraction. In contrast, patients in the carvedilol group did not show an increase in cardiac volumes but experienced an increase in left ventricular ejection fraction. Between-group differences in favor of carvedilol were statistically significant for all three variables. The benefits of carvedilol were apparent after 1 month and became larger with longer treatment, Table 19. These findings suggest that carvedilol exerts a favorable effect on cardiac remodeling in post-infarction patients similar to that previously reported for ACE inhibitors in this setting.

Table 18. CAPRICORN: Effect of Carvedilol on Left Ventricular Function and Chamber Size After 6 Months of Treatment

	Placebo (n=67)		Carvedilol (n=62)		Between-group P value
	Baseline	6 months	Baseline	6 months	
LVEDV, ml	133.2 ± 47.3	144.3 ± 48.8	130.5 ± 40	133.2 ± 39.9	0.04
LVESV, ml	82.5 ± 38	88.6 ± 41.9	79.8 ± 30.3	75.2 ± 33.3	0.0023
LVEF, %	39.6 ± 8.2	40.7 ± 10.4	39.4 ± 7.4	44.9 ± 9.6	0.0096

LVEDV = left ventricular end-diastolic volume; LVESV= left ventricular end-systolic volume; LVEF=left ventricular ejection fraction.

Table 19. CAPRICORN: Placebo-Corrected Change in Left Ventricular Function and Chamber Size After 1, 3 and 6 Months of Treatment with Carvedilol

	1 month	3 months	6 months
LVEDV, ml	- 1.1	- 2.1	- 8.6
LVESV, ml	- 6.3	- 7.2	- 10.8
LVEF, %	+ 3.8	+ 4.0	+ 4.1

LVEDV = left ventricular end-diastolic volume; LVESV= left ventricular end-systolic volume; LVEF=left ventricular ejection fraction.

4.2.4.6. Effect on Cardiac Arrhythmias

In light of the known antiarrhythmic effect of beta-blockers, the CAPRICORN investigators carried out a post hoc analysis of the effects of carvedilol on cardiac arrhythmias. Reports of all adverse events describing the occurrence of a cardiac arrhythmia were reviewed blindly, and the risk of carvedilol versus placebo was quantified using a time-to-event analysis. Carvedilol reduced the risk of any supraventricular arrhythmia; atrial flutter or atrial fibrillation; any ventricular arrhythmia; and ventricular tachycardia or ventricular fibrillation (all nominal $P < 0.005$), Table 20. Time to event analyses supported the existence of a favorable effect of treatment (Figures 7 and 8).

Table 20. CAPRICORN: Effect of Carvedilol on Occurrence of Cardiac Arrhythmia (Reported as an Adverse Event)

	Placebo (n=984)	Carvedilol (n=975)	Hazard Ratio (95% CI)	P value
Any supraventricular arrhythmia	54	26	0.48 (0.30-0.76)	0.0015
Atrial flutter or atrial fibrillation	53	22	0.41 (0.25-0.68)	0.0003
Any ventricular arrhythmia	69	26	0.37 (0.24-0.58)	< 0.0001
Ventricular tachycardia or ventricular fibrillation	40	12	0.30 (0.16-0.57)	< 0.0001

All analyses reflect hazard ratio of carvedilol:placebo with 95% confidence intervals. P values for these post hoc analyses were derived from the log rank test and are nominal.

Figure 7. CAPRICORN: Time to Event Analysis of the Effect of Carvedilol on Reports of Atrial Flutter or Atrial Fibrillation

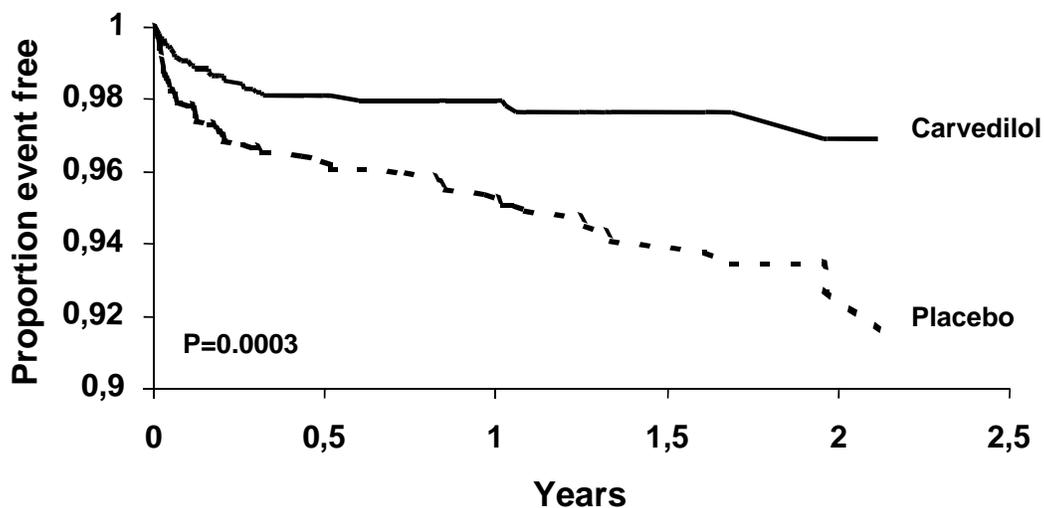
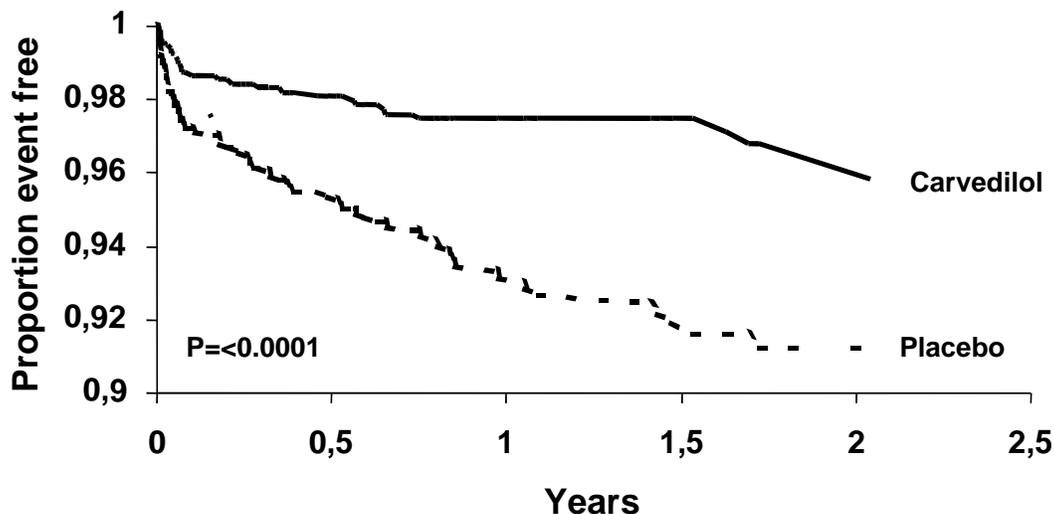


Figure 8. CAPRICORN: Time to Event Analysis of the Effect of Carvedilol on Reports of Ventricular Tachycardia or Ventricular Fibrillation



4.2.4.7. Analysis of First and Recurrent Hospitalizations

All analyses presented thus far reflect the occurrence of a hospitalization as a first event and do not include repeated hospitalizations. A summary of the frequency and reasons for all hospitalizations that occurred in the CAPRICORN trial is provided in Table 21.

There were fewer hospitalizations for any reason, for worsening heart failure and for a nonfatal myocardial infarction in the carvedilol group than in the placebo group. [It should be noted that 28 patients (18 in the placebo group and 10 in the carvedilol group) were hospitalized for an acute myocardial infarction complicated by heart failure and according to the hierarchy described in the footnote were classified as hospitalizations for myocardial infarction. If they had been classified as hospitalizations for heart failure, then the number of hospitalizations for heart failure would have been 199 in the placebo group and 161 in the carvedilol group.] There was no excess of hospitalizations for a noncardiovascular reason in the carvedilol group.

Table 21. Total Number of Hospitalizations for Specified Reasons

	Placebo (n=984)	Carvedilol (n=975)
Hospitalizations for any reason	693	621
Hospitalization due to myocardial infarction	60	37
Hospitalization due to worsening heart failure	181	151
Hospitalization due to unstable angina	53	56
Hospitalization due to stroke or TIA	18	17
Hospitalization due to other angina or chest pain	84	92
Hospitalizations for presumed or other CV reason	70	79
Hospitalization for cardiovascular procedure	93	84
Hospitalization for non-cardiovascular reasons	123	96
Failed to meet criteria for hospitalization	11	9

Results based on all hospitalizations reported by the investigator (including repeat hospitalizations) and following blinded adjudication of cause(s) of hospitalization by the Endpoint Committee. Hospitalizations with more than one cause were counted only once and attributed to the worst event listed as a reason for the admission (myocardial infarction > heart failure > unstable angina > stroke > TIA > other angina or chest pain > nonclassified or other > cardiovascular procedure > noncardiovascular). The Endpoint Committee generally assumed that patients hospitalized with chest pain that was not due to a myocardial infarction or unstable angina was “other angina”, unless there was a good reason to suspect otherwise.

4.2.5. Changes in Physiological Variables

4.2.5.1. Vital Signs and Body Weight

As expected from the drug’s β -blocking actions, heart rates were lower in the carvedilol group than in the placebo group at all visits ($P < 0.001$). At the end of the uptitration period, heart rate had declined by 7.1 beats/min more in the carvedilol group than in the placebo group ($P < 0.001$). Both systolic and diastolic blood pressure were similar in the two groups during the early part of the uptitration period but were slightly lower in the carvedilol group than in the placebo group at the end of the uptitration period (by 3.6 mm Hg systolic and by 3.0 mm Hg diastolic), both $P < 0.001$. These small between-group differences in systolic and diastolic blood pressure were generally maintained for the duration of the trial. Changes in body weight were similar and negligible in both treatment groups during the uptitration period and during long-term maintenance therapy.

4.2.5.2. Laboratory Changes

Patients treated with carvedilol had slightly higher values for serum potassium during maintenance therapy; this effect can be explained by the drug’s ability to

block β 2-mediated transport of potassium into cells.[50] Carvedilol-treated patients had slightly increased values for blood urea nitrogen and serum creatinine during the first 6 months of treatment, but not thereafter. [Please see below for further comments on changes in renal function during the study.]

4.2.6. Safety

4.2.6.1. Adverse Events

The proportion of patients who reported at least one adverse event was similar in the two treatment groups (79% in the placebo group and 80% in the carvedilol group). Patients in the carvedilol group were more likely to experience adverse events previously associated with drugs that block alpha or beta-adrenergic receptors (e.g., hypotension, dizziness, bradycardia, syncope, peripheral edema and peripheral vascular disease) and were less likely to experience adverse events reflecting worsening of the underlying disease (e.g., myocardial infarction, atrial fibrillation, tachycardia, or ventricular tachycardia), Table 22.

As in earlier trials with the drug, initiation of therapy with carvedilol was associated with an early risk of worsening heart failure in some patients. Lung edema was reported as an adverse event more frequently in the carvedilol group during the first 60 days (2.8% vs 1.3%), but somewhat less frequently in the carvedilol group thereafter (1.5% vs 1.8%).

Table 22 shows that kidney failure was reported as an adverse event more frequently in the carvedilol group than in the placebo group (25 vs 9 patients). However, there were only 3 patients among these (1 in the placebo group and 2 in the carvedilol group) who had a recorded increase in serum creatinine from randomization to follow-up of greater than 50% and to a level greater than 154 μ mol/l (which was the protocol-specified threshold for reporting an increased serum creatinine). Furthermore, the placebo and carvedilol groups were similar with respect to the frequency of reports of acute renal failure and of kidney failure as a serious adverse event, and were similar in the frequency of discontinuations of the study drug due to kidney failure. Finally, the number of patients who had laboratory values while on therapy that exceeded predefined thresholds was similar in the placebo and carvedilol groups for both blood urea nitrogen (placebo 9, carvedilol 12) and serum creatinine (placebo 16, carvedilol 9).

Table 22. CAPRICORN: Adverse Events with a Frequency \geq 2% in Either Treatment Group

	Placebo (n=980)	Carvedilol (n=969)
Heart failure	142 (14.5%)	149 (15.4%)
Hypotension	114 (11.6%)	176 (18.2%)
Dizziness	105 (10.7%)	144 (14.9%)
Angina pectoris	119 (12.1%)	108 (11.1%)
Chest pain	109 (11.1%)	97 (10.0%)
Dyspnea	88 (9.0%)	94 (9.7%)
Hypertension	77 (7.9%)	79 (8.2%)
Myocardial infarction	89 (9.1%)	55 (5.7%)
Upper respiratory infection	66 (6.7%)	66 (6.8%)
Cough increased	76 (7.8%)	54 (5.6%)
Unstable angina pectoris	64 (6.5%)	60 (6.2%)
Asthenia	56 (5.7%)	66 (6.8%)
Bradycardia	37 (3.8%)	63 (6.5%)
Hypercholesterolemia	42 (4.3%)	32 (3.3%)
Lung edema	31 (3.2%)	42 (4.3%)
Peripheral edema	28 (2.9%)	43 (4.4%)
Thorax pain	40 (4.1%)	28 (2.9%)
Syncope	19 (1.9%)	38 (3.9%)
Anemia	20 (2.0%)	35 (3.6%)
Atrial fibrillation	40 (4.1%)	13 (1.3%)
Peripheral vascular disorder	16 (1.6%)	30 (3.1%)
Tachycardia	27 (2.8%)	14 (1.4%)
Depression	15 (1.5%)	25 (2.6%)
Nonspecified cardiovascular disorder	25 (2.6%)	11 (1.1%)
Kidney failure	9 (0.9%)	25 (2.6%)
Postural hypotension	9 (0.9%)	20 (2.1%)
Ventricular tachycardia	20 (2.0%)	2 (0.2%)

Excluded from this list are the following adverse events whose frequency was $<$ 5% in both groups and did not differ by $>$ 1.0% between the two treatment groups: pneumonia, nausea, diarrhea, hyperglycemia, headache, lung disorder, bronchitis, rash, constipation, dyspepsia, anxiety, back pain, creatinine increased, pain, pain in extremity, sudden death, insomnia, hyperuricemia, and palpitations.

The number of patients in the analyses of safety are 10 fewer than in the analyses of efficacy, since 10 patients were randomized but not treated and thus were included in the analyses of efficacy (according to the intention-to-treat principle) but not the analyses of safety.

4.2.6.2. Serious Adverse Events

The proportion of patients who reported at least one serious adverse event was similar in the carvedilol group and the placebo group (41% vs 44%, respectively).

Again, patients in the carvedilol group were more likely to experience adverse events previously associated with drugs that block alpha or beta-adrenergic receptors (e.g., hypotension, syncope) and were less likely to experience adverse events reflecting worsening of the underlying disease (e.g., heart failure, myocardial infarction, heart arrest, atrial fibrillation and ventricular tachycardia), Table 23.

Table 23. CAPRICORN: Serious Adverse Events with a Frequency > 1% in Either Treatment Group

	Placebo (n=980)	Carvedilol (n=969)
Heart failure	91 (9.3%)	78 (8.0%)
Myocardial infarction	88 (9.0%)	54 (5.6%)
Unstable angina pectoris	61 (6.2%)	59 (6.1%)
Chest pain	43 (4.4%)	42 (4.3%)
Angina pectoris	41 (4.2%)	34 (3.5%)
Lung edema	26 (2.7%)	36 (3.7%)
Sudden death	20 (2.0%)	17 (1.8%)
Pneumonia	15 (1.5%)	16 (1.7%)
Cerebrovascular accident	11 (1.1%)	11 (1.1%)
Heart arrest	14 (1.4%)	6 (0.6%)
Atrial fibrillation	16 (1.6%)	2 (0.2%)
Coronary artery disorder	10 (1.0%)	7 (0.7%)
Syncope	5 (0.5%)	12 (1.2%)
Ventricular tachycardia	15 (1.5%)	1 (0.1%)
Hypotension	2 (0.2%)	13 (1.3%)

The number of patients in the analyses of safety are 10 fewer than in the analyses of efficacy, since 10 patients were randomized but not treated and thus were included in the analyses of efficacy (according to the intention-to-treat principle) but not the analyses of safety.

4.2.6.3. Adverse Events Leading to Permanent Withdrawal of the Study Drug

A total of 290 patients (139 on placebo, 151 on carvedilol) had adverse events recorded as leading to premature withdrawal of the study medication. Again, patients in the carvedilol group were more likely to experience adverse events previously associated with drugs that block alpha or beta-adrenergic receptors (e.g., hypotension and syncope) and were less likely to experience adverse events reflecting worsening of the underlying disease (e.g., myocardial infarction and ventricular tachycardia), Table 24. Lung edema (reported as an adverse event) led to discontinuation of treatment more frequently in the carvedilol group than in the placebo group during the first 60 days (1.1% vs 0.3%, respectively), but less frequently in the carvedilol group thereafter (0.2% vs 0.4%).

Table 24. CAPRICORN: Adverse Events Leading to Permanent Withdrawal of the Study Medication with a Frequency > 0.5% in Either Treatment Group

	Placebo (n=980)	Carvedilol (n=969)
Heart failure	20 (2.0%)	24 (2.5%)
Myocardial infarction	23 (2.3%)	8 (0.8%)
Angina pectoris	11 (1.1%)	11 (1.1%)
Lung edema	7 (0.7%)	13 (1.3%)
Hypotension	2 (0.2%)	15 (1.5%)
Dizziness	2 (0.2%)	10 (1.0%)
Unstable angina pectoris	8 (0.8%)	5 (0.5%)
Dyspnea	5 (0.5%)	7 (0.7%)
Tachycardia	7 (0.7%)	3 (0.3%)
Syncope	0 (0.0%)	9 (0.9%)
Chest pain	2 (0.2%)	5 (0.5%)
Ventricular tachycardia	5 (0.5%)	0 (0.0%)

The number of patients in the analyses of safety are 10 fewer than in the analyses of efficacy, since 10 patients were randomized but not treated and thus were included in the analyses of efficacy (according to the intention-to-treat principle) but not the analyses of safety.

4.3. Summary

The CAPRICORN trial evaluated the efficacy of carvedilol in patients with left ventricular dysfunction and a recent myocardial infarction (< 21 days), who were at high risk and were receiving all appropriate treatments for the immediate and long-term management of the post-infarction patients, including ACE inhibitors in all patients. The trial collected complete data on fatal and non-fatal events whether or not patients continued receiving their study medication.

The original primary endpoint of the CAPRICORN trial was all-cause mortality, and carvedilol reduced the risk of death by 23% (P=0.03). Although the level of significance achieved was less than specified in a protocol amendment ($\alpha=0.005$) triggered by DSMB concerns about the low frequency of use of open-label beta-blockers in patients with established heart failure, the trial achieved its original objective, both in terms of the magnitude of the expected treatment effect (i.e., > 20%) and the level of statistical significance (i.e., < 0.05).

Carvedilol reduced the risk of death or cardiovascular hospitalization by 8% (P=0.297), but the effect on this endpoint became substantially larger (17%) and nominally significant (P=0.019) when only hospitalization for major

cardiovascular events (heart failure, myocardial infarction, unstable angina, supraventricular and ventricular arrhythmias, stroke and TIA, and bradycardia and heart block) were included in the analysis, as has been done prospectively in other post-infarction trials of patients with left ventricular dysfunction/heart failure.[15,45-47]

Secondary, supplemental and post hoc analyses demonstrated that (with nominal P values):

- Carvedilol reduced the risk of a cardiovascular death by 25% (P=0.024); the risk of sudden death by 26% (P=0.099); and the risk of death due to worsening heart failure by 40% (P=0.083).
- Carvedilol reduced the risk of a non-fatal myocardial infarction by 41% (P=0.014); the combined risk of a fatal or non-fatal myocardial infarction by 40% (P=0.010); the combined risk of cardiovascular death or a non-fatal myocardial infarction by 30% (P=0.002); and the combined risk of all-cause mortality or non-fatal myocardial infarction by 29% (P=0.002).
- Carvedilol reduced the combined risk of all-cause mortality or hospitalization for heart failure by 15% (P=0.079).
- Carvedilol reduced the risk of any supraventricular arrhythmia by 52% (P=0.0015); the combined risk of atrial flutter or atrial fibrillation by 59% (P=0.0003); the risk of any ventricular arrhythmia by 63% (P<0.0001); and the combined risk of ventricular tachycardia or ventricular fibrillation by 70% (P<0.0001), all based on spontaneous reports of adverse events.
- Carvedilol increased left ventricular ejection fraction and reduced left ventricular systolic and diastolic volumes after 6 months of double-blind therapy (P < 0.05).

Carvedilol was well tolerated in the current study, and no new safety concerns were identified. As in earlier trials with the drug,[38,39] patients in the carvedilol group were more likely to experience adverse events previously associated with drugs that block alpha or beta-adrenergic receptors (e.g., hypotension, dizziness, bradycardia, syncope, peripheral edema and peripheral vascular disease) and were less likely to experience adverse events reflecting worsening of the underlying

disease (e.g., myocardial infarction, atrial fibrillation, tachycardia, or ventricular tachycardia).

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5. DISCUSSION

5.1. Background

The benefits of beta-blockers in post-infarction patients were established in clinical trials carried out 15-20 years ago — before the advent of thrombolytic agents, aspirin, heparin, angioplasty or ACE inhibitors in the treatment of the acute ischemic event.[1,2] Modern-day treatments for the patients with an acute myocardial infarction are known to attenuate the magnitude of cardiac necrosis, reduce the degree of cardiac remodeling decrease the risk of reinfarction, and minimize the adverse effects of neurohormonal activation. In particular, during the past decade, ACE inhibitors have emerged as the most commonly used neurohormonal antagonist in post-infarction patients, especially in those who have substantial left ventricular systolic dysfunction following the acute event.

Only a minority of patients with left ventricular systolic dysfunction presently receive a beta-blocker following their myocardial infarction because of:

- concerns that beta-blockers may no longer be needed when patients are already receiving other treatments that reduce the degree of cardiac remodeling, the risk of reinfarction, and the adverse effects of neurohormonal activation.
- fears that beta-blockers can precipitate the development of heart failure in patients at risk — a risk that is not present with the use of ACE inhibitors, thrombolytic drugs or angioplasty, intravenous nitroglycerin or intravenous heparin.
- fears that the administration of beta-blockers to patients already receiving an ACE inhibitor may precipitate hypotension, particularly in patients whose blood pressure is low prior to treatment.

The CAPRICORN trial was designed to evaluate the effect of the beta-blocker carvedilol in post-infarction patients with left ventricular systolic dysfunction who were receiving modern-day therapy for and following their acute myocardial infarction. Nearly 40% had received a thrombolytic drug, 73% had received intravenous nitroglycerin, 64% had received intravenous heparin, 85% were receiving aspirin, and 20-25% were receiving a lipid lowering drug. In addition,

all patients had received an ACE inhibitor, which in most cases was started following the acute ischemic event.

Patients in the CAPRICORN trial were at higher risk than patients in earlier beta-blocker trials. In earlier trials,[3,4,6,9] a depressed left ventricular ejection fraction was probably present in a minority of patients (although these trials did not evaluate left ventricular function as an entry criterion), and heart failure was uncommon (< 15% of patients[3]) and was required to be well compensated prior to randomization. In contrast, in the CAPRICORN trial, all of the patients had a depressed left ventricular ejection fraction; nearly half of the patients in the CAPRICORN trial had a history of heart failure; and many continued to show evidence of pulmonary congestion prior to randomization. Blood pressure was largely preserved in earlier beta-blocker trials, which generally excluded patients with a systolic blood pressure < 100 mm Hg;[3,4,9] in the Goteborg Metoprolol Trial, only 3-4% had a systolic blood pressure less than 110 mm Hg.[4] In contrast, the CAPRICORN trial excluded patients only if they had a systolic blood pressure < 90 mm Hg, and 23% had a systolic blood pressure < 110 mm Hg. The annual mortality rate in the placebo group was only 5-6% in earlier beta-blocker trials[3,4,6,9] but was 12% in the CAPRICORN study.

Therefore, the CAPRICORN trial evaluated the efficacy of the beta-blocker carvedilol in high-risk patients receiving optimal modern treatment for and following an acute myocardial infarction. Such patients generally do not receive a beta-blocker in clinical practice despite the fact that carvedilol and other beta-blockers have been shown to reduce the risk of death and hospitalization in patients with symptomatic left ventricular dysfunction, who have experienced an acute myocardial infarction at least 1-3 months earlier.[38,39,51] The CAPRICORN trial was designed to determine whether treatment with carvedilol would be effective and safe if initiated earlier (within 3 weeks of an acute infarction) in the very type of patients who would be likely to receive the drug in the future.

5.2. Principal Findings of the CAPRICORN Study

5.2.1. Effect on All-Cause Mortality

Treatment with carvedilol was associated with a 23% reduction in the risk of death ($P=0.03$). Although this effect did not reach levels of statistical significance specified in the amended protocol ($\alpha=0.005$), the trial did demonstrate an effect on the primary endpoint as defined in the original protocol and at the magnitude ($\geq 20\%$) and the significance level ($P \leq 0.05$) specified in the original protocol.

[It should be noted that the protocol was amended not as a result of any initiative of the investigators or sponsors, but occurred following a strong recommendation to do so from the trial's Data and Safety Monitoring Board which wished to encourage the use of open-label beta-blockers. This recommendation necessitated accelerated closure of the trial.]

The effects of carvedilol in the CAPRICORN study were strikingly similar to those reported in earlier post-infarction studies that evaluated the efficacy of long-term treatment with beta-blockers. The 23% lower risk of death with carvedilol was identical to that reported in a recent meta-analysis of post-infarction trials with beta-blockers[2] (Table 25). Importantly, the number of deaths in the CAPRICORN trial was comparable to that seen in large-scale trials with other beta-blockers approved for use in post-infarction patients (Table 26).

Subgroup analysis also suggested strong concordance between the results of the CAPRICORN study and earlier post-infarction beta-blocker trials. The effects of carvedilol were similar in direction and magnitude in most subgroups examined, as was the case in earlier trials with other beta-blockers. However, earlier post-infarction trials showed that the benefits of beta-blockade were largely confined to patients with enzymatic confirmation of their index infarction[4] and to patients whose systolic blood pressure was greater than 100-120 mm Hg systolic.[10,44] [Some trials restricted their enrollment to patients fulfilling these two characteristics.] It is therefore noteworthy that in the CAPRICORN trial patients with enzymatic confirmation of their index infarction and with a systolic blood pressure > 110 mm Hg showed the greatest effects of carvedilol (Tables 9 and 10).

Table 25. Comparison of Results of the CAPRICORN Trial with Earlier Post-Infarction Trials (Hazard Ratios and 95% CI)

	Meta-analysis of earlier post-MI trials*	CAPRICORN Trial
All-cause mortality	0.77 (0.69-0.85)	0.77 (0.60-0.98)

* Source: Freemantle et al, Br Med J 1999; 318:1730-7. The meta-analysis is based on 2415 deaths among 24,974 who were enrolled in 31 long-term trials of beta-blockers in survivors of an acute myocardial infarction. MI=myocardial infarction.

Table 26. Comparison of Results of the CAPRICORN Trial with Earlier Post-Infarction Trials Carried Out with Beta-Blockers Approved for Use in Post-Infarction Patients

Study Name (Year Published)	Treatment Groups -- Study Drugs (# of patients)	Average duration of F/U	# Patients Who Died		P value
			PBO	β□B	
Norwegian Multi-Centre Study (1981)[3]	Placebo (n=939) Timolol (n=945)	17 months	152 (16.2%)	98 (10.3%)	< 0.001
Goteborg Metoprolol Trial (1981)[4]	Placebo (n=697) Metoprolol (n=698)	3 months	62 (8.9%)	40 (5.7%)	= 0.03
Beta-Blocker Heart Attack Trial (1982)[6]	Placebo (n=1921) Propranolol (n=1916)	25 months	188 (9.8%)	138 (7.2%)	< 0.01
Lopressor Intervention Trial (1987)[9]	Placebo (n=1200) Metoprolol (n=1195)	18 months	93 (7.8%)	86 (7.2%)	NS
CAPRICORN Trial (2001)[41]	Placebo (n=984) Carvedilol (n=975)	15 months	151 (15.3%)	116 (11.9%)	= 0.03

The table lists all long-term trials with timolol, metoprolol and carvedilol which enrolled more than 1000 patients and recorded more than 75 deaths. *The Goteborg Metoprolol Trial is unique among the 5 trials in that patients received the study medication initially during the acute phase of their illness by the IV route followed by double-blind oral treatment for only 3 months. PBO=placebo; β□B=beta-blocker; NS=not significant; F/U=follow-up.

[Although the P value for the mortality analysis in the CAPRICORN trial was not less than the alpha assigned to this analysis in the final statistical plan, none of the P values in Table 26 are adjusted for the presence of multiple primary endpoints or interim analyses.]

5.2.2. Effect on Cardiovascular Hospitalization

Although the CAPRICORN trial demonstrated the expected effect on all-cause mortality, it did not show the hoped-for effect of carvedilol on the combined risk of all-cause mortality or cardiovascular hospitalization. Carvedilol reduced the combined risk of death or cardiovascular hospitalization in the CAPRICORN by only 8% (Table 27); the amended protocol had projected a 23% reduction in risk.

A review of the results of earlier post-infarction trials provides a potential explanation as to why carvedilol had such a small effect on the combined cardiovascular endpoint.

-
- The combined endpoint of death or cardiovascular hospitalization was not evaluated in earlier post-infarction studies with beta-blockers, because data on the occurrence of hospitalization were not collected in these studies. Therefore, the effect of other beta-blockers on this endpoint is unknown.
 - In earlier post-infarction studies with beta-blockers, patients in the beta-blocker group generally showed no decrease or even an increase in the frequency of heart failure (including pulmonary edema), angina or other myocardial ischemic events, hypotension, dizziness, bradycardia, heart block and peripheral vascular symptoms, many of which led to the withdrawal of treatment.[3,5,7,8] Thus, if an analysis of cardiovascular hospitalization had been carried out which included admissions for any cardiovascular reason, it might have been difficult for these earlier trials to have shown a favorable effect of treatment.
 - Earlier trials of post-infarction patients with left ventricular dysfunction (e.g., SAVE,[46] AIRE,[45] TRACE[15] and EPHEBUS[47]) did not include all cardiovascular admissions in their definitions of a cardiovascular hospitalization. Instead, in these trials, the analysis of cardiovascular hospitalization included only admissions for specific reasons, generally those that reflected the occurrence of a major cardiovascular event (e.g., myocardial infarction, unstable angina, heart failure, arrhythmia, stroke).
 - One earlier large-scale trial with carvedilol (COPERNICUS) also restricted the definition of a cardiovascular hospitalization to include only major cardiovascular events (i.e., (e.g., myocardial infarction, unstable angina, heart failure, arrhythmia, stroke, bradycardia and heart block). If such a definition had been used in the CAPRICORN trial, the effect of carvedilol on the co-primary endpoint of all-cause mortality or major cardiovascular hospitalization would have been significant (P=0.019, post hoc), Table 27.

Table 27. CAPRICORN: Effects of Carvedilol on the Risk of Cardiovascular Events

	Placebo (n=984)	Carvedilol (n=975)	Hazard Ratio (95% CI)	P value
Cardiovascular death	139	104	0.75 (0.58-0.96)	0.024
Death or CV hospitalization (CAPRICORN definition)	367	340	0.92 (0.80-1.07)	0.297
Death or CV hospitalization (COPERNICUS definition)	327	275	0.83 (0.70-0.97)	0.019

All randomized patients, analyzed according to the intention-to-treat principle, with all events that occurred until the end of the trial included whether or not patients remained on their assigned treatment. CV= cardiovascular. The CAPRICORN definition of a CV hospitalization included all CV admissions (as adjudicated by the Endpoint Committee) except for those for a cardiovascular procedure. The COPERNICUS definition of a CV hospitalization included all CV admissions (as adjudicated by the Endpoint Committee) for major CV events (heart failure, stroke or TIA, myocardial infarction or unstable angina, supraventricular or ventricular arrhythmia, heart block or bradycardia).

The only non-fatal cardiovascular endpoint that was consistently examined in previous post-infarction studies was the risk of non-fatal myocardial infarction (Table 28). Although there is a widespread perception that beta-blockers consistently reduce the risk of reinfarction,[1,2] only the currently approved labeling for timolol reflects this benefit. This is because large-scale trials with metoprolol and propranolol did not observe a significant reduction in the risk of nonfatal myocardial infarction. However, it should be noted that — although the Norwegian Timolol Trial reported a decrease in the risk of nonfatal reinfarction — this study did not include non-fatal reinfarctions that occurred more than 28 days following withdrawal of the study drug in their analysis.[3] Nevertheless, several meta-analyses have concluded that beta-blockers reduce the risk of reinfarction when administered long-term to post-infarction patients.[1,2]

Given the focus of earlier trials on nonfatal reinfarction, it is noteworthy that, in a post hoc analysis of the CAPRICORN trial, patients in the carvedilol group had a 41% lower risk of a nonfatal myocardial infarction (P=0.014), a 29% lower risk of death for any reason or nonfatal myocardial infarction (P=0.002) and a 40% lower risk of fatal or nonfatal myocardial infarction (P=0.0098) than patients in the placebo group, Table 29. In these three analyses, all events that occurred until the end of the trial were included regardless of whether patients were taking their assigned medication or the duration of time that the study medication had been discontinued.

Table 28. Comparison of Results of the CAPRICORN Trial with Earlier Post-Infarction Trials Carried Out with Beta-Blockers Approved for Use in Post-Infarction Patients

Study Name (Year Published)	Treatment Groups -- Study Drugs (# of patients)	Average duration of F/U	# Patients with Nonfatal MI		P value
			PBO	βB	
Norwegian Multi-Centre Study (1981)[3]	Placebo (n=939) Timolol (n=945)	17 months	141 (15.0%)	88 (9.3%)	< 0.001
Goteborg Metoprolol Trial (1981)[4]	Placebo (n=697) Metoprolol (n=698)	3 months	39 (5.6%)	26 (3.7%)	= 0.12
Beta-Blocker Heart Attack Trial (1982)[6]	Placebo (n=1921) Propranolol (n=1916)	25 months	101 (5.3%)	85 (4.4%)	= 0.84
Lopressor Intervention Trial (1987)[9]	Placebo (n=1200) Metoprolol (n=1195)	18 months	NA	NA	NA
CAPRICORN Trial (2001)[41]	Placebo (n=984) Carvedilol (n=975)	15 months	57 (5.8%)	34 (3.5%)	= 0.01

The table lists all long-term trials with timolol, metoprolol and carvedilol which enrolled more than 1000 patients and recorded more than 75 deaths. *The Goteborg Metoprolol Trial is unique among the 5 trials in that patients received the study medication initially during the acute phase of their illness by the IV route followed by double-blind oral treatment for only 3 months. The Norwegian Timolol Trial analysis of reinfarctions did not include events occurring > 28 days following withdrawal of the study drug. PBO=placebo; βB=beta-blocker; MI=myocardial infarction; NA=not available.

Table 29. CAPRICORN: Effect of Carvedilol on Occurrence of Myocardial Infarction

	Placebo (n=984)	Carvedilol (n=975)	Hazard Ratio (95% CI)	P value
Hospitalization for non-fatal myocardial infarction	57	34	0.59 (0.39-0.90)	0.014
Fatal or non-fatal occurrence of myocardial infarction	66	40	0.60 (0.40-0.89)	0.010
CV death or non-fatal myocardial infarction	181	128	0.70 (0.56-0.87)	0.002
Any death or non-fatal myocardial infarction	192	139	0.71 (0.57-0.89)	0.002

All analyses reflect hazard ratio of carvedilol:placebo with 95% confidence intervals. P values were derived from the log rank test and are based on post hoc analyses. CV=cardiovascular.

It should be noted that most post-infarction trials with beta-blockers observed that patients randomized to the beta-blocker had a lower risk of a cardiac arrhythmia

(reported as an adverse event). It is therefore noteworthy that, when arrhythmias reported as adverse events were analyzed post hoc in the CAPRICORN trial, patients in the carvedilol group had a 52% lower risk of a supraventricular arrhythmia (P=0.0015); a 59% lower combined risk of atrial flutter or atrial fibrillation (P=0.0003); a 63% lower risk of a ventricular arrhythmia (P<0.0001); and a 70% lower combined risk of ventricular tachycardia or ventricular fibrillation (P<0.0001), Table 30.

Table 30. CAPRICORN: Effect of Carvedilol on Occurrence of Cardiac Arrhythmia (Reported as an Adverse Event)

	Placebo (n=984)	Carvedilol (n=975)	Hazard Ratio (95% CI)	P value
Any supraventricular arrhythmia	54	26	0.48 (0.30-0.76)	0.0015
Atrial flutter or atrial fibrillation	53	22	0.41 (0.25-0.68)	0.0003
Any ventricular arrhythmia	69	26	0.37 (0.24-0.58)	< 0.0001
Ventricular tachycardia or ventricular fibrillation	40	12	0.30 (0.16-0.57)	< 0.0001

All analyses reflect hazard ratio of carvedilol:placebo with 95% confidence intervals. P values were derived from the log rank test.

Finally, in the CAPRICORN trial, reports of serious adverse events related to the occurrence of heart failure, myocardial infarction, heart arrest and arrhythmias were all less frequent in patients in the carvedilol group, as compared with the placebo group (Table 31).

Table 31. CAPRICORN: Number of Patients Who Experienced Serious Adverse Events for Selected Cardiovascular Reasons

	Placebo	Carvedilol
Heart failure reported as serious AE	91	78
Myocardial infarction reported as serious AE	88	54
Cerebrovascular accident reported as serious AE	11	11
Heart arrest reported as serious AE	14	6
Atrial fibrillation reported as serious AE	16	2
Ventricular tachycardia reported as serious AE	15	1

5.2.3. Use of Open-Label Beta-Blocker Therapy

A high frequency of use of open-label beta-blockers was not anticipated when the CAPRICORN study was originally designed, but occurred due to the announcement during the course of the CAPRICORN trial of favorable results in two large-scale trials of beta-blockers in chronic heart failure (CIBIS II[42] and MERIT-HF[43]). The announcement of favorable results in these two trials led the Data and Safety Monitoring Board (DSMB) of the CAPRICORN trial to recommend that the protocol-specified prohibition of open-label beta-blocker use be abandoned. As a result of the announcement of the CIBIS II and MERIT-HF trial results, the frequency of use of open-label beta-blockers was 12% in the CAPRICORN trial, as compared with 3-5% in most of the earlier post-infarction trials with beta-blockers (Table 32) and less than 5% in the COPERNICUS trial.[39]

Table 32. Comparison of the CAPRICORN Trial with Earlier Post-Infarction Trials Carried Out with Beta-Blockers Approved for Use in Post-Infarction Patients

Study Name (Year Published)	Treatment Groups Study Drugs (# of patients)	Average Duration of F/U	Patients Who Discontinued Double-Blind Therapy	Patients Who Received Open-Label β-Blocker
Norwegian Multi-Centre Study (1981)[3]	Placebo (n=939) Timolol (n=945)	17 months	27%	5%
Goteborg Metoprolol Trial (1981)[4]	Placebo (n=697) Metoprolol (n=698)	3 months	19%	5%
Beta-Blocker Heart Attack Trial (1982)[6]	Placebo (n=1921) Propranolol (n=1916)	25 months	24%	10%
Lopressor Intervention Trial (1987)[9]	Placebo (n=1200) Metoprolol (n=1195)	18 months	31%	≈ 5%
CAPRICORN Trial (2001)[41]	Placebo (n=984) Carvedilol (n=975)	15 months	24%	12%

The table lists all long-term trials with timolol, metoprolol and carvedilol which enrolled more than 1000 patients and recorded more than 100 deaths. *The Goteborg Metoprolol Trial is unique among the 5 trials in that patients received the study medication initially during the acute phase of their illness by the IV route followed by double-blind oral treatment for only 3 months. PBO=placebo; β□B=beta-blocker; MI=myocardial infarction; NA=not available.

The high frequency of use of open-label beta-blockade may have acted to minimize the risk of an occurrence of a major cardiovascular event in patients

randomized to placebo and thus minimize the observed difference between placebo and carvedilol. The impact of open-label beta-blocker use is particularly relevant given the fact that beta-blockers were used in an open-label manner more frequently in patients randomized to placebo than to carvedilol (145 vs 91 patients, 15% vs 9%, respectively). Such impairment probably did not occur in earlier post-infarction trials with other beta-blockers because they had a lower frequency of open-label use of beta-blockers (Table 26) and because they did not collect data on the occurrence of major clinical events following the withdrawal of the study drug (and thus during the use of open-label beta-blockers).

Therefore, it is possible that the frequent use of an open-label beta-blocker in the CAPRICORN trial could contribute to the lack of an effect of carvedilol on the combined risk of death or cardiovascular hospitalization. In the CAPRICORN study, carvedilol reduced the combined risk of death or cardiovascular hospitalization by only 8%, but 12% of the patients received open-label treatment with a beta-blocker. In contrast, carvedilol was successful in reducing the combined risk of death or cardiovascular hospitalization by 20-30% in three heart failure studies (US Carvedilol Trials,[38] Australia-New Zealand Trial[36] and COPERNICUS[39]), all of which had a very low use of open-label beta-blockers (2-5%).

5.2.4. Safety and Tolerability

The safety profile of carvedilol in the CAPRICORN trial was nearly identical to that seen in other controlled trials of carvedilol and other beta-blockers. Patients in the carvedilol group were more likely to experience adverse events previously associated with drugs that block alpha or beta-adrenergic receptors (e.g., hypotension, dizziness, bradycardia, syncope, peripheral vascular disease and edema) and were less likely to experience adverse events reflecting worsening of the underlying disease (e.g., myocardial infarction, atrial fibrillation, tachycardia, or ventricular tachycardia). No new safety issues were identified in the current study.

5.3. Summary and Conclusions

The data summarized in this document support the following conclusions:

Based upon several trials in patients with mild, moderate or severe heart failure, carvedilol has been shown to reduce the risk of death and the combined risk of

death or cardiovascular hospitalization in patients with left ventricular systolic dysfunction, including those whose left ventricular dysfunction is the result of a remote myocardial infarction (> 1 month).

1. Previous post-infarction trials with beta-blockers (timolol, propranolol and metoprolol) demonstrated the efficacy of these drugs in reducing the risk of death (and probably of reinfarction), but the results of these studies are difficult to apply to the current era since (1) high risk patients were generally not enrolled in these studies, including those with heart failure prior to randomization or with a systolic blood pressure < 100 mm Hg; (2) many currently available treatments for the *immediate* management of the post-infarction patient (e.g., ACE inhibitors, intravenous nitroglycerin and intravenous heparin, and thrombolytics) were not available or were not generally used; (3) patients receiving appropriate treatments for the *long-term* management of the post-infarction patient (e.g., aspirin, anticoagulants and lipid lowering drugs) were not allowed in the trials to minimize the likelihood that these concomitant treatments might diminish the ability to detect a benefit of beta-blockade; and (4) the trials frequently had multiple primary endpoints (without correction for such multiplicity), and data on non-fatal events was generally incomplete in patients who discontinued treatment with the study drug
2. The CAPRICORN trial evaluated the efficacy of carvedilol in patients with left ventricular dysfunction and a recent myocardial infarction (< 21 days), who were at high risk and were receiving all appropriate treatments for the immediate and long-term management of the post-infarction patients, including ACE inhibitors in all patients. The trial collected complete data on fatal and non-fatal events whether or not patients continued receiving their study medication.
3. The original primary endpoint of the CAPRICORN trial was all-cause mortality, and carvedilol reduced the risk of death by 23% (P=0.03). Although the level of significance achieved was less than that specified in a protocol amendment ($\alpha=0.005$) triggered by DSMB concerns related to newly evolving data from the CIBIS II and MERIT-HF trials, the trial achieved its original objective, both in terms of the magnitude of the expected treatment effect (i.e., $\geq 20\%$) and the level of statistical significance (i.e., ≤ 0.05). The

- observed magnitude of the mortality effect (23%) is identical to that observed in a recent meta-analysis of post-infarction beta-blocker trials carried out before the widespread use of ACE inhibitors in post-infarction patients.
4. Carvedilol reduced the risk of death or cardiovascular hospitalization by 8% ($P=0.297$), but the effect on this endpoint became substantially larger (17%) and nominally significant ($P=0.019$, post hoc analysis) when only hospitalization for major cardiovascular events (heart failure, myocardial infarction, unstable angina, supraventricular and ventricular arrhythmias, stroke and TIA, and bradycardia and heart block) were included in the analysis. The results of the latter analysis is noteworthy since all other large-scale trials of post-infarction patients with left ventricular dysfunction (trials with ACE inhibitors and eplerenone) as well as many trials in chronic heart failure (e.g., COPERNICUS and PRAISE[52]) included only major cardiovascular events in the analysis of cardiovascular hospitalizations.
 5. • Secondary and post hoc analyses demonstrated that carvedilol reduced the risk of a cardiovascular death by 25% (nominal $P=0.024$); the risk of sudden death by 26% (nominal $P=0.099$); and the risk of death due to worsening heart failure by 40% (nominal $P=0.083$). In addition, carvedilol reduced the risk of a non-fatal myocardial infarction by 41% (nominal $P=0.014$); the combined risk of a fatal or non-fatal myocardial infarction by 40% (nominal $P=0.010$); the combined risk of cardiovascular death or a non-fatal myocardial infarction by 30% (nominal $P=0.002$); and the combined risk of all-cause mortality or non-fatal myocardial infarction by 29% (nominal $P=0.002$). These effects are similar to those reported in earlier post-infarction trials with other beta-blockers.
 6. Carvedilol was well tolerated in the current study, and no new safety concerns were identified. As in earlier beta-blocker trials, patients in the carvedilol group were more likely to experience adverse events previously associated with drugs that block alpha or beta-adrenergic receptors (e.g., hypotension, dizziness, bradycardia, syncope, peripheral edema and peripheral vascular disease) and were less likely to experience adverse events reflecting worsening of the underlying disease (e.g., myocardial infarction, atrial fibrillation, tachycardia, or ventricular tachycardia).

7. All of these benefits were seen even though the use of open-label beta-blockers was substantially higher in the CAPRICORN trial than in earlier trials of beta-blockers in post-infarction patients or in patients with heart failure. The high frequency of use of open-label beta-blockade would have been expected to reduce observed differences between the placebo and carvedilol groups. The impact of open-label beta-blocker use is particularly relevant given the fact that beta-blockers were used in an open-label manner earlier and more frequently in patients randomized to placebo than to carvedilol.

Therefore, the CAPRICORN trial demonstrated that the administration of carvedilol to high-risk patients receiving optimal modern treatment for and following an acute myocardial infarction was associated with effects extremely similar to those reported in earlier post-infarction trials with other beta-blockers in lower risk patients not receiving intensive adjunctive treatments.

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6. REGULATORY PERSPECTIVE

The Advisory Committee is being asked by the Division of Cardio-Renal Drug Products to provide recommendations to the FDA as to how the results of the CAPRICORN trial might best be communicated to physicians, and if deemed appropriate, how the current labeling for carvedilol might be modified. The Committee is being asked two questions: (1) Should the results of the CAPRICORN trial be incorporated into labeling? If yes, (2) how should the results of the CAPRICORN trial be incorporated into labeling?

6.1. Should the Results of CAPRICORN Be Incorporated into Labeling?

The results of large-scale trials are most easily interpreted when the trials show an effect of treatment on a clinically relevant prespecified primary endpoint at prespecified levels of statistical significance. However, if this were the only criterion for approval of labeling for drugs, there would be no need for a review of the current application by the Advisory Committee, since there is general agreement that the results of the CAPRICORN trial do not fulfill this criterion. Indeed, the FDA has allowed drugs to be labeled for use based on the results of trials that did not achieve their primary endpoint. For example,

- Digoxin is currently indicated for the treatment of mild to moderate heart failure to reduce heart failure-related hospitalizations. The trial that observed this benefit (the DIG trial[53]) did not achieve its primary endpoint (all-cause mortality). A detailed description of the results of the trial are incorporated into the approved labeling, including the lack of an effect on the primary endpoint of all-cause mortality.
- Enalapril is currently indicated for the treatment of clinically stable asymptomatic patients with left ventricular dysfunction (ejection fraction \leq 35%) to decrease the rate of development of overt heart failure and decrease the incidence of hospitalization for heart failure. The trial that observed this benefit (the SOLVD Prevention Trial[54]) did not achieve its primary endpoint (all-cause mortality). A detailed description of the results of the trial are incorporated into the approved labeling, including the lack of an effect on the primary endpoint of all-cause mortality.

In both instances, the evidence supporting the existence of a favorable effect of treatment on an important measure of clinical outcome was deemed to be persuasive, even though the measure that had been identified a priori to be of primary importance was not influenced by therapy.

Therefore, the primary purpose of a review of the CAPRICORN trial by the Advisory Committee is to consider whether the circumstances surrounding the use of carvedilol in post-infarction patients with left ventricular dysfunction are persuasive and would justify the incorporation of the results of the CAPRICORN trial into current labeling for carvedilol.

The CAPRICORN trial observed a nominally significant reduction in mortality in a large-scale trial that did not achieve its primary endpoints at prespecified levels of statistical significance. Should the finding of a mortality benefit be incorporated into labeling if the trial did not achieve its primary endpoint? Death is a unique and exceptionally compelling endpoint, since it is unbiased, can be readily assessed (even in patients who drop out of the study), prevents the evaluation of other endpoints, and is of paramount clinical importance. It is arguably more persuasive that a reduction in hospitalizations for heart failure (the benefit described in current labeling for digoxin and enalapril). For these reasons, in the past, the FDA has allowed mortality finding to be described in labeling even when the trial that noted the survival effect did not intend to evaluate mortality and had insufficient power to do so and even when the primary endpoint of the trial was not met. In doing so, it has acted as if all trials implicitly have an $\alpha=0.05$ assigned to mortality, even if it were not prespecified.

Some might argue that such an approach carries too much risk and that not every trial showing a mortality reduction should be viewed with enthusiasm. Indeed, recent large-scale clinical trials in heart failure with losartan and vesnarinone suggest that striking mortality benefits observed in trials designed and powered to evaluate some other effect of the drug may not be reproduced when a larger trial is carried out to confirm the encouraging observation. For example, the initial observation that vesnarinone reduced mortality by 50% was based on an analysis of a secondary endpoint in a trial[55] that recorded only 46 deaths and was not designed to evaluate the effect of the drug on the risk of death. In a larger trial[56] that was designed to look at mortality, vesnarinone was shown to increase mortality rates. Similarly, the initial observation that losartan reduced mortality by 46% when compared with captopril was based on an analysis of a secondary endpoint in a trial[57] that recorded only 49 deaths and was not designed to compare the survival effects of two drugs. A larger trial[58] that was specifically designed to compare the mortality effects of losartan and captopril

failed to confirm the earlier finding. These experiences indicate that great caution is needed when striking (and improbable) mortality benefits are observed in trials not designed to discern them, especially when the survival analysis is based on a small number of events.

Do the lessons learned in trials with vesnarinone and losartan apply to the interpretation of the results of CAPRICORN? Unlike the initial trials with vesnarinone and losartan, the CAPRICORN trial was specifically designed to evaluate the effects of carvedilol on survival, and consequently, all-cause mortality was originally designated as the primary endpoint and was the primary variable used to determine the power of the study and to guide monitoring by the Data and Safety Monitoring Board. As a result, the trial recorded a large number of deaths (n=267), a number comparable to that recorded in earlier post-infarction beta-blocker trials (Table 26). [The large number of events is particularly relevant in light of the fact that the annual mortality rate in the CAPRICORN trial was higher than in earlier post-infarction trials.] Furthermore, the magnitude of the observed reduction in the risk of death in the CAPRICORN trial was neither dramatic nor improbable but was actually identical to that observed in several earlier studies of beta-blockers in post-infarction patients (Table 33). Hence, the experience with carvedilol in CAPRICORN can be and should be distinguished from the experiences with vesnarinone and losartan in that (1) CAPRICORN was designed as a mortality study; and (2) the results of CAPRICORN have been reproduced in other post-infarction beta-blocker trials.

Table 33. Comparison of Results of the CAPRICORN Trial with Earlier Post-Infarction Trials (Hazard Ratios and 95% CI)

	Meta-analysis of earlier post-MI trials*	CAPRICORN Trial
All-cause mortality	0.77 (0.69-0.85)	0.77 (0.60-0.98)

* Source: Freemantle et al, Br Med J 1999; 318:1730-7. The meta-analysis is based on 2415 deaths among 24,974 who were enrolled in 31 long-term trials of beta-blockers in survivors of an acute myocardial infarction.

Despite this reasoning, it would not be appropriate to suggest that the Advisory Committee ignore the fact that the α assigned to the primary endpoint of mortality was changed during the course of the trial and that the observed mortality effect did not achieve the levels of significance prespecified in the protocol amendment. However, it is important to place this failure into the proper perspective. The

Committee is presented with the data from a large-scale clinical trial that was designed to evaluate survival and observed a nominally significant reduction in mortality that was identical in magnitude to that seen in other large-scale trials with other members of the same class of drug when used in the same clinical setting. The trial failed to achieve its primary endpoint at the prespecified α because of a strong recommendation by the Data and Safety Monitoring Board to change the primary endpoint — a recommendation that would have been difficult for the Steering Committee and the sponsor to ignore. Given these unique circumstances, the risk of erroneously concluding that carvedilol reduces mortality in post-infarction patients with left ventricular systolic dysfunction would seem to be extremely low.

How appropriate is it to consider the results of earlier trials in modifying the level of persuasiveness needed to reach conclusions about efficacy from a single study? The Advisory Committee has recently had the opportunity of addressing this specific issue. In its deliberations concerning the efficacy of losartan in patients with diabetic nephropathy, the Committee expressed skepticism about the persuasiveness of the losartan data based on a single trial[59] that observed a $P < 0.05$ but > 0.01 on a primary combined endpoint, which included a component of uncertain clinical significance.[60] The comfort level of the Committee increased when post hoc reanalysis of the primary endpoint (excluding the questionable component) continued to demonstrate a treatment effect. However, the Committee determined that the results reached a critical level of persuasiveness when the findings in the losartan trial were considered together with the findings of a similar trial with irbesartan[61] in the same disease — a trial which when viewed alone did not lead the Committee to recommend the approval of irbesartan.[62] Therefore, the Committee determined that the results of earlier trials with the same class of drug in the same disease could be used to add meaningfully to the persuasiveness of data from a single trial with a member of the same class evaluated in the same condition.

However, the principle formulated by the Committee during its review of losartan in diabetic nephropathy would logically apply to the current situation with carvedilol only if (1) the Committee were comfortable concluding that the effect of β -blockers on mortality in post-infarction patients was due to blockade of the β -adrenergic receptor; and (2) carvedilol had no other properties that might detract from the ability of its β -blocking actions to reduce the risk of death. Fulfillment of these two criteria would lead to a situation precisely parallel to the consideration of the approval of angiotensin II antagonists for the treatment of diabetic nephropathy. In that example, the Committee believed that (1) the benefits of treatment were related to blockade of the angiotensin II receptor and

that (2) neither losartan nor irbesartan were likely to have effects other than angiotensin II antagonism that might detract from their benefits in preventing the progression of renal disease.

Are the effects of β -blockers on mortality in post-infarction patients the result of their antagonistic actions on the β -adrenergic receptor? Large-scale controlled clinical trials[3,4,6,63] with at least four different β -blockers (e.g., timolol, propranolol, metoprolol and acebutolol) have shown a reduction in mortality when these drugs were administered long-term to post-infarction patients. These drugs vary in their degree of β selectivity, lipophilicity, membrane-stabilizing properties and intrinsic sympathomimetic activity; yet, each agent is a potent antagonist of the β -1 adrenergic receptor. Such evidence provides strong support for the hypothesis that the effect of β -blockers on mortality in post-infarction patients is due to blockade of the β -1 adrenergic receptor.

That is not to say that all drugs that block β -1 adrenergic receptors have similar effects in reducing mortality in post-infarction patients. Table 34 summarizes the findings of a recent meta-analysis by Freemantle et al.[2] that explored possible relations between the pharmacological properties of specific β -blockers and their effects on mortality in long-term post-infarction trials. Overall, long-term treatment with a β -blocker was accompanied by a 23% reduction in the risk of death. However, the magnitude of the effect appeared to be attenuated in trials with β -blockers that had intrinsic sympathomimetic activity (odds ratio for the interaction test = 1.19 [0.96-1.47]). An earlier meta-analysis by Yusuf et al.[1] also indicated diminished efficacy with β -blockers that have intrinsic sympathomimetic activity.

Table 34. Relation of Pharmacological Properties and Survival Effects of Specific Beta-Blockers in Placebo-Controlled Trials of Post-Infarction Patients

Drug	β -1 receptor blockade	Cardio-selective	Intrinsic sympathomimetic activity	Odds ratio vs placebo (95% CI)
Timolol	+	—	—	0.59 (0.46-0.77)
Propranolol	+	—	—	0.71 (0.59-0.85)
Sotalol	+	—	—	0.80 (0.54-1.21)
Metoprolol	+	+	—	0.80 (0.66-0.96)
Practolol	+	+	+	0.80 (0.63-1.02)
Alprenolol	+	—	+	0.83 (0.59-1.17)
Oxprenolol	+	—	+	0.91 (0.71-1.17)
Pindolol	+	—	+	0.96 (0.60-1.55)
All β -blockers				0.77 (0.69-0.85)

Included in this table are all β -blockers that have been evaluated in placebo-controlled trials that recorded (collectively) more than more than 75 deaths. Drugs are listed in order of increasing odds ratios. Data are from Freemantle et al (ref 2).

In light of these findings, it is noteworthy that carvedilol is a nonselective β -blocker that has no intrinsic sympathomimetic activity, and it is not known to possess any other pharmacological property that might diminish its survival benefit. In fact, if one adds the data from the CAPRICORN trial to Table 34, the effects of carvedilol are consistent with those that might be anticipated from its known pharmacological actions (Table 35).

**Table 35. Relation of Pharmacological Properties and Survival Effects of Specific Beta-Blockers in Placebo-Controlled Trials of Post-Infarction Patients
(Including CAPRICORN)**

Drug	β -1 receptor blockade	Cardio-selective	Intrinsic sympatho-mimetic activity	Odds ratio vs placebo (95% CI)
Timolol	+	—	—	0.59 (0.46-0.77)
Propranolol	+	—	—	0.71 (0.59-0.85)
Carvedilol	+	—	—	0.74 (0.57-0.95)
Sotalol	+	—	—	0.80 (0.54-1.21)
Metoprolol	+	+	—	0.80 (0.66-0.96)
Practolol	+	+	+	0.80 (0.63-1.02)
Alprenolol	+	—	+	0.83 (0.59-1.17)
Oxprenolol	+	—	+	0.91 (0.71-1.17)
Pindolol	+	—	+	0.96 (0.60-1.55)
All β -blockers				0.77 (0.69-0.85)

Included in this table are all β -blockers that have been evaluated in placebo-controlled trials that recorded (collectively) more than more than 75 deaths. Drugs are listed in order of increasing odds ratios. Odds ratios for carvedilol are based on the data from both the CHAPS and CAPRICORN trials. Data for other beta-blockers are from Freemantle et al (ref 2).

Despite the analyses presented in Tables 34 and 35, is it still possible for carvedilol to exert a pharmacological effect (known or unknown) that might detract from its survival benefit? To answer this question, it is useful to examine the effect of β -blockers in a disorder closely related to left ventricular dysfunction following a recent myocardial infarction, i.e., left ventricular dysfunction following a remote myocardial infarction. [Both disorders include patients with symptoms of heart failure (nearly 50% of the patients in CAPRICORN had heart failure before randomization).] The two disorders are part of a single disease continuum, with patients moving from one phase of the disease to the next over a period of weeks, months or years. Furthermore, similar neurohormonal factors are believed to be important both early and late in the disease process, thereby explaining why both ACE inhibitors and β -blockers are effective in improving outcomes at both time points in the disease continuum.

Three β -blockers have been shown to reduce mortality in patients with left ventricular dysfunction and chronic heart failure (bisoprolol, carvedilol and

extended-release metoprolol) [Table 36], and the magnitude of this benefit is similar in patients with and without a remote history of an acute myocardial infarction. Carvedilol has been shown to reduce mortality in patients with left ventricular dysfunction and chronic heart failure (many of whom had survived a myocardial infarction),[38,39] and the magnitude of this benefit is extremely similar to that produced by other β -blockers in this disorder,[42,43] both in patients with and without a history of a remote myocardial infarction (Table 36).[64] If carvedilol had a pharmacological property that detracted from its ability to reduce mortality, such an action should have been apparent in trials with the drug in chronic heart failure and should have negated or diminished its effect relative to other β -blockers. Indeed, the single property that has been associated with reduced survival efficacy in patients with a recent myocardial infarction — intrinsic sympathomimetic activity — has also been associated with reduced survival efficacy in patients with chronic heart failure. Specifically, the presence of intrinsic sympathomimetic activity has been proposed to explain the lack of efficacy with bucindolol in the BEST trial[65] (bucindolol has mild sympathomimetic effects[66-68]) and the increased mortality observed in a trial with xamoterol[69] (xamoterol has major sympathomimetic effects[70]).

These observations indicate that (1) the pharmacological properties of β -blockers that may diminish their survival effects appear to be similar in post-infarction patients and in patients with chronic heart failure; and (2) carvedilol is not likely to exert effects that detract from the ability of its β -blocking actions to reduce mortality in patients with left ventricular dysfunction.

Table 36. Effect of Long-Term Treatment with Beta-blockers on the Survival of Patients with Chronic Heart Failure

Study Name	Treatment Groups (# of patients)	Hazard ratio for mortality (95% CI): All Patients	Hazard ratio for mortality (95% CI): Prior MI
CIBIS II[42]	Placebo (n=1320) Bisoprolol (n=1327)	0.66 (0.54-0.81) P < 0.001	0.60 (0.45-0.80)
MERIT-HF[43,59]	Placebo (n=2001) Metoprolol (n=1990)	0.66 (0.53-0.81) P < 0.001	0.60 (0.45-0.80)
COPERNICUS[39]	Placebo (n=1133) Carvedilol (n=1156)	0.65 (0.52-0.81) P < 0.001	0.61 (0.45-0.83)
BEST[60]	Placebo (n=1354) Bucindolol (n=1354)	0.90 (0.78-1.02) P = 0.13	0.95 (0.80-1.10)
Xamoterol Severe Heart Failure Study[64]	Placebo (n=164) Xamoterol (n=352)	2.54 (1.04-6.18) P = 0.02	Not evaluated

* In the Xamoterol Severe Heart Failure Study, there were 32 deaths in the placebo group and 6 deaths in the placebo group. Four studies were stopped by their DSMBs, three because of a mortality benefit (CIBIS II, MERIT-HF and COPERNICUS) and one because of futility (BEST). The effects of carvedilol and metoprolol in post-infarction patients were calculated directly by the sponsor (for carvedilol) or have been published in abstract form (reference 59). The effects of bisoprolol and bucindolol in post-infarction patients were assumed to be identical to the effects of these drugs in the subgroup of patients with an ischemic cardiomyopathy and were estimated from the graphs provided in the papers describing the primary results of the studies. MI=myocardial infarction.

In light of all of these observations, the Committee is being asked whether the mortality reduction observed in CAPRICORN represents a credible finding. In considering this question, the Committee might be wondering: Would it not be setting a dangerous precedent if it recommended a labeling change based on a trial that did not achieve its primary endpoint? In the past, the FDA has determined that the finding of a favorable effect on a major outcome variable can form the basis for an indication even when the trial did not achieve its primary endpoint. In addition, the FDA has allowed mortality benefits to be described in labeling even when the trial that noted the survival effect did not intend to evaluate mortality and had insufficient power to do so (the concept that all trials implicitly have an $\alpha=0.05$ assigned to mortality). If this principle were the only argument put forth in favor of a favorable recommendation by the Committee on behalf of carvedilol, then the mortality benefit in CAPRICORN — considered entirely on its own — might be viewed as a credible finding.

However, in the case of carvedilol, the strength of evidence pertaining to this issue is far greater than the usual set of circumstances and exceeds the standard that might be suggested by the concept that all trials implicitly have an $\alpha=0.05$ assigned to mortality. This is because, in addition to the finding of a nominally significant mortality reduction, there are several unique aspects of the current database:

- The CAPRICORN trial was actually designed to evaluate the effect of carvedilol on survival, and the number of deaths recorded in the trial was comparable to that seen in other mortality trials in post-infarction patients.
- The mortality finding in CAPRICORN has been replicated in other trials that evaluated the effect of beta-blockers in post-infarction patients. The magnitude of the reduction in mortality risk with carvedilol was very similar to that seen in these earlier trials. The effects of treatment with carvedilol on non-fatal events in the CAPRICORN study was also similar (both in direction and magnitude) to those seen in these earlier studies.
- Data from other trials with carvedilol in patients with chronic heart failure indicate that treatment with the drug reduces mortality in a disorder which is closely related to that seen in the post-infarction patient. The magnitude of the benefit of carvedilol is almost identical to that seen with other β -blockers in chronic heart failure. These additional findings indicate that carvedilol does not exert effects that may detract from the ability of its β -blocking actions to reduce mortality in patients with left ventricular dysfunction.

This unique combination of circumstances should greatly reduce the risk of reaching incorrect conclusions about the existence of a survival benefit with carvedilol in post-infarction patients and thus should minimize the need to require a highly significant mortality reduction as a prerequisite to reaching a favorable interpretation of the results of the CAPRICORN trial. [Given the α assigned to the mortality analysis in the amended protocol, one would have had to have observed a highly significant mortality reduction for the CAPRICORN trial to have met its primary mortality endpoint.] Hence, if the Committee were to set a very high standard before recommending a favorable regulatory action on data

from a trial that did not achieve its primary endpoint, such a standard would appear to be fulfilled by the current circumstances.

It is recognized that none of these deliberations would be necessary if carvedilol had had a favorable effect on the combined risk of death or cardiovascular hospitalization, the co-primary endpoint to which most of the alpha was assigned following the protocol amendment. Given the favorable effect on the risk of death or cardiovascular hospitalization in other large-scale outcome trials with carvedilol in severe chronic heart failure and with ACE inhibitors in post-infarction patients with left ventricular systolic dysfunction, such an effect was anticipated. However, it should be recognized that this endpoint was defined differently in the CAPRICORN trial than in the other studies referred to in the previous sentence. Cardiovascular hospitalization in the CAPRICORN trial was defined as a hospitalization for any cardiovascular reason (except for an elective procedure), whereas a cardiovascular hospitalization in the SAVE, AIRE, TRACE and COPERNICUS studies[15,39,45,46] included only major and specific cardiovascular events. The decision to include all nonprocedural cardiovascular hospitalizations in the definition of a cardiovascular hospitalization had an important influence on the results of the CAPRICORN study, since post hoc reanalysis of the primary endpoint using a definition that focused only on major cardiovascular hospitalizations revealed a nominally significant effect ($P=0.019$) in favor of carvedilol. It should also be noted the effect of treatment on the broad range of cardiovascular hospitalizations in earlier post-infarction beta-blocker trials is unknown, since the only non-fatal cause of hospitalization analyzed in these earlier studies was recurrent myocardial infarction — although reports of these trials make clear that many cardiovascular events other than death or reinfarction appeared to be unchanged or increased as a result of treatment. None of these lines of evidence is offered with the intent of persuading the Advisory Committee that carvedilol reduces the risk of death or cardiovascular hospitalization, but in the hope that this information can provide a credible explanation why this expected effect was not found.

If the Committee were to agree that the mortality finding in the CAPRICORN trial is credible, it would still need to consider why it should recommend incorporation of this information into current labeling for carvedilol. Some might argue that carvedilol is already approved for the treatment of post-infarction patients, albeit those with a *remote* history of an infarction and current symptoms of heart failure, and that other beta-blockers (e.g., timolol, propranolol and immediate-release metoprolol) are already approved for use in survivors of an acute myocardial infarction. Conceivably, these other beta-blockers could be used in the immediate post-infarction period, and patients could be switched to

carvedilol (if deemed appropriate) when the acute phase had passed and symptoms of dyspnea became apparent. However, there are insufficient data to recommend the addition of *any* beta-blocker currently approved for use in infarct survivors to an ACE inhibitor in patients who have left ventricular systolic dysfunction following their acute infarction. Furthermore, *all* beta-blockers currently approved for use in infarct survivors carry a contraindication for use in patients with heart failure. As a result, the frequency of use of *any* beta-blocker in patients with left ventricular dysfunction following an acute myocardial infarction is extremely low, even in academic medical centers.[15] If the Committee believed (based on the totality of available evidence) that such patients would benefit from early treatment with a beta-blocker, it would be reasonable to allow information regarding such use to be incorporated into labeling. The only beta-blocker with controlled clinical trial data in this setting is carvedilol.

6.2. How Should the Results of CAPRICORN Be Incorporated into Labeling?

If deemed appropriate by the Division and the Advisory Committee, two approaches to a labeling revision are possible: (1) a description of the findings of the CAPRICORN trial may be added to the Clinical Trials section of labeling; and (2) a description of the findings of the CAPRICORN trial may be added to the Indications section of labeling (with or without an actual indication).

7. REFERENCES

1. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Prog Cardiovasc Dis* 1985;27:335-71
2. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ* 1999;318:1730-7.
3. Norwegian Multicentre Study Group. Timolol-induced Reduction in Mortality and Reinfarction in Patients Surviving Acute Myocardial Infarction . *N Engl J Med* 1981;304:801-7.
4. Hjalmarson A, Herlitz J, Malek, I, Ryden L , Vedin A, Waldenstrom A, Wedel H, Elmfeldt D, Holmberg S, Nyberg G, Swedberg K, Waagstein F, Waldenstrom J, Wilhelmsen L, Wilhelmsson C. Effects on mortality of metoprolol in acute myocardial infarction: A double-blind randomized trial. *Lancet* 1981;2:823-7.
5. Herlitz J, Hjalmarson A, Holmberg S, Swedberg K, Vedin A, Waagstein F, Waldenstrom A, Wedel H, Wilhelmsen L, Wilhelmsson C. Development of congestive heart failure after treatment with metoprolol in acute myocardial infarction. *Br Heart J* 1984;51:539-44.
6. A randomized trial of propranolol in patients with acute myocardial infarction. I. Mortality results. *JAMA* 1982;247:1707-14.
7. A randomized trial of propranolol in patients with acute myocardial infarction. II. Morbidity results. *JAMA* 1983;250:2814-9.
8. Chadda K, Goldstein S, Byington R, Curb JD. Effect of propranolol after acute myocardial infarction in patients with congestive heart failure. *Circulation* 1986;73:503-10.
9. Lopressor Intervention Trial Research Group. The Lopressor Intervention Trial: multicentre study of metoprolol in survivors of acute myocardial infarction. *Eur Heart J* 1987;8:1056-64.

-
10. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet* 1986 Jul 12;2(8498):57-66.
 11. Held P, Yusuf S. Early intravenous beta-blockade in acute myocardial infarction *Cardiology* 1989;76(2):132-43
 12. Nicholls SJ, McElduff P, Dobson AJ, Jamrozik KD, Hobbs MS, Leitch JW. Underuse of beta-blockers following myocardial infarction: a tale of two cities. *Intern Med J* 2001;31:391-6.
 13. Fehrenbach SN, Budnitz DS, Gazmararian JA, Krumholz HM. Physician characteristics and the initiation of beta-adrenergic blocking agent therapy after acute myocardial infarction in a managed care population. *Am J Manag Care* 2001;7:717-23.
 14. Bradford WD, Chen J, Krumholz HM. Under-utilisation of beta-blockers after acute myocardial infarction. Pharmacoeconomic implications. *Pharmacoeconomics* 1999;15:257-68.
 15. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliassen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC for the Trandolapril Cardiac Evaluation (TRACE) Study Group.. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995;333:1670-6.
 16. Vantrimpont P, Rouleau JL, Wun CC, Ciampi A, Klein M, Sussex B, Arnold JM, Moye L, Pfeffer M. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. SAVE Investigators. *J Am Coll Cardiol* 1997;29:229-36.
 17. Smith EF 3rd, Griswold DE, Hillegass LM, Slivjak MJ, Davis PA, DiMartino MJ. Cardioprotective effects of the vasodilator/beta-adrenoceptor blocker, carvedilol, in two models of myocardial infarction in the rat. *Pharmacology* 1992;44:297-305.
 18. Ma XL, Yue TL, Lopez BL, Barone FC, Christopher TA, Ruffolo RR Jr, Feuerstein GZ. Carvedilol, a new beta adrenoreceptor blocker and free radical scavenger, attenuates myocardial ischemic-reperfusion injury in hypercholesterolemic rabbits. *J Pharmacol Exp Ther* 1996; 277: 128-36.

-
19. Yue TL, Ma XL, Romanic AM, Liu GL, Louden C, Gu JL, Kumar S, Poste G, Ruffolo RR Jr, Feuerstein GZ. Possible involvement of stress-activated protein kinase signaling pathway and Fas receptor in prevention of ischemia/reperfusion-induced cardiomyocyte apoptosis by carvedilol. *Circ Res* 1998; 82: 166-74.
 20. Gao F, Chen J, Lopez BL, Christopher TA, Gu J, Lysko P, Ruffolo RR Jr, Ohlstein EH, Ma XL, Yue TL. Comparison of bisoprolol and carvedilol cardioprotection in a rabbit ischemia and reperfusion model. *Eur J Pharmacol* 2000;406:109-16
 21. Feuerstein G, Liu GL, Yue TL, Cheng HY, Hieble JP, Arch JR, Ruffolo RR Jr, Ma XL. Comparison of metoprolol and carvedilol pharmacology and cardioprotection in rabbit ischemia and reperfusion model. *Eur J Pharmacol* 1998; 351: 341-50.
 22. Brunvand H, Frlyland L, Hexeberg E, Rynning SE, Berge RK, Grong K. Carvedilol improves function and reduces infarct size in the feline myocardium by protecting against lethal reperfusion injury. *Eur J Pharmacol* 1996; 314: 99-107.
 23. Brunvand H, Kvitting PM, Rynning SE, Grong K. Carvedilol protects against lethal reperfusion injury through antiadrenergic mechanisms. *J Cardiovasc Pharmacol* 1996; 28: 409-17.
 24. Hamburger SA, Barone FC, Feuerstein GZ, Ruffolo RR Jr. Carvedilol reduces infarct size in a canine model of acute myocardial infarction. *Pharmacology* 1991; 43:113-20.
 25. Feuerstein GZ, Yue TL, Cheng HY, Ruffolo RR Jr. Myocardial protection by the novel vasodilating beta-blocker, carvedilol: potential relevance of anti-oxidant activity. *J Hypertens* 1193; 11 (suppl): S41-S48.
 26. Bril A, Slivjak M, DiMartino J, Feuerstein GZ, Linee P, Poyser RH, Ruffolo RR Jr, Smith EF. Cardioprotective effects of carvedilol, a novel beta-adrenoceptor antagonist with vasodilating properties, in anaesthetised minipigs: comparison with propranolol. *Cardiovasc Res* 1992; 26,:518-25.

-
27. Ohlstein EH, Vickery L, Arleth A, Barone F, Sung CP, Camden A, McCartney L. Carvedilol, a novel cardiovascular agent, inhibits development of vascular and ventricular hypertrophy in spontaneously hypertensive rats. *Clin Exper Hypertension* 1994, 16:163-77.
 28. Yang Y, Tang Y, Ruan Y, Li Y, Zhou Y, Gao R, Chen J, Chen Z. Comparative effects of cilazapril, carvedilol and their combination in preventing left ventricular remodelling after acute myocardial infarction in rats. *J Renin Angiotensin Aldosterone Syst* 2002;3:31-5.
 29. Khandoudi N, Percevault-Albadine J, Bril A. Comparative effects of carvedilol and metoprolol on cardiac ischemia-reperfusion injury. *J Cardiovasc Pharmacol* 1998; 32: 443-51.
 30. Yue TL, Wang X, Gu JL, Ruffolo RR Jr, Feuerstein GZ. Carvedilol prevents low-density lipoprotein (LDL)-enhanced monocyte adhesion to endothelial cells by inhibition of LDL oxidation. *Eur J Pharmacol* 1995; 294: 585-91.
 31. Yue TL, Wang X, Gu JL, Ruffolo RR Jr, Feuerstein GZ. Carvedilol, a new vasodilating beta-adrenoceptor blocker, inhibits oxidation of low-density lipoproteins by vascular smooth muscle cells and prevents leukocyte adhesion to smooth muscle cells. *J Pharmacol Exp Ther* 1995; 273: 1442-9.
 32. Ohlstein EH, Douglas SA, Sung C-P, Yue T-L, Louden C, Arleth A, Poste G, Ruffolo RR Jr, Feuerstein GZ. Carvedilol, a cardiovascular drug, prevents vascular smooth muscle cell proliferation, migration, and neointimal formation following vascular injury. *Proc Natl Acad Sci USA* 1993, 90:6189-93.
 33. Donetti E, Soma MR, Barberi L, Paoletti R, Fumagalli R, Roma P, Catapano AL. Dual effects of the antioxidant agents probucol and carvedilol on proliferative and fatty lesions in hypercholesterolemic rabbits. *Atherosclerosis* 1998; 141:45-51.
 34. Rodriguez-Perez JC, Losada A, Anabitarte A, Cabrera-Galvan J, Garcia P, Palop L, Plaza C. Effects of carvedilol, a new agent with multiple action on the preservation of renal structure and function in the rat remnant kidney. *J Am Soc Nephrol* 1993; 21:221-7.

-
35. Barone FC, Nelson AH, Ohlstein EH, Willette RN, Sealey JE, Laragh JH, Campbell WG Jr, Feuerstein GZ. Chronic carvedilol and propranolol reduces mortality and renal damage in hypertensive stroke-prone rats. *J Pharmacol Exp Ther*, 1996, 279:948-55.
 36. Australia-New Zealand Heart Failure Research Collaborative Group. Randomized, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischemic heart disease. *Lancet* 1997; 349: 375-80.
 37. Tillmann HC, Sharpe N, Sponer G, Wehling M. Does intention-to-treat analysis answer all questions in long-term mortality trials? Considerations on the basis of the ANZ trial. *Int J Clin Pharmacol Ther* 2001;39:205-12.
 38. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med* 1996; 334: 1349-1355.
 39. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; 344:1651-8.
 40. Basu S, Senior R, Raval U, van der Does R, Bruckner T, Lahiri A. Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction. A placebo-controlled, randomized trial. *Circulation* 1997;96:183-91.
 41. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;357:1385-90.
 42. CIBIS II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study (CIBIS II): a randomised trial. *Lancet* 1999;353:9-13.
 43. Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) Study Group. Effect of metoprolol CR/XL in chronic heart failure. *Lancet* 1999;353:2001-7.

-
44. Prescribing Information, Tenormin[®] I.V Injection (atenolol), AstraZeneca, Physicians Desk Reference, 2002.
 45. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:821-8.
 46. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ Jr, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1992;327:669-77.
 47. Pitt B, Williams G, Remme W, Martinez F, Lopez-Sendon J, Zannad F, Neaton J, Roniker B, Hurley S, Burns D, Bittman R, Kleiman J. The EPHEBUS trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. *Cardiovasc Drugs Ther* 2001;15:79-87.
 48. Doughty RN, Whalley GA, Gamble GD, et al. Effects of carvedilol on left ventricular remodelling in patients following acute myocardial infarction: The CAPRICORN Echo Substudy. *Circulation* 2001;104 (suppl II):II-517.
 49. Doughty RN, Whalley GA, Gamble GD, et al. Carvedilol and left ventricular remodeling post acute myocardial Infarction: variable effects over time and possible mechanisms. The CAPRICORN Echo Substudy. *Circulation* 2002;106 (suppl II):II-708.
 50. Reid JL, Whyte KF, Struthers AD. Epinephrine-induced hypokalemia: the role of beta adrenoceptors. *Am J Cardiol* 1986 Apr 25;57(12):23F-27F.
 51. Packer M, Fowler MB, Roecker EB, Coats AJ, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Staiger C, Holcslaw TL, Amann-Zalan I, DeMets DL for the COPERNICUS Study. Effect of carvedilol on the morbidity of patients with severe chronic heart failure. *Circulation* 2002;106:2194-9.
 52. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer JH, Cropp AB, DeMets DL for Prospective Randomized Amlodipine Survival Evaluation Study

-
- Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. *N Engl J Med* 1996;335:1107-14.
53. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525-33.
54. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91.
55. Feldman AM, Bristow MR, Parmley WW, Carson PE, Pepine CJ, Gilbert EM, Strobeck JE, Hendrix GH, Powers ER, Bain RP, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. *N Engl J Med* 1993;329:149-55.
56. Cohn JN, Goldstein SO, Greenberg BH, Lorell BH, Bourge RC, Jaski BE, Gottlieb SO, McGrew F 3rd, DeMets DL, White BG. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. *N Engl J Med* 1998;339:1810-6.
57. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snaveley DB, Chang PI. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;349:747-52.
58. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klinger GH, Neaton J, Sharma D, Thiyagarajan B. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. *Lancet* 2000;355:1582-7
59. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861-9.
60. Cardiovascular and Renal Drug Products Advisory Committee. Evaluation of losartan for diabetic nephropathy, April 12, 2002.

-
61. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851-60.
 62. Cardiovascular and Renal Drug Products Advisory Committee. Evaluation of irbesartan for diabetic nephropathy, January 17, 2002.
 63. Boissel JP, Leizorovicz A, Picolet H, Peyrieux JC. Secondary prevention after high-risk acute myocardial infarction with low-dose acebutolol. *Am J Cardiol* 1990;66:251-60
 64. Hjalmarson A, Wikstrand JC, Klibaner M, Czuriga I, Herlitz J, Janosi A, Ghali JK. Metoprolol CR/XL in post-myocardial infarction patients with chronic heart failure: experiences from MERIT-HF. *Circulation* 2002; 106 (suppl II): II-685.
 65. 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;344:1659-67.
 66. Bundkirchen A, Brixius K, Bolck B, Schwinger RH. Bucindolol exerts agonistic activity on the propranolol-insensitive state of beta1-adrenoceptors in human myocardium. *J Pharmacol Exp Ther* 2002;300:794-801.
 67. Andreka P, Aiyar N, Olson LC, Wei JQ, Turner MS, Webster KA, Ohlstein EH, Bishopric NH. Bucindolol displays intrinsic sympathomimetic activity in human myocardium. *Circulation* 2002;105:2429-34.
 68. Maack C, Cremers B, Flesch M, Hoper A, Sudkamp M, Bohm M. Different intrinsic activities of bucindolol, carvedilol and metoprolol in human failing myocardium. *Br J Pharmacol* 2000;130:1131-9.
 69. Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. *Lancet* 1990;336:1-6
 70. Nuttall A, Snow HM. The cardiovascular effects of ICI 118,587: A beta 1-adrenoceptor partial agonist. *Br J Pharmacol* 1982;77:381-8.