Articles

Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial

*The CAPRICORN Investigators**

Summary

Background The beneficial effects of β-blockers on long-term outcome after acute myocardial infarction were shown before the introduction of thrombolysis and angiotensin-converting-enzyme (ACE) inhibitors. Generally, the patients recruited to these trials were at low risk: few had heart failure, and none had measurements of left-ventricular function taken. We investigated the long-term efficacy of carvedilol on morbidity and mortality in patients with left-ventricular dysfunction after acute myocardial infarction treated according to current evidence-based practice.

Methods In a multicentre, randomised, placebo-controlled trial, 1959 patients with a proven acute myocardial infarction and a left-ventricular ejection fraction of ⩽40% were randomly assigned 6·25 mg carvedilol (n=975) or placebo (n=984). Study medication was progressively increased to a maximum of 25 mg twice daily during the next 4–6 weeks, and patients were followed up until the requisite number of primary endpoints had occurred. The primary endpoint was all-cause mortality or hospital admission for cardiovascular problems. Analysis was by intention to treat.

Findings Although there was no difference between the carvedilol and placebo groups in the number of patients with the primary endpoint (340 [35%] *vs* 367 [37%], hazard ratio 0·92 [95% CI 0·80–1·07]), all-cause mortality alone was lower in the carvedilol group than in the placebo group (116 [12%] *vs* 151 [15%], 0·77 [0·60–0·98], p=0·03). Cardiovascular mortality, non-fatal myocardial infarctions, and all-cause mortality or non-fatal myocardial infarction were also lower on carvedilol than on placebo.

Interpretation In patients treated long-term after an acute myocardial infarction complicated by left-ventricular systolic dysfunction, carvedilol reduced the frequency of all-cause and cardiovascular mortality, and recurrent, non-fatal myocardial infarctions. These beneficial effects are additional to those of evidence-based treatments for acute myocardial infarction including ACE inhibitors.

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Introduction

The efficacy of β-blockers in reducing major coronary events and improving short-term and long-term outcome has established their beneficial role in the management of acute myocardial infarction.[1–3] However, the randomised trials whose results showed these effects were done before thrombolysis or primary angioplasty were used for reperfusion, and before the introduction of angiotensin-converting-enzyme (ACE) inhibitors. β-blockers have now been shown to reduce mortality and morbidity substantially, and improve left-ventricular function in patients with chronic heart failure when given together with ACE inhibitors.[4–7]

Since coronary heart disease is a major cause of heart failure, attention has focused once more on the use of β-blockers in patients with acute myocardial infarction. Although there have been many randomised, placebo-controlled trials of β blockade in acute myocardial infarction, none has studied patients with confirmed left-ventricular systolic dysfunction who might also have had clinical evidence of heart failure during the index hospital admission. Post-hoc subgroup analyses of previous trials, however, have suggested a similar mortality benefit in patients with heart failure.[8–10] Conversely, several trials of ACE inhibitors have conclusively shown substantial improvement in mortality and morbidity in this group of patients.[11–13]

Registries from Europe and the USA indicate that the use of β-blockers in eligible patients post myocardial infarction is substantially lower than would be expected from the convincingly positive results of the older trials.[14,15] One explanation for this finding could be the absence of contemporary data from trials in the post-thrombolytic era, specifically in patients who have substantial left-ventricular dysfunction, who might also have heart failure, and in whom ACE inhibitors will have been prescribed. We designed the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study to test the hypothesis that the addition of carvedilol to standard modern management of acute myocardial infarction in patients with left-ventricular dysfunction with or without heart failure would improve outcome in terms of mortality and morbidity.

Patients and methods

Patients

The CAPRICORN study, whose design and protocol have been published elsewhere,[16] was a multicentre, double-blind, randomised controlled trial of carvedilol versus placebo involving 17 countries and 163 centres worldwide. Eligible patients were aged 18 years or older with a stable, definite myocardial infarction occurring

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3–21 days before randomisation. Other inclusion criteria were: left-ventricular ejection fraction of 40% or less by two-dimensional echocardiography or by radionuclide or contrast ventriculography, or wall-motion-score index of 1·3 or less; and receipt of concurrent treatment with ACE inhibitors for at least 48 h and stable dose for more than 24 h unless there was proven intolerance of ACE inhibitors. We included patients who had heart failure appropriately treated with diuretics and ACE inhibitors during the acute phase, but excluded those who continued to require intravenous diuretics or inotropes, or who had uncontrolled heart failure. Unstable angina, hypotension (systolic blood pressure <90 mm Hg), uncontrolled hypertension, bradycardia (heart rate <60 beats per min), and unstable insulin-dependent diabetes mellitus were further reasons for exclusion. Patients with a continuing indication for β-blockers for any clinical indication other than heart failure were excluded, as were those requiring ongoing therapy with inhaled β_2-agonists or steroids.

Informed consent was obtained from all patients, and ethics committees from all participating countries gave their approval.

Methods

Patients were randomly assigned carvedilol or identical-looking placebo by use of permuted blocks with stratification by centre. Study medication was uptitrated to the highest tolerated dose for each patient, to a maximum of 25 mg twice daily. The initial dose of 6·250 mg, if tolerated, was continued on a twice daily basis. If it was not tolerated, the same dose was readministered or reduced by half. If that dose was not tolerated, the patient received no study medication, but was followed up anyway. After successful initial dosing, the patient returned as an outpatient every 3–10 days for assessment of tolerability and further uptitration. In the absence of adverse events or evidence of clinical heart failure, and if the heart rate was greater than 50 beats per min and the systolic blood pressure greater than 80 mm Hg, the dosew as increased to the next level. The patient remained in the outpatient department for 2 h to ensure no side effects ensued.

During the maintenance period, patients were reviewed every 3 months during the first year, and every 4 months thereafter. Investigators were encouraged to review the dose of study medication at each visit and to ensure that doses of other drugs, especially ACE inhibitors, were adjusted accordingly to ensure optimum dose levels. At specified visits, an electrocardiogram was done, New York Heart Association class ascertained, and venous blood taken for routine biochemistry and haematological analysis.

The maintenance phase continued until 633 validated primary endpoints had occurred, whereupon down-titration began. All patients had a minimum of 3 months' follow up. Study medication was withdrawn in a stepwise manner over 1–2 weeks, decreasing one dose level at a time every 3–4 days. Subsequent use of open-label β-blockade was at the discretion of the investigator.

The original primary endpoint was all-cause mortality, but, during a masked analysis, the data and safety monitoring board noted that overall mortality was lower than had been predicted and that the study could not be completed with the sample size and power originally planned. The steering committee therefore decided to adopt co-primary endpoints of all-cause mortality (the original primary endpoint), together with all-cause mortality or cardiovascular hospital admissions (the first prespecified secondary endpoint). The other secondary endpoints were sudden death and hospital admission for heart failure. Other outcomes assessed were recurrent non-fatal myocardial infarction, and all-cause mortality or recurrent non-fatal myocardial infarction.

The trial was overseen by a steering committee, which met monthly by teleconference and at face-to-face meetings at least twice a year. An endpoints committee was responsible for masked adjudication of all prespecified endpoints, which were described in detail in a manual of operating procedures agreed by the steering committee.

Statistical analysis

The target sample size was revised on the basis of the new co-primary endpoint of all-cause mortality or cardiovascular hospital admission. For 90% power, and assuming a hazard ratio of 0·77, we calculated that recruitment of a minimum of 1850 patients randomised on a one/one basis with 633 deaths or cardiovascular hospital admissions would be required. In view of the advice from the data and safety monitoring board concerning the mortality rate, we decided to divide the α=0·05 adopted for the previous primary endpoint of all-cause mortality alone into 0·005 for all-cause mortality and 0·045 for all-cause mortality or cardiovascular hospital admissions.

All analyses were by intention to treat. The basis of all principal analyses was time to first event, and results were assessed by the log-rank test and quantified by hazard ratios and 95% CIs, calculated with Cox's proportional hazards model.

Results

We recruited 1959 patients, of whom 975 were assigned carvedilol and 984 placebo, and who were followed up for a mean of 1·3 years (figure 1). The trial continued to its planned conclusion when 633 primary endpoints had been validated. In total, 707 such events were judged by the endpoints committee to have occurred.

Baseline characteristics, which were similar between the two groups, are shown in table 1. The mean left-

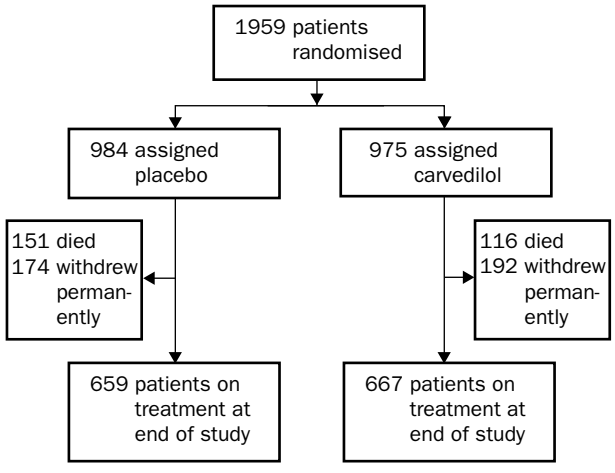

Figure 1: **Trial profile**

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	Carvedilol group (n=975)	Placebo group (n=984)
Demographics		
Mean (range) age (years)	63 (29–88)	63 (25–90)
Sex		
Men	716 (73%)	724 (74%)
Women	259 (27%)	260 (26%)
Smoking history		
Current	326 (33%)	319 (32%)
Previous	264 (27%)	243 (25%)
Never	383 (39%)	418 (43%)
Medical history		
Previous MI	299 (31%)	290 (29%)
Previous angina	559 (57%)	531 (54%)
Previous hypertension	541 (55%)	514 (52%)
Previous diabetes	207 (21%)	230 (23%)
Other vascular disease	168 (17%)	159 (16%)
Previous revascularisation	118 (12%)	107 (11%)
Hyperlipidaemia	315 (32%)	322 (33%)
Infarct characteristics		
Mean (SD) LVEF (%)	32·9 (6·4)	32·7 (6·4)
Mean (SD) SBP (mm Hg)	121·6 (17·3)	120·7 (16·1)
Mean (SD) DBP (mm Hg)	73·7 (10·3)	73·4 (10·0)
Mean (SD) heart rate (beats/min)	77·3 (11·4)	77·2 (11·3)
Site of MI		
Anterior	572 (59%)	536 (54%)
Inferior	205 (21%)	205 (21%)
Other	198 (20%)	243 (25%)
Treatment for index myocardial infarction		
Nitrates	715 (73%)	717 (73%)
Intravenous β-blockers	112 (11%)	100 (10%)
Intravenous heparin	617 (63%)	635 (65%)
Subcutaneous heparin	460 (47%)	481 (49%)
Intravenous diuretics	338 (35%)	320 (33%)
Thrombolysis/primary angioplasty	442 (45%)	465 (47%)
Medications at time of randomisation		
ACE inhibitor	953 (98%)	955 (97%)
Aspirin	838 (86%)	847 (86%)

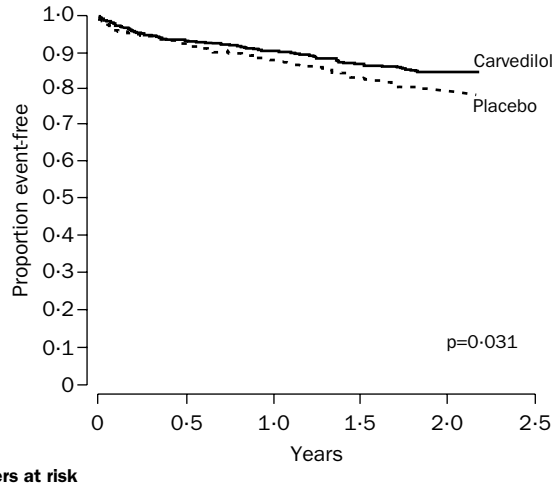
MI=myocardial infarction; LVEF=left-ventricular ejection fraction; SBP=systolic blood pressure; DBP=diastolic blood pressure; ACE=angiotensin-converting enzyme.

Table 1: **Baseline characteristics**

ventricular ejection fraction was 32·8%, and intravenous diuretics and nitrates were required in about a third and three-quarters of patients, respectively, as treatment for the acute event. Reperfusion therapy, mainly by thrombolysis but also by primary angioplasty, was applied in 46% of all patients. The site of the index myocardial infarction was anterior in 57%, and there was a history of previous myocardial infarction or angina in 30% and 56% of all patients. Hypertension, diabetes, or hyperlipidaemia were present in 54, 22, and 33%, respectively.

Of the 940 patients who entered the maintenance phase in the carvedilol group, 692 (74%) reached the maximum attainable dose of 25 mg twice daily, and 103 (11%) and 65 (7%), respectively, reached 12·5 mg and 6·25 mg twice daily. Excluding deaths, carvedilol and placebo were withdrawn permanently in 192 (20%) and 174 (18%) of patients, respectively.

Fewer patients in the carvedilol group than in the placebo group died (table 2, figure 2); however, there was no significant difference between the two groups in the co-primary endpoint of death or cardiovascular hospital admission (table 2, figure 3), or in the secondary endpoints of sudden death and admission to hospital because of heart failure (table 2). Fewer patients on carvedilol than on placebo died from cardiovascular causes, including heart failure, or had a non-fatal myocardial infarction (table 2, figure 4).



Numbers at risk

Carvedilol	975	856	648	364	117	16
Placebo	984	861	638	358	123	8

Figure 2: **Kaplan-Meier estimates of all-cause mortality**

Discussion

The results of this study show substantial benefit from carvedilol with respect to major coronary events. The 23% relative reduction in mortality is identical to that reported in a meta-analysis of 22 long-term, randomised, controlled trials of β-blockers in acute myocardial infarction.[3] However, in CAPRICORN, the all-cause mortality rate on placebo was 15% compared with 12% on carvedilol after an average follow-up of 1·3 years, whereas in the previous trials, the average mortality was 10% on placebo and 8% on β-blockers. Although these benefits cannot be compared exactly because of variations in length of follow-up in the trials included in the meta-analysis, the higher mortality on placebo in the CAPRICORN study emphasises that these patients were at particularly high risk. The reduction in all-cause mortality was additional to the effects of ACE inhibitors and reperfusion therapy, which were prescribed in 98% and 46% of patients, respectively.

The reduction in all-cause mortality was unexpected, since concern about insufficient power to detect a significant difference in all-cause mortality had persuaded the steering committee to change the primary endpoint from all-cause mortality to all-cause mortality or cardiovascular hospital admissions. Although nominally significant for the outcome of all-cause mortality alone, the p value of 0·03 does not meet the higher level of significance specified when the primary endpoint was adopted. Nevertheless, death is the most important outcome, it was the original primary endpoint, and, in practical terms, the observed 23% reduction in all-cause mortality represents a clinically important outcome.

Despite these benefits in terms of major coronary events, the new co-primary endpoint of all-cause mortality or cardiovascular hospital admission was only 8% lower for carvedilol than for placebo. The apparent inconsistency between the results for these two endpoints was not caused by an excess of cardiovascular hospital admissions in the carvedilol group. The numbers of cardiovascular hospital admissions for any reason other than myocardial infarction and heart failure were about equal in the two treatment groups. However, many of these events preceded episodes of myocardial infarction, heart failure, and death, and hence masked the benefit on

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	Carvedilol group (n=975)	Placebo group (n=984)	Hazard ratio (95% CI)	p
Primary endpoints				
All-cause mortality	116 (12%)	151 (15%)	0·77 (0·60–0·98)	0·031
All-cause mortality or cardiovascular-cause hospital admission	340 (35%)	367 (37%)	0·92 (0·80–1·07)	0·296
Secondary endpoints				
Sudden death	51 (5%)	69 (7%)	0·74 (0·51–1·06)	0.098
Hospital admission for heart failure	118 (12%)	138 (14%)	0·86 (0·67–1·09)	0·215
Other endpoints				
Cardiovascular-cause mortality	104 (11%)	139 (14%)	0·75 (0·58–0·96)	0·024
Death due to heart failure	18 (2%)	30 (3%)	0·60 (0·33–1·07)	0·083
Non-fatal myocardial infarction	34 (3%)	57 (6%)	0·59 (0·39–0·90)	0·014
All-cause mortality or non-fatal myocardial infarction	139 (14%)	192 (20%)	0·71 (0·57–0·89)	0·002

Table 2: **Primary, secondary, and other endpoints**

these outcomes in a time to first event analysis. In fact, 289 patients in the placebo group were admitted to hospital with cardiovascular problems compared with 275 in the carvedilol group. Overall, 14% fewer patients were admitted to hospital for heart failure in the carvedilol group than in the placebo group, and fewer died from heart failure.

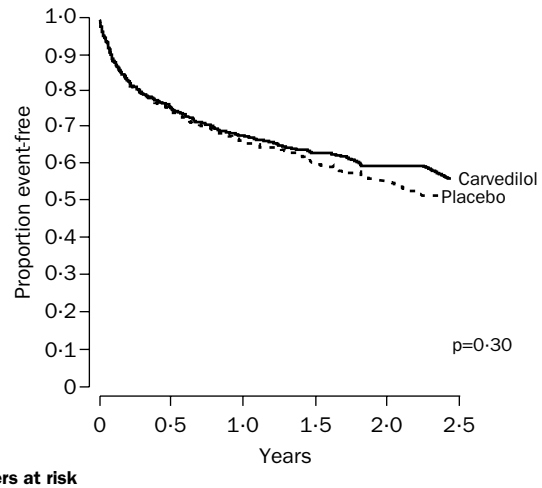
We cannot directly compare CAPRICORN with earlier β-blocker trials with regard to endpoints, such as hospital admissions for heart failure, that were not assessed in these trials. Nevertheless, in the Norwegian study of timolol and the BHAT trial of propranolol—the two largest landmark trials of β-blockers in myocardial infarction—there were more reports of heart failure as an adverse event in the groups treated with β-blockers than in the placebo groups. In both these trials, there was a rapid escalation (over1–2 days) to the maximum dose of study medication. By comparison, dose titration in CAPRICORN was more gradual.

In CAPRICORN, all-cause mortality or non-fatal recurrent myocardial infarction—the most commonly adopted primary endpoint in contemporary clinical trials of acute coronary disease—was 29% lower with carvedilol than with placebo (p=0·002). The reduction in deaths and recurrent myocardial infarction occurred during acute and chronic phases, as it has done in trials of β-blockers in acute myocardial infarction and chronic heart failure. The results of our trial show that these improvements in outcome apply equally to patients with objective evidence of clinically significant left-ventricular dysfunction.

The acute phase of myocardial infarction is an intrinsically unstable period, especially in those with left-ventricular dysfunction. In our study, the mean left-ventricular ejection fraction was substantially impaired (32·8%), and treatment with intravenous diuretics was required in a third of patients during the acute event. In the trials of β-blockers in heart failure, evidence of stability was required, not only in clinical status but also in terms of drug therapy for heart failure. By contrast, in addition to being started on increasing doses of carvedilol, almost all patients in CAPRICORN were treated with an ACE inhibitor at the same time.

Recruitment to CAPRICORN was slow in some countries where it was widely perceived that the case for β-blockers in all patients with myocardial infarction was proven and that the previous specific contraindication of heart failure did not apply after the results of the trials of β-blockers in heart failure. The results of our study show that the approach to high-risk patients with left-ventricular dysfunction after a myocardial infarction should resemble that of the studies of β-blockers in heart failure rather than the previous trials of β-blockers in myocardial infarction.

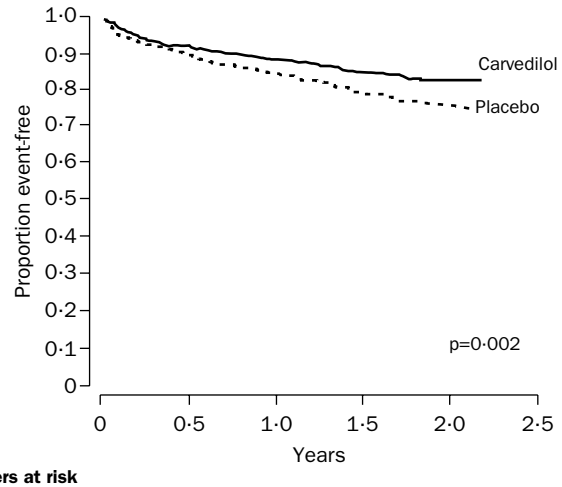
In light of these results, especially when taken together with those of the previous trials of β-blockers for heart



Numbers at risk

Carvedilol	975	693	481	266	75	9
Placebo	984	701	473	246	78	4

Figure 3: **Kaplan-Meier estimates of all-cause mortality or cardiovascular hospital admission**



Numbers at risk

Carvedilol	975	842	634	355	108	15
Placebo	984	834	615	338	112	8

Figure 4: **Kaplan-Meier estimates of all-cause mortality or non-fatal myocardial infarction**

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attack and heart failure, future studies of β-blockers in acute myocardial infarction should probably not be done. Although these results might be generalisable to other β-blockers, the CAPRICORN trial has provided the basis of a clinical template for future clinical practice in high-risk patients with left-ventricular dysfunction after a myocardial infarction. CAPRICORN reaffirms that patients with left-ventricular dysfunction after myocardial infarction remain at high risk despite the benefits afforded by modern care. In a meta-analysis of the three large trials of ACE inhibitors in patients with left-ventricular dysfunction or heart failure after an acute myocardial infarction—SAVE, AIRE, and TRACE—the absolute reduction in risk was 2·3%. The number of patients who need to be treated for 1 year with an ACE inhibitor to save one life is, therefore, 43.[17] This finding highlights the benefits of ACE inhibitors in patients with heart failure or left-ventricular dysfunction after an acute myocardial infarction. The absolute reduction in mortality in CAPRICORN at 1 year was also 2·3%, resulting in an identical number needed to treat for 1 year. However, this benefit is additional to those of ACE inhibitors alone.

Our results indicate that treatment with carvedilol provides a mechanism to further reduce the high rate of mortality and other major coronary events in patients with left-ventricular dysfunction after acute myocardial infarction.

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