

Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF)

MERIT-HF Study Group*

Summary

Background Metoprolol can improve haemodynamics in chronic heart failure, but survival benefit has not been proven. We investigated whether metoprolol controlled release/extended release (CR/XL) once daily, in addition to standard therapy, would lower mortality in patients with decreased ejection fraction and symptoms of heart failure.

Methods We enrolled 3991 patients with chronic heart failure in New York Heart Association (NYHA) functional class II–IV and with ejection fraction of 0.40 or less, stabilised with optimum standard therapy, in a double-blind randomised controlled study. Randomisation was preceded by a 2-week single-blind placebo run-in period. 1990 patients were randomly assigned metoprolol CR/XL 12.5 mg (NYHA III–IV) or 25.0 mg once daily (NYHA II) and 2001 were assigned placebo. The target dose was 200 mg once daily and doses were up-titrated over 8 weeks. Our primary endpoint was all-cause mortality, analysed by intention to treat.

Findings The study was stopped early on the recommendation of the independent safety committee. Mean follow-up time was 1 year. All-cause mortality was lower in the metoprolol CR/XL group than in the placebo group (145 [7.2%, per patient-year of follow-up] vs 217 deaths [11.0%], relative risk 0.66 [95% CI 0.53–0.81]; $p=0.00009$ or adjusted for interim analyses $p=0.0062$). There were fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (79 vs 132, 0.59 [0.45–0.78]; $p=0.0002$) and deaths from worsening heart failure (30 vs 58, 0.51 [0.33–0.79]; $p=0.0023$).

Interpretation Metoprolol CR/XL once daily in addition to optimum standard therapy improved survival. The drug was well tolerated.

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See *Commentary page 1988*

Introduction

Chronic heart failure is a major disorder that is becoming increasingly prevalent as the proportion of elderly in the population increases.¹ Although inhibitors of angiotensin-converting enzyme (ACE) have improved the treatment of heart failure, mortality related to this disorder remains unacceptably high.^{2–4} Prevalence remains high partly because current standard therapy does not prevent sudden cardiac death, which constitutes a high proportion of all deaths in patients with chronic heart failure.^{2–4}

Results from studies started more than 25 years ago in Sweden suggested that long-term therapy with β -blockers, including metoprolol, could improve haemodynamics and increase survival in patients with heart failure secondary to idiopathic dilated cardiomyopathy.^{5,6} Subsequent studies, including other β -blockers such as propranolol, timolol, bisoprolol, and carvedilol, corroborated and extended these early observations also in patients with ischaemic heart disease.^{7–12} When the current study was planned there was no previously published study with power to prove survival benefit.

Metoprolol is a lipophilic β_1 -selective antagonist with no intrinsic sympathomimetic activity. In patients with chronic heart failure, metoprolol improves cardiac function, left-ventricular remodelling, and capacity for physical exercise, and lessens the symptoms of heart failure.^{9,13} As with all β -blockers, patients can experience an initial negative inotropic effect that necessitates a low starting dose and an up-titration schedule.¹

We did a large-scale randomised placebo-controlled trial to investigate whether metoprolol controlled release/extended release (CR/XL) once daily added to optimum standard therapy lowers mortality in patients with decreased ejection fraction and symptoms of heart failure.

Patients and methods

We did the study at 313 investigational sites in 13 European countries and in the USA, according to a previously published description of the study design.¹⁴ The study was approved by local ethics committees. All patients gave written informed consent.

Patients

Between Feb 14, 1997, and April 14, 1998, we enrolled 3991 patients. Eligible patients were men and women, aged 40–80 years, who had had symptomatic heart failure (New York Heart Association [NYHA] functional class II–IV) for 3 months or more before randomisation and who were receiving optimum standard therapy at enrolment (2 weeks before randomisation), defined as any combination of diuretics and an ACE inhibitor. If an ACE inhibitor was not tolerated, hydralazine, long-acting nitrate, or an angiotensin-II-receptor antagonist could be used. Digitalis could also be prescribed. Other inclusion criteria were a stable clinical condition during the 2-week run-in phase between enrolment and randomisation, and a left-ventricular ejection fraction of 0.40 or lower within 3 months before enrolment.

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Characteristics	Metoprolol CR/XL group (n=1990)	Placebo group (n=2001)
Demography		
Male/female	1539 (77%)/451 (23%)	1554 (78%)/447 (22%)
Age (years)		
<60	656 (33%)	682 (34%)
60-69	706 (35%)	702 (35%)
≥70	628 (32%)	617 (31%)
Mean (SD)	63.9 (9.6)	63.7 (9.7)
Ethnic origin		
White	1870 (94%)	1886 (94%)
Black	107 (5%)	101 (5%)
Other	13 (1%)	14 (1%)
Current daily smoker	281 (14%)	297 (15%)
Clinical		
Heart failure		
Ischaemic	1294 (65%)	1312 (66%)
Non-ischaemic	696 (35%)	689 (34%)
NYHA class		
II	811 (41%)	825 (41%)
III	1110 (56%)	1100 (55%)
IV	69 (3.4%)	76 (3.8%)
Previous myocardial infarction	950 (48%)	974 (49%)
Time since last myocardial infarction (years)*		
<1	151 (8%)	139 (7%)
1-5	341 (17%)	366 (18%)
≥5	457 (23%)	469 (23%)
Atrial fibrillation	324 (16%)	341 (17%)
Hypertension	871 (44%)	876 (44%)
Diabetes mellitus	495 (25%)	489 (24%)
Mean (SD) measurements		
Ejection fraction	0.28 (0.07)	0.28 (0.07)
Heart rate (bpm)	82.4 (10.1)	82.7 (10.3)
Systolic blood pressure (mm Hg)	130.0 (17.0)	129.5 (17.3)
Diastolic blood pressure (mm Hg)	78.4 (9.2)	78.1 (9.1)
Weight (kg)	80.5 (16.3)	80.7 (15.9)
Drug therapy		
Diuretics	1804 (91%)	1801 (90%)
ACE inhibitor	1773 (89%)	1798 (90%)
Angiotensin II blocker	133 (7%)	129 (6%)
ACE inhibitor or angiotensin II blocker	1897 (95%)	1922 (96%)
Digitalis	1258 (63%)	1281 (64%)
Aspirin	908 (46%)	920 (46%)
Lipid-lowering agents	507 (25%)	541 (27%)

*Time since last myocardial infarction missing in one patient.

Baseline characteristics of patients

Patients with ejection fractions between 0.36 and 0.40 were included only if their maximum walking distance was 450 m or less in a 6 min walk test. Supine resting heart rate had to be 68 beats per min or more at enrolment.

The exclusion criteria were: acute myocardial infarction or unstable angina within 28 days before randomisation; indication or contraindication for treatment with β -blockade or drugs with β -blocking properties such as amiodarone; β -blockade within 6 weeks before enrolment; heart failure secondary to systemic disease or alcohol abuse; scheduled or performed heart transplantation or cardiomyoplasty, or implanted cardioversion defibrillator (expected or performed), or procedures such as coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty planned or performed in the past 4 months; atrioventricular block of the second and third degree, unless the patient had an implanted pacemaker and a spontaneous heart rate of 68 beats per min or more; unstable decompensated heart failure (pulmonary oedema, hypoperfusion) or supine systolic blood pressure lower than 100 mm Hg at enrolment; any other serious disease that might complicate management and follow-up according to the protocol; use of calcium antagonists such as diltiazem or verapamil; use of amiodarone within 6 months before enrolment; or poor compliance, defined as more than a 25% deviation of the number of observed compared with number of expected consumed placebo tablets during the run-in period.

Methods

The study was preceded by a single-blind, 2-week placebo run-in period. We did randomisation according to an optimum assignment procedure, which balanced the metoprolol CR/XL and placebo groups for ten factors: investigational site, age, sex,

ethnic origin, cause of heart failure, previous acute myocardial infarction, and, in patients with previous myocardial infarction, time since last myocardial infarction, diabetes mellitus, ejection fraction, and NYHA functional class. An interactive voice recording system was used to provide the investigators with the computer-generated study-medication number, based on the optimum assignment procedure (minimisation method).

At the randomisation visit, patients were assigned treatment with metoprolol CR/XL (n=1990) or placebo (n=2001). The starting dose was 12.5 mg or 25 mg once daily (half a 25 mg tablet was recommended for patients who were in NYHA III-IV). After 2 weeks we increased the dose to the recommended 50 mg once daily for 2 weeks, then 100 mg once daily for 2 weeks, and finally up to the target dose of 200 mg once daily. Dose regimen could be modified according to the judgement of the investigator. If a patient did not tolerate increases in dose, temporary decrease in study drug or increase in diuretic dose was recommended. We asked patients to attend follow-up visits every 3 months. We defined tolerability as permanent early discontinuation of treatment.

An independent endpoint committee, whose members were unaware of treatment status, classified all deaths according to prespecified definitions from medical records and other documents. Each event was classified by two members and agreement between the two constituted a final classification. The predefined endpoints were: vital status, which was verified with the patient, a close relative, or through valid documentation; cardiovascular death, which included deaths for which a non-cardiovascular cause had not been identified; death from heart failure, which was any of cardiogenic shock, pulmonary oedema, heart-failure symptoms or signs requiring intravenous

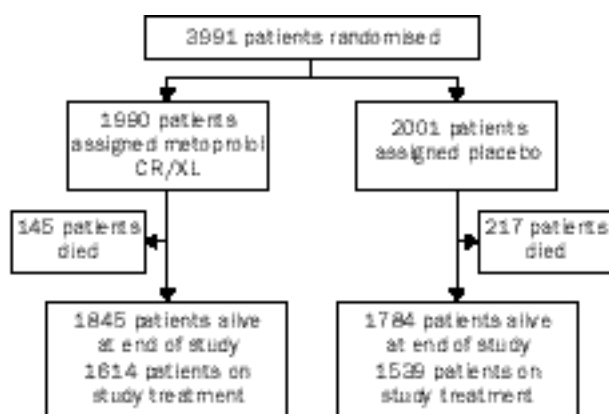


Figure 1: Trial profile

therapy or oxygen, confinement to bed because of heart-failure symptoms, or sudden death during hospital stay for aggravated heart failure; and sudden death, which was any of witnessed instantaneous death in the absence of progressive circulatory failure lasting for 60 min or more, unwitnessed death in the absence of pre-existence progressive circulatory failure or other causes of death, or death within 28 days after resuscitation from cardiac arrest in the absence of pre-existing circulatory failure or other causes of death, death during attempted resuscitation, or death within 60 min from the onset of new symptoms unless a cause other than cardiac was obvious.¹⁵

Statistical analysis

The power calculation showed that the mean follow-up time had to be 2.4 years if 1600 patients were randomised to each treatment group during 14 months. This calculation was based on a significance level of $\alpha=0.04$ for all-cause mortality (two-sided, intention to treat, $\alpha=0.01$ was used for the second primary endpoint) and a power of at least 80% ($\beta \leq 0.20$) and the following assumptions: 9.4% mean annual mortality in the placebo group, a mean risk-reducing effect of 30% on metoprolol CR/XL, a withdrawal rate of 20% in the first year, and 5% annually thereafter.¹⁴ Since patients were recruited faster than planned, 3991 patients were randomised during the recruitment period, which increased the power of the study.

Safety was monitored by an independent safety committee during the study. The predefined stopping rule for efficacy was based on all-cause mortality, analysed by intention to treat, with predetermined interim analyses, done when 25%, 50%, and 75% of expected total deaths had occurred. We used an asymmetric group-sequential procedure.¹⁴ The cumulative probability of early stopping for benefit was 0.0036, and for harm was 0.015, based on log-rank statistics.

The two primary endpoints were all-cause mortality and all-cause mortality in combination with all-cause admission to hospital (time to first event). The results for the first primary endpoint, all-cause mortality are presented in this report. Analysis was by intention to treat. For the main analyses we used the log-rank test to compare the two groups, and Cox's proportional hazards model to calculate relative risks and 95% CI. We calculated a second p value for total mortality adjusted for the two predefined interim analyses, which were done by the independent safety committee before the end of the study.

We used Cox's proportional hazards regression analyses of total mortality to explore any unfavourable outcome in prespecified risk groups, defined by entry characteristics. For ejection fraction, systolic and diastolic blood pressure, and heart rate, these risk groups were defined by the lowest tertile, for age by the upper tertile. NYHA class, cause of heart failure, smoking status, sex, previous myocardial infarction, diabetes mellitus, and hypertension were also prespecified for these analyses. The two major causes of heart disease were ischaemic and non-ischaemic heart disease. The former was based on a history of myocardial infarction or angina pectoris (judged to be secondary to coronary

heart disease), or on the results of coronary angiography or other relevant method indicating coronary heart disease. All cases not classified as ischaemic disease were classified as non-ischaemic heart disease. Hypertension was defined as pharmacologically treated high blood pressure, and diabetes mellitus as a clinical diagnosis made by the investigator. More than 180 deaths in any such subgroup would yield a power of at least 70% to detect a 30% increase in risk. Data on complementary subgroups with fewer than 180 deaths are also depicted.

Results

The international steering committee stopped the study on Oct 31, 1998, on the recommendation of the independent safety committee. The second preplanned interim analysis (50%) showed that the predefined criterion for ending the study had been met and exceeded ($Z=3.807$ vs a boundary value of 2.98). 3980 patient-years were accumulated and the mean follow-up time was 1 year.

The two study groups were similar for baseline characteristics and concomitant therapies at entry (table). No patient was lost to follow-up (figure 1).

Mortality data are shown in figures 2–4. 145 patients in the metoprolol CR/XL group and 217 in the placebo group died ($p=0.00009$, $p=0.0062$ after adjustment for the first and second interim analyses, figure 2). The mortality rates were 7.2% and 11.0% per patient-year of follow-up, respectively, with a relative risk of 0.66 (95% CI 0.53–0.81). There were 128 cardiovascular deaths in the metoprolol CR/XL group and 203 in the placebo group (0.62 [0.50–0.78], $p=0.00003$). There were fewer sudden deaths in the metoprolol CR/XL group than in the placebo group (79 vs 132, 0.59 [0.45–0.78], $p=0.0002$). Death from aggravated heart failure occurred in 30 patients in the actively treated group and in 58 patients in the placebo group, with a relative risk of 0.51 (0.33–0.79, $p=0.0023$, figure 3). No significant increase in risk was seen in any of the predefined subgroups, analysed for safety (figure 5).

In a post-hoc analysis, we analysed total mortality and mode of death in relation to NYHA functional class at randomisation. In NYHA class II, 44 deaths occurred in the metoprolol CR/XL group and 59 deaths in the placebo group (5.3 vs 7.1% per patient-year of follow-up). Corresponding figures in NYHA III were 90 and 142

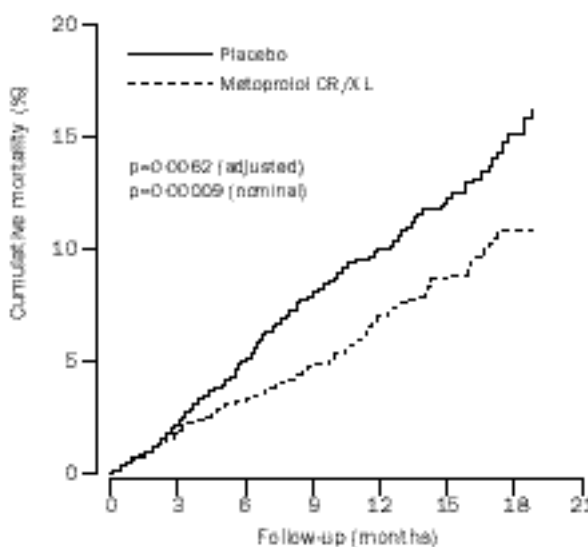


Figure 2: Kaplan-Meier curves of cumulative percentage of total mortality
p value adjusted for two interim analyses.

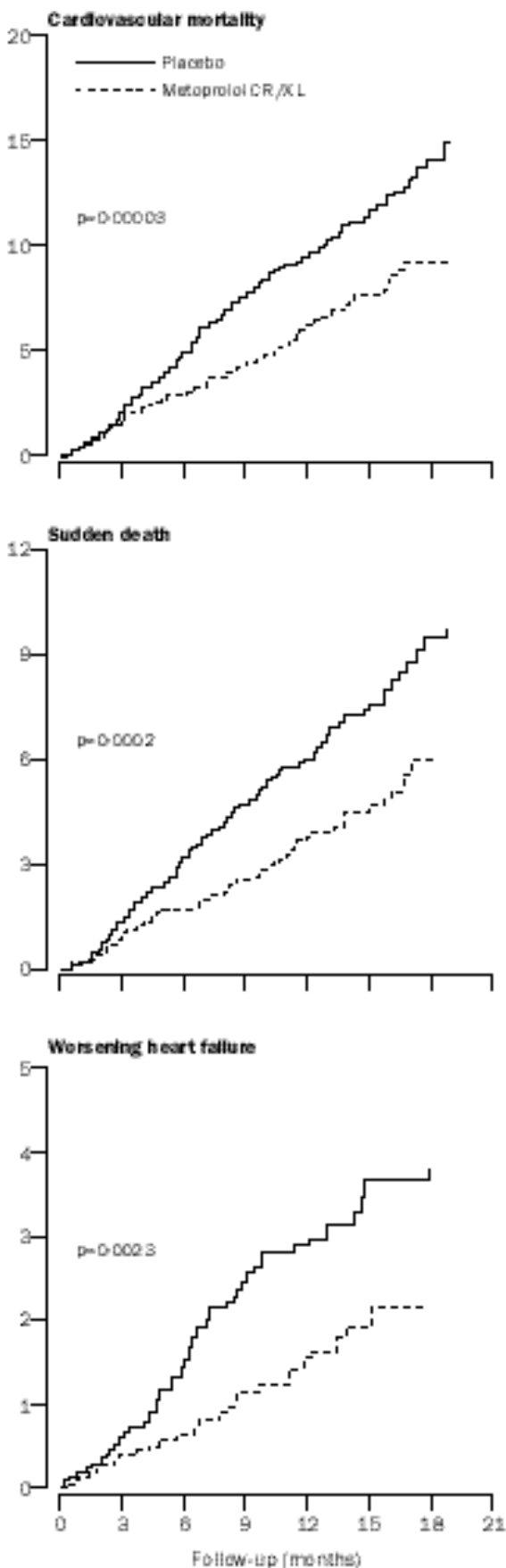


Figure 3: Kaplan-Meier curves of cumulative percentage of cardiovascular deaths, sudden deaths, and deaths from worsening heart failure

deaths (8.1 vs 13.2%) and in NYHA IV 11 and 16 deaths (16.7 vs 24.9%, figure 6). The proportion of sudden deaths generally decreased with increasing severity of heart failure according to NYHA functional class. Conversely, the proportion of patients who died from worsening heart failure increased with increasing severity of heart failure (figure 6).

Study drug was permanently stopped early in 13.9% of the metoprolol CR/XL group and in 15.3% of the placebo group (0.90 [0.77–1.06]). The mean daily dose of study drug at the end of the study in the metoprolol CR/XL group was 159 mg once daily, with 87% patients receiving 100 mg or more, and 64% receiving the target dose of 200 mg once daily. In the placebo group the corresponding values were 179 mg, 91% and 82%, respectively.

6 months after randomisation, heart rate had decreased from baseline by 14 beats per min in the metoprolol CR/XL group and by 3 beats per min in the placebo group ($p < 0.0001$). Systolic blood pressure decreased less in the metoprolol CR/XL group than in the placebo group (-2.1 vs 3.5 mm Hg, $p = 0.013$). There was no difference between groups in the change of diastolic blood pressure (-2.6 vs 2.3 mm Hg, $p = 0.38$).

Discussion

Once-daily metoprolol CR/XL added to optimum standard treatment with primarily ACE inhibitors and diuretics lessened all-cause mortality by 34% in clinically stable patients with symptomatic chronic heart failure and lowered ejection fraction in NYHA functional classes II–IV. Therefore, treatment of 27 patients with metoprolol CR/XL for 1 year can prevent one death.

Meta-analyses of previous smaller randomised placebo-controlled studies in heart failure patients, in which primary endpoints were not mortality, have shown that β -blockade may decrease total mortality by 30–35%.^{16–18} Only two studies have assessed the effect of β -blockade on survival as the predefined endpoint in heart failure—the MERIT-HF study and the Cardiac Insufficiency Bisoprolol Study II (CIBIS II).¹⁹ The two β -blockers studied are lipophilic and highly β_1 -selective, and the results of the two studies are in close agreement with a few exceptions. The CIBIS II study randomised patients in NYHA functional class III–IV with ejection fraction at or less than 0.35, whereas the MERIT-HF study included patients in class II and allowed an ejection fraction up to 0.40. In the two studies there were similar survival benefits in patients who were in NYHA classes III and IV: the decrease in mortality was 38% in MERIT-HF (95% CI 0.48–0.79) and 34% in CIBIS II (0.54–0.81).

Decreases in sudden death were also similar in the two studies—41% in MERIT-HF and 44% in CIBIS II. Death from worsening heart failure was lowered by 49% (0.33–0.79) in our study compared with 26% (0.48–1.14) in CIBIS II. Although the outcome was not significant in CIBIS II, the two studies taken together show that β_1 -blockade also has a clinically important effect on this mode of death.

During the past decade the combination of ACE inhibitors and diuretics has become the cornerstone in the treatment of patients with chronic heart failure due to left-ventricular systolic dysfunction. However, mortality remains high, which may have several explanations. Thus, there is no consistent impact of ACE-inhibitor treatment on sudden death in patients with chronic heart failure.^{2,4} Furthermore, there seems to be little or no survival benefit

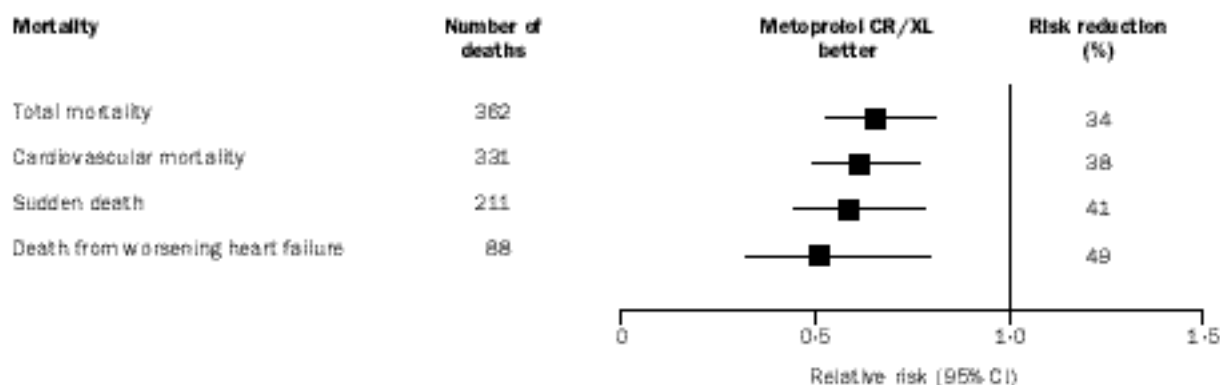


Figure 4: **Relative risk (95% CI) for total mortality, cardiovascular mortality, sudden death, and death from worsening heart failure**

of ACE-inhibitor treatment in patients with chronic heart failure who have ejection fractions higher than 0.30.^{3,4} The MERIT-HF results show that metoprolol CR/XL added to ACE-inhibitor treatment lowered the risk of sudden death and death from aggravated heart failure, and was equally effective across different subgroups of ejection fraction.

A better knowledge of the mechanisms of death in heart failure is of clinical importance. Accurate knowledge of how patients die could strongly influence treatment strategies, such as prevention of sudden death, that may require different therapy than that used to improve only pump function. Well-defined classifications are needed to clarify how patients who have chronic heart failure are dying. However, an overview has shown that there is heterogeneity between studies in the classifications of death in patients with chronic heart failure.¹⁵ We applied proposed definitions of sudden death and death from worsening heart failure, together with a classification procedure based on access to detailed information on each death by endpoint committee members who were masked to treatment status.¹⁵

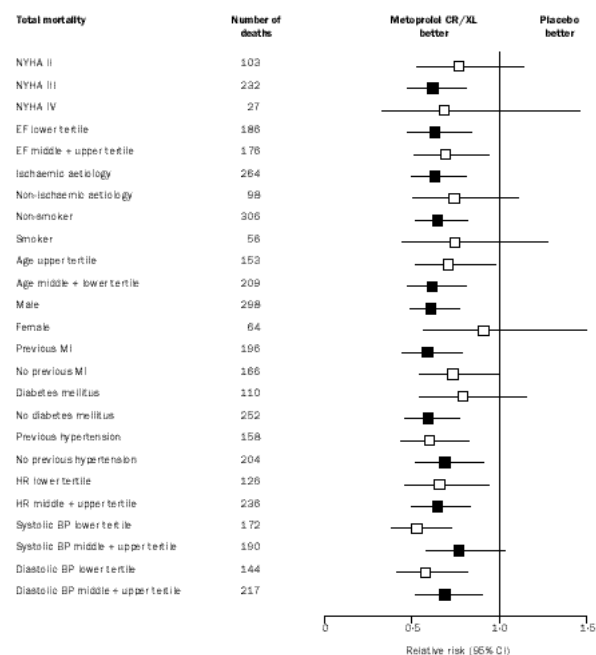


Figure 5: **Relative risk (95% CI) for total mortality in predefined subgroups defined according to characteristics at baseline**

Subgroups with ≥ 180 deaths have filled symbols, < 180 deaths unfilled symbols, indicating low power. Diastolic blood pressure at baseline not available in one patient who died later. EF=ejection fraction; MI=myocardial infarction; HR=heart rate; BP=blood pressure.

As previously reported, we found that sudden death was more common among patients with a less severe degree of chronic heart failure (NYHA class II), whereas death from worsening heart failure increased with increasing severity of heart failure.²⁰ Sudden death occurred in nearly 60% of patients who died. This high proportion is explained by the fact that although we randomised patients in NYHA functional class II–IV with an ejection fraction of 0.40 or lower, most patients (96%) had mild to moderate chronic heart failure (NYHA class II–III). These patients are more likely to die suddenly than from progressive heart failure than those with severe heart failure. Although our study was not powered for a separate analysis of mortality in patients with mild heart failure, the data are in accordance with a survival benefit also in this subgroup. Such benefit is important because patients with NYHA class II constitute a large proportion of heart-failure patients in clinical practice. We included few patients in NYHA functional class IV. The efficacy and safety of β -blocker treatment in patients with severe chronic heart failure therefore remains to be assessed.

In patients with chronic heart failure, sudden death may have cardiac and non-cardiac causes.^{19,20} The evidence suggests that a substantial proportion of sudden deaths are due to ventricular fibrillation.²⁰ Metoprolol has a protective effect on sudden death after acute myocardial infarction²¹ and data suggests a similar effect on sudden death in hypertensive patients.²² This information in combination with the decreased incidence of sudden death in our study suggest an antifibrillatory effect of metoprolol.^{23,24} The mechanisms underlying sudden death in patients with chronic heart failure may, however, not be identical with those operating in ischaemic conditions. This study was not designed to assess these mechanisms further.

About a quarter of our patients died from worsening heart failure and metoprolol CR/XL lowered the risk of this cause of death significantly. This effect was caused by

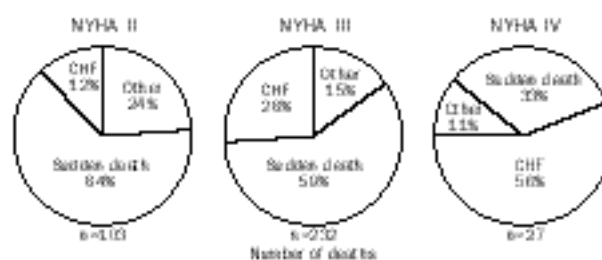


Figure 6: **Severity of heart failure and mode of death**

β_1 -receptor blockade, and involved mechanisms may be related to autonomic activity, receptor kinetics, myocardial energy balance, electrophysiology, neuroendocrine deactivation, and ventricular remodelling.¹⁶ Interestingly, we found that systolic blood pressure was decreased less by metoprolol CR/XL than by placebo, which supports previous reports, and which shows improved left-ventricular geometry and function.^{9,13}

Our study was not designed or powered for a separate analysis of patients with idiopathic dilated cardiomyopathy, and did not include patients younger than 40 years. However, for this category of patients some evidence is provided by the Metoprolol in Dilated Cardiomyopathy (MDC) trial.^{9,25} The results of that study showed a 34% (–6 to 62) decrease in the combined endpoint of death or need for heart transplantation.

In our study, we used once-daily metoprolol CR/XL. In comparison to conventional immediate-release metoprolol tartrate tablets, this preparation leads to a more pronounced and even β -blockade over 24 h.²⁶ Furthermore the target dose can be increased from 50 mg three times daily to 200 mg once daily in patients with heart failure without increasing the peak plasma concentration of the drug.²⁷ In the MDC study, the target dose was 50 mg three times daily. The mean daily dose in that study was 108 mg, which should be compared with 159 mg in this study. The better β -blockade may be important in protecting the heart from the surges in sympathetic nervous activity and vagal withdrawal, which may trigger ventricular fibrillation and sudden death.²³ A more pronounced and even β -blockade may also be of importance for the long-term myocardial performance of the failing heart.

The value of β -blockade has to be further studied in patients with NYHA class IV, in elderly patients with symptoms of heart failure and normal ejection fraction, and in those with left-ventricular dysfunction and heart failure early after acute myocardial infarction. In the latter category of patients, some positive evidence is available from earlier studies.^{7,8,28,29}

Our study showed that treatment with once daily metoprolol CR/XL added to standard therapy improved survival and lowered the risk of sudden death and death from worsening heart failure in patients with mild to severe chronic heart failure secondary to left-ventricular systolic dysfunction of ischaemic or non-ischaemic cause. The patients were in a stable clinical condition during the 2 weeks before randomisation. Metoprolol CR/XL added to standard therapy with diuretics and ACE inhibitors was well tolerated. The up-titration schedule of metoprolol CR/XL, starting with a low dose and gradually increasing over 2 months, should be feasible for ambulatory heart-failure patients in clinical practice.

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