

Articles

The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial

*CIBIS-II Investigators and Committees**

Summary

Background In patients with heart failure, β -blockade has improved morbidity and left-ventricular function, but the impact on survival is uncertain. We investigated the efficacy of bisoprolol, a β_1 selective adrenoceptor blocker in decreasing all-cause mortality in chronic heart failure.

Methods In a multicentre double-blind randomised placebo-controlled trial in Europe, we enrolled 2647 symptomatic patients in New York Heart Association class III or IV, with left-ventricular ejection fraction of 35% or less receiving standard therapy with diuretics and inhibitors of angiotensin-converting enzyme. We randomly assigned patients bisoprolol 1.25 mg (n=1327) or placebo (n=1320) daily, the drug being progressively increased to a maximum of 10 mg per day. Patients were followed up for a mean of 1.3 years. Analysis was by intention to treat.

Findings CIBIS-II was stopped early, after the second interim analysis, because bisoprolol showed a significant mortality benefit. All-cause mortality was significantly lower with bisoprolol than on placebo (156 [11.8%] vs 228 [17.3%] deaths with a hazard ratio of 0.66 (95% CI 0.54–0.81, $p < 0.0001$). There were significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (48 [3.6%] vs 83 [6.3%] deaths), with a hazard ratio of 0.56 (0.39–0.80, $p = 0.0011$). Treatment effects were independent of the severity or cause of heart failure.

Interpretation β -blocker therapy had benefits for survival in stable heart-failure patients. Results should not, however, be extrapolated to patients with severe class IV symptoms and recent instability because safety and efficacy has not been established in these patients.

Lancet 1999; **353**: 9–13

See *Commentary page*

Introduction

Experimental and clinical trials have shown beneficial effects with β -blockade in heart failure.^{1–3} There is reluctance to use β -blockade therapy, however, and unequivocal evidence of benefit from randomised placebo controlled trials is needed to convince the medical community of its safety and efficacy.

Clinical trials in heart failure have tested compounds with different pharmacological profiles.^{2,3} Meta-analyses of placebo-controlled trials of β -blockers have suggested an overall effect on mortality of 32%.^{4–6} The Cardiac Insufficiency Bisoprolol Study (CIBIS) studied bisoprolol, a highly selective antagonist of β_1 adrenoceptors, which are found mainly in the heart and especially in ventricular tissue.⁷ That trial showed a non-significant trend towards 20% lower mortality in the bisoprolol group and 30% fewer admissions to hospital for worsening heart failure.⁸ We designed the CIBIS-II trial to test this evidence further, based on the CIBIS trial results.

Methods

The study design and protocol of CIBIS has been published.⁹ We did a double-blind placebo-controlled randomised trial, analysed by intention to treat.

Patients

Eligible patients were ambulatory, aged 18–80 years, and had a left-ventricular ejection fraction, measured within 6 weeks of randomisation, of 35% or less. Symptoms had to include dyspnoea on exertion, orthopnoea, or paroxysmal nocturnal dyspnoea, with or without oedema, and fatigue, corresponding to class III or IV of the New York Heart Association (NYHA). We recruited patients from 274 hospitals in 18 countries in western and eastern Europe.

Patients had to have a diagnosis of chronic heart failure, made at least 3 months previously, with clinical stability during the preceding 6 weeks for heart failure or 3 months for acute myocardial infarction or unstable angina. Cardiovascular therapy had to have been unchanged in the 2 weeks before randomisation. Treatment had to include a diuretic and an angiotensin-converting-enzyme (ACE) inhibitor, although we allowed other vasodilators if patients were intolerant of ACE inhibitors; the use of digoxin was optional. We measured left-ventricular ejection fraction by echocardiography with the Teicholz formula for M-mode recordings, or the modified Simpson's rule for measurements of end-diastolic and end-systolic volume on apical two-dimensional views. If adequate views could not be obtained by echocardiography, we used contrast or radionuclide ventriculography.

The main exclusion criteria were uncontrolled hypertension, myocardial infarction or unstable angina pectoris in the previous 3 months, percutaneous transluminal coronary angioplasty or coronary-artery bypass graft in the previous 6 months, previous or scheduled heart transplant, atrioventricular block greater than first degree without a chronically implanted pacemaker, resting heart rate of less than 60 beats per min, systolic blood pressure

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Characteristics	Placebo (n=1320)	Bisoprolol (n=1327)
Demographic		
Mean (range) age (years)	61 (22-80)	61 (26-80)
Sex (M/F)	1062 (80%)/ 258 (20%)	1070 (81%)/ 257 (19%)
NYHA class		
III	1096 (83%)	1106 (83%)
IV	224 (17%)	221 (17%)
Heart failure		
Documented ischaemic heart disease	654 (50%)	662 (50%)
Primary dilated cardiomyopathy	157 (12%)	160 (12%)
Others*	509 (40%)	505 (38%)
Duration of heart failure (median/mean)	2.31/3.60	2.25/3.49
Mean (SD) systolic blood pressure (mm Hg)	130.2 (19.5)	129.2 (19.2)
Mean (SD) diastolic blood pressure (mm Hg)	80.0 (10.9)	79.4 (11.2)
Mean (SD) heart rate (beats/min)	81.0 (15.5)	79.9 (14.5)
Mean (SD) left-ventricular ejection fraction (%)	27.6 (5.5)	27.5 (6.0)
Mean (SD) left-ventricular end-diastolic diameter (cm)	6.7 (0.9)	6.7 (0.9)
Mean (SD) left-ventricular end-systolic diameter (cm)	5.7 (0.9)	5.7 (1.0)
Mean (SD) left-ventricular fractional shortening	15.5 (5.7)	15.5 (5.7)
Atrial fibrillation	264 (20%)	257 (20%)
Concomitant medications		
Diuretic	1310 (99%)	1305 (98%)
ACE inhibitor	1274 (96%)	1273 (96%)
Dihydropyridine-type calcium antagonists	23 (2%)	23 (2%)
Nitrates	762 (58%)	773 (58%)
Digoxin	670 (51%)	697 (53%)
Amiodarone	206 (16%)	185 (14%)
Anticoagulants	413 (31%)	399 (30%)
Antiplatelet agents	558 (42%)	537 (40%)

*Coronary angiography unavailable or no history of myocardial infarction.

Table 1: Baseline characteristics of patients

at rest of less than 100 mm Hg, renal failure (serum creatinine ≥ 300 $\mu\text{mol/L}$), reversible obstructive lung disease, or pre-existing or planned therapy with β -adrenoreceptor blockers.

We did not allow treatment with β -blockers (including eye drops), calcium antagonists, inotropic agents except digitalis, and antiarrhythmic drugs other than amiodarone during the trial.

We identified three mutually exclusive aetiological groups: patients with definite ischaemic heart disease with at least one important coronary arterial stenosis of 70% or more of luminal diameter seen on angiography, or a confirmed myocardial infarction; those with idiopathic dilated cardiomyopathy if normal coronary arteries were seen on angiography; and patients with valvular heart disease or hypertension, together with those with suspected but unproved ischaemic heart disease or cardiomyopathy. We used a non-parallel structure to describe these groups.

Methods

Randomisation was done by random numbers generated on computer at the independent statistical centre, sent to study centres by telefax. The code was kept at the statistical centre and was not broken until the trial was stopped.

The study treatments were identical in appearance. Patients were started on bisoprolol 1.25 mg (n=1327) or placebo (n=1320) daily, the drug being increased successively to 2.50 mg, 3.75 mg, 5.00 mg, 7.50 mg, and 10.00 mg, according to tolerance. Patients received the first three concentrations of each dose for 1 week, and the higher concentrations for 4 weeks. Investigators were asked to ensure that the highest tolerated dose was reached and maintained, if possible, for the duration of the trial. In patients with worsening heart failure, we recommended that the baseline heart-failure treatments were increased before the study drug was decreased. We followed up until the end of the study all patients in whom study medication was withdrawn, with follow-up visits every 3 months. There was no run-in period.

The primary endpoint was all-cause mortality. Secondary endpoints were all-cause hospital admissions, cardiovascular mortality, cardiovascular mortality and cardiovascular hospital admissions, a composite endpoint, and permanent premature

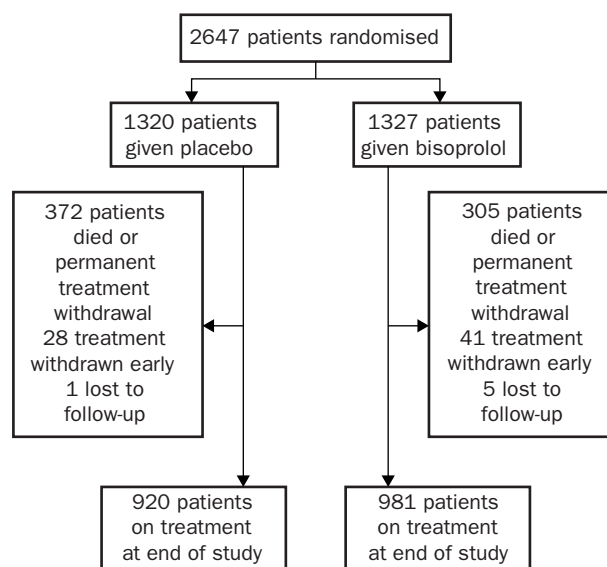


Figure 1: Trial profile

treatment withdrawals.

All important clinical circumstances were analysed by the members of the critical events committee, who were masked to treatment status. They classified all endpoints according to strict definitions of critical events, only the most important of which are defined here.

Sudden death was defined as death occurring within 1 h without previous worsening of symptoms of heart failure. We also took unexpected deaths occurring during sleep to be sudden when patients were found dead by family members sharing the same room in the morning. We generally classified other unwitnessed deaths as unknown. We classified pump failure when death occurred as a consequence of progressive deterioration of heart failure, acute pulmonary oedema, or cardiogenic shock. We recorded non-cardiovascular death if cardiovascular events were excluded as cause of death. Death was classified as being due to unknown cause when there was insufficient evidence to confirm cardiovascular or non-cardiovascular cause.

We recorded permanent treatment withdrawal when a medical need for a β -blocker arose, when intolerance to study medication occurred despite increases in baseline therapy, if study-drug dose was decreased or temporarily withdrawn, if patients experienced intolerance to first dose, and for all other circumstances in which

	Placebo (n=1320)	Bisoprolol (n=1327)	Hazard ratio (95% CI)	p
Primary endpoint				
All-cause mortality	228 (17%)	156 (12%)	0.66 (0.54-0.81)	<0.0001
Secondary endpoints				
All-cause hospital admission	513 (39%)	440 (33%)	0.80 (0.71-0.91)	0.0006
All cardiovascular deaths	161 (12%)	119 (9%)	0.71 (0.56-0.90)	0.0049
Combined endpoint	463 (35)	388 (29%)	0.79 (0.69-0.90)	0.0004
Permanent treatment withdrawals	192 (15%)	194 (15%)	1.00 (0.82-1.22)	0.98
Exploratory analyses				
Sudden death	83 (6%)	48 (4%)	0.56 (0.39-0.80)	0.0011
Pump failure	47 (4%)	36 (3%)	0.74 (0.48-1.14)	0.17
Myocardial infarction	8 (1%)	7 (1%)	0.85 (0.31-2.34)	0.75
Other cardiovascular	23 (2%)	28 (2%)	1.17 (0.67-2.03)	0.58
Non-cardiovascular deaths	18 (1%)	14 (1%)	0.75 (0.37-1.50)	0.41
Unknown cause of death	49 (4%)	23 (2%)	0.45 (0.27-0.74)	0.0012
Hospital admission for worsening heart failure	232 (18%)	159 (12%)	0.64 (0.53-0.79)	0.0001

Numbers refer to patients who presented at least once with given event. For hospital admissions, numbers refer to patients admitted at least once with any cause.

Table 2: Primary and secondary endpoints and exploratory analyses

study drug was permanently stopped.

Statistical analysis

Based on the CIBIS survival curves, we estimated the annual mortality rate to be about 11.2% in the placebo group. To obtain a minimum of 25% lower mortality in the bisoprolol group in a 1-year recruitment period and 2-year follow-up, we calculated that for an α risk of 5% and a power of 95%, we needed to recruit 2500 patients.

We planned two interim analyses at 2500 patient-years and 5000 patient-years. The study could be stopped according to Peto's rule¹⁰ if a significant difference in all-cause mortality was seen between the two groups at $p < 0.001$ (two-tailed log-rank test).

We did analyses by intention to treat. We calculated Kaplan-Meier survival curves on total mortality, and assessed differences between the treatment groups with the log-rank test (time to event). Hazard ratios and 95% CIs were calculated with Cox's proportional hazards regression model. We used the Breslow-Day test to calculate homogeneity of odds ratios between treatment groups, according to NYHA class and cause of heart failure. We compared baseline variables between the two groups with Student's *t* or Wilcoxon's rank-sum tests for continuous variables, and Fisher's exact or χ^2 tests for categorical variables.

Results

2647 patients were enrolled into the study and followed up for a mean of 1.3 years. Baseline characteristics were similar in the two groups (table 1).

The trial was stopped early because all-cause mortality was significantly less in the bisoprolol group than in the placebo group (figure 1). In the bisoprolol group, 156 (11.8%) patients died, compared with 228 (17.3%) in the placebo group ($p < 0.0001$). The estimated annual mortality rate was 8.8% in the bisoprolol group and 13.2% in the placebo group (hazard ratio 0.66 [95% CI 0.54–0.81], figure 2).

There were significantly fewer cardiovascular deaths among patients on bisoprolol than among those on placebo ($p = 0.0049$). Significantly fewer patients on bisoprolol were admitted to hospital for all causes than patients on placebo ($p = 0.0006$) as well as for the combined endpoint of cardiovascular death and admission to hospital for cardiovascular events ($p = 0.0004$). The number of permanent treatment withdrawals was similar in the two groups (table 2).

We did subgroup analyses by cause of heart failure and severity of disease at baseline (figure 3). Mortality and admissions to hospital did not differ significantly between

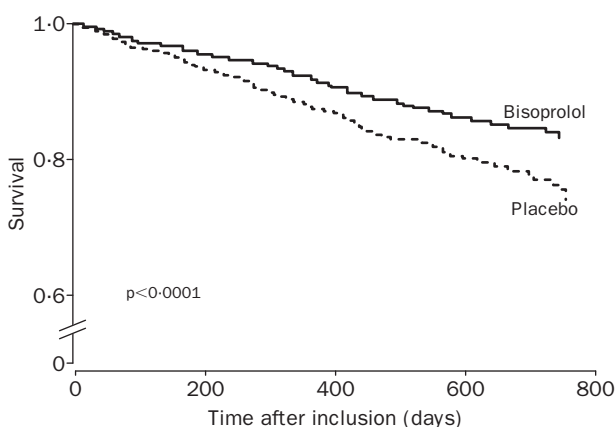


Figure 2: Survival curves

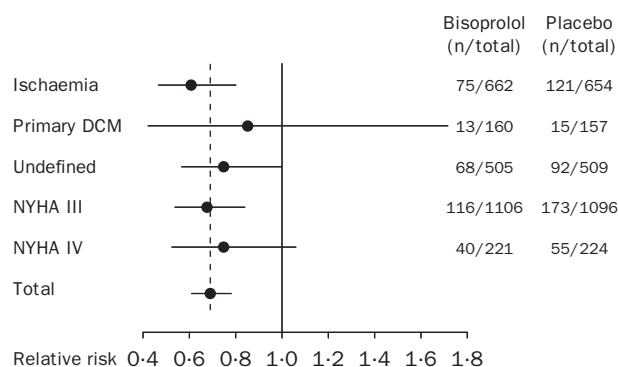


Figure 3: Relative risk of treatment effect on mortality by aetiology and functional class at baseline

Horizontal bars represent 95% CIs.

groups for any subgroup of aetiology of heart failure or class of disease severity.

Circumstances and causes of deaths are shown in table 2. There were 48 sudden deaths in the bisoprolol groups compared with 83 in the placebo group, a difference of 42% ($p = 0.0011$).

The difference in admissions to hospital for worsening heart failure between the two groups was 32% ($p < 0.0001$, table 2). There were, however, more admissions to hospital for stroke in the bisoprolol group than in the placebo group (31 *vs* 16, $p = 0.04$). Hospital admissions were significantly fewer in the bisoprolol group than in the placebo group for ventricular tachycardia and ventricular fibrillation (six *vs* 20, $p = 0.006$) and for hypotension (three *vs* 11, $p = 0.03$), but were more common for bradycardia (14 *vs* two, $p < 0.004$). The rate of heart transplantation was low and similar in the two groups. The number of hospital admissions did not differ significantly for angina, myocardial infarction, supraventricular arrhythmias, cardiogenic shock, or coronary revascularisation.

The most common dose of bisoprolol during the maintenance phase was 10.0 mg, which was reached in 564 patients; 152 reached 7.5 mg and 176 reached 5.0 mg.

Treatment effect did not differ between the participating countries.

Discussion

β -blockade had benefits for all-cause mortality in patients with chronic heart failure. Benefits were also seen for morbidity, assessed by admissions to hospital for all causes, especially for worsening heart failure.

The magnitude of the treatment effect (a 32% lower risk of mortality and admission to hospital for heart failure) is in accordance with findings from meta-analyses of previous randomised placebo-controlled trials.⁴ Our results were obtained in patients already taking diuretics and ACE inhibitors and not patients selected for tolerance of bisoprolol, since we had no run-in period. Benefit occurred irrespective of the cause of heart failure or NYHA class of severity. The greatest effect was, however, seen in patients with ischaemic heart disease who were in NYHA class III at baseline.

With the inclusion of our results, the cumulative experience with β -blockade therapy in chronic heart failure (more than 6000 patients in randomised trials) approaches that of ACE inhibitors in heart-failure patients with symptoms.¹¹ Benefit from the addition of β -

blockade to ACE inhibitors after acute myocardial infarction has also been suggested in post-hoc analyses,¹² but this strategy has not been supported by randomised controlled trials with sufficient power to address outcome in patients with left-ventricular dysfunction, with or without heart failure.

Neuroendocrine activation may underlie this therapeutic benefit by inhibition of the potential harmful effects of compensatory mechanisms, the renin-angiotensin-aldosterone system for ACE inhibitors, and sympathetic activity with β -blockers. Cardiac work and energy consumption are decreased by unloading with ACE inhibitors, slowing of heart rate with β -blockers, and lowering of blood pressure with both. The neuroendocrine hypothesis in heart failure includes the possibility that ACE inhibitors prevent direct toxic cardiac effects of angiotensin II and aldosterone, and β -blockers prevent the toxic effects of catecholamines.

The greatest effect on mortality was a 42% lower rate of sudden deaths among patients on bisoprolol, as well as non-significantly fewer deaths related to pump failure. This finding suggests that bisoprolol was acting principally as an antiarrhythmic agent rather than having a specific effect on myocardial function. Given what is known already about the positive effects of β -blockade on cardiac structure and function, the way in which we classified the cause of death should be taken into account. Sudden deaths or those associated with pump failure had strict definitions. Many deaths had, therefore, to be classified for the purposes of the trial as being of unknown cause. Unwitnessed or insufficiently documented deaths classified as unknown were probably sudden and some deaths associated with pump failure, which can also seem to be sudden. Moreover, bisoprolol led to a significantly lower death rate in the unknown group, which strongly implies that most of the deaths in this category were cardiac. These difficulties of classification reinforce the value of all-cause mortality as the major mortality endpoint in similar trials.

The strikingly lower frequency of sudden deaths among patients on bisoprolol in our trial suggests an important antiarrhythmic effect. Although a similar difference was not seen in CIBIS, a significant trend was found in the USA carvedilol studies.¹³ In CIBIS, the rate of ventricular tachycardia episodes was lower in a substudy, in which vagally dependent variability in heart rate was higher in the bisoprolol group than in the placebo group,^{14,15} an effect that has been linked to improved long-term prognosis after myocardial infarction and in heart failure.^{16,17} This finding and the significantly lower rate of admission to hospital for ventricular tachycardia or fibrillation in the CIBIS-II bisoprolol group supports the drug's potential antiarrhythmic effect.

Improvement or preservation of left-ventricular function could also improve long-term prognosis. Increased left-ventricular ejection fraction has been seen with other β -blockers,⁴ which may be dose-dependent.¹⁸ We did not measure left-ventricular function sequentially, but in CIBIS prognostic improvement was significantly linked to increased left-ventricular ejection fraction.¹⁹

A meta-analysis of randomised trials showed a trend towards better survival with non-selective compounds.⁴ This finding was mainly related to the strikingly lower mortality rate seen in the US trials of carvedilol,⁸ differences in design, especially the presence of a run-in phase in the carvedilol trials, makes comparison of results

with our trial impossible. In theory, blockade of β_1 -adrenoceptors and β_2 adrenoceptors should provide more complete protection against the harmful effects of catecholamines, but our results show that selective inhibition of β_1 receptors is sufficient to lower the rate of sudden death presumed to be associated with arrhythmia. Differences in effects according to the pharmacological profiles of β -blockers is, however, important and continuing trials of drugs such as bucindolol,²⁰ carvedilol, and metoprolol with carvedilol will provide essential information.

The lack of difference in treatment effects on mortality and secondary endpoints by cause or severity of disease contrasts with the findings of CIBIS, in which bisoprolol had greatest benefits in patients with non-ischaemic heart failure. Given the consistent and striking benefit of β -blockers in secondary prevention after myocardial infarction,^{7,21} there is no plausible scientific explanation for this apparent anomaly. This observation did, however, result from a post-hoc analysis and highlights the limitations of such analyses.

We saw benefits of bisoprolol for patients in NYHA class IV; however, we included only stable patients and the use of β -blocker treatment in non-ambulatory patients with class IV symptoms, especially those with recent instability, needs to be defined.

The addition of a β -blocker to standard therapy with a diuretic and an ACE inhibitor can be recommended in appropriate, stable, ambulatory patients who have heart failure caused by impaired left-ventricular systolic function. The limited use of β -blocker therapy after myocardial infarction, despite the cumulative evidence of double-blind, randomised, controlled trials, suggests that anxiety about safety or lack of clarity about the target population are common. The continued accumulation of information about β -blockers in heart failure is, therefore, important, since the population of patients with heart failure is much less well-defined than that for patients with myocardial infarction. Without further information from large randomised controlled trials, the uptake of β -blockade in clinical practice outside specialist departments will be slow.

For all heart-failure patients, administration of β -blocker therapy should be gradual and progressive, starting with low doses. The optimum rate of dose increase and the maximum dose need to be more accurately defined. Use of the maximum tolerated dose seems acceptable; at present, recommendations on rates of dose increase can be based only on those adopted in clinical trials.

Patients with severe class IV heart failure, those with heart failure after acute myocardial infarction, and those with symptomless left-ventricular dysfunction are being studied in the continuing clinical trials COPERNICUS, CAPRICORN, and CARMEN with carvedilol.

In our trial the mean age of patients was 61 years, at least a decade younger than that of patients seen in clinical practice. In most clinical trials in heart failure, there is, therefore, inadequate information about the effects of treatment in older patients and more data in the very old are urgently needed.

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Acknowledgment

This study was sponsored by E Merck, Darmstadt.

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