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Metoprolol Controlled Release/Extended Release in Patients With Severe Heart Failure

Analysis of the Experience in the MERIT-HF Study

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OBJECTIVES This study analyzed the effect of the beta$_1$-selective beta-blocker metoprolol succinate controlled release/extended release (CR/XL) once daily on mortality, hospitalizations and tolerability in patients with severe heart failure.

BACKGROUND There continues to be resistance to the incorporation of beta-blockers into clinical care, largely due to concerns about their benefit in patients with more severe heart failure.

METHODS A subgroup of patients from Metoprolol CR/XL Randomized Intervention Trial in chronic Heart Failure (MERIT-HF) in New York Heart Association (NYHA) functional class III/IV with left ventricular ejection fraction <0.25 were identified (n = 795). The analysis was by intention-to-treat.

RESULTS The mean ejection fraction at baseline was 0.19, and the yearly placebo mortality during follow-up was 19.1%. Treatment with metoprolol CR/XL compared to placebo resulted in significant reductions in all predefined mortality end points including: total mortality, 45 versus 72 deaths (risk reduction 39%; 95% confidence interval 11% to 58%; p = 0.0086); sudden death, 22 vs. 39 deaths (45% [7% to 67%]; p = 0.024); and death due to worsening heart failure, 13 vs. 28 deaths (55% [13% to 77%]; p = 0.015). Metoprolol CR/XL also reduced the number of hospitalizations for worsening heart failure by 45% compared with placebo (p < 0.0001). The NYHA functional class improved in the metoprolol CR/XL group compared with placebo (p = 0.0031). Metoprolol CR/XL was well tolerated, with 31% fewer patients withdrawn from study medicine (all causes) compared with placebo (p = 0.027).

CONCLUSIONS This subgroup analysis of the MERIT-HF study shows that patients with severe heart failure receive a similar mortality benefit and a similar reduction in hospitalizations for worsening heart failure with metoprolol CR/XL treatment as those patients included in the total study. (J Am Coll Cardiol 2001;38:932–8) © 2001 by the American College of Cardiology

Beta-adrenergic receptor blockers have become established therapy for a broad spectrum of patients with heart failure due to left ventricular systolic dysfunction as a result of the experience from the U.S. Carvedilol Program and two dedicated survival trials, the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), and the Metoprolol CR/XL [controlled release/extended release] Randomized Intervention Trial in chronic Heart Failure (MERIT-HF) (1–4). In the two survival trials, the beta-blockers bisoprolol and metoprolol CR/XL have been shown to significantly decrease mortality by 34%. Speculation about the benefit of beta-blockers in heart failure has been ongoing for more than two decades. The results from these recent trials, however, have clearly established their beneficial effects on total mortality, death due to progressive heart failure and sudden death when added to standard therapy with diuretics and angiotensin-converting enzyme (ACE) inhibitors. In addition to their effects on mortality, they also exert a significant effect on the need for hospitalization for worsening heart failure, and they are remarkably well tolerated (1–5). The results of these trials have changed the attitude about the use of these drugs. Nevertheless, resistance to their incorporation into clinical care continues, largely due to concerns about their benefit in patients with more severe heart failure.

The recent Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial investigated the effect of carvedilol in 2,289 patients with more severe heart failure characterized as having symptoms at rest or with minimal exertion and with a left ventricular ejection fraction <0.25 (5). The COPERNICUS trial showed a 35% decrease in mortality (95% confidence interval [CI] 19% to 48%; p = 0.00014) in a patient population with a mean baseline ejection fraction of 0.20, and a yearly placebo mortality of 19.7% per patient year of follow-up. To increase our

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
BEST	= Beta-blocker Evaluation of Survival Trial
CI	= confidence interval
CIBIS II	= Cardiac Insufficiency Bisoprolol Study II
COPERNICUS	= Carvedilol Prospective Randomized Cumulative Survival trial
CR/XL	= controlled release/extended release
MERIT-HF	= Metoprolol CR/XL Randomized Intervention Trial in chronic Heart Failure
NYHA	= New York Heart Association

understanding of the benefit and safety of beta-blockers in patients with severe heart failure, a subgroup analysis of patients enrolled in MERIT-HF in New York Heart Association (NYHA) functional class III/IV with ejection fraction <0.25 was carried out.

METHODS

The MERIT-HF study enrolled 3,991 patients from February 14, 1997, to April 14, 1998, in 14 countries, including the U.S. The two primary outcome events were total mortality and the combined end point of all-cause mortality or all-cause hospitalization (time to first event). The results of the MERIT-HF study have been published previously (3,4). The study was stopped early, on October 31, 1998, when the second preplanned interim analysis showed a highly significant reduction in total mortality in the metoprolol CR/XL group compared to placebo (6). The present post hoc analysis deals with the subgroup of patients in the original study in NYHA functional class III/IV with ejection fraction <0.25 (n = 795). The cutoff limit for ejection fraction (<0.25) was chosen to correspond with the inclusion criterion for ejection fraction in the COPERNICUS trial (5).

Patients enrolled in the MERIT-HF study were men and women aged 40 to 80 years who had had symptomatic heart failure NYHA functional class II to IV for three months or more before randomization, and who at the time of enrollment had a heart rate at or above 68 beats/min receiving optimum standard therapy of diuretics and an ACE inhibitor. If an ACE inhibitor was not tolerated, other vasodilators, preferably angiotensin II receptor blockers, could be used. Digitalis could also be prescribed. Other inclusion criteria were a stable clinical condition during the two-week run-in phase between enrollment and randomization and an ejection fraction ≤0.40 within three months of enrollment.

Exclusion criteria included an acute myocardial infarction or unstable angina within 28 days before randomization, indication or contraindication for treatment with beta-blockers or drugs with beta-blocking properties such as amiodarone; beta-blocker treatment within six weeks before enrollment; heart failure secondary to systemic disease or alcohol abuse; scheduled or performed heart transplantation or cardiomyoplasty, implanted cardiac defibrillator or a procedure such as coronary artery bypass grafting or percutaneous transluminal coronary angioplasty planned or performed in the past four months; atrioventricular block of second or third degree unless the patient had an implanted pacemaker and spontaneous heart rate at or above 68 beats/min; unstable decompensated heart failure with pulmonary edema or hypoperfusion or supine systolic blood pressure consistently <100 mm Hg at enrollment; other serious diseases that might complicate management during follow-up; use of calcium antagonist such as diltiazem or verapamil; use of amiodarone within six months before enrollment.

After a single blind placebo run-in phase of two weeks, patients were randomized to metoprolol CR/XL or placebo with starting doses of 12.5 or 25 mg once daily. The lower starting dose was recommended for patients in NYHA functional class III/IV. It was recommended to double the dose every second week to a target dose of 200 mg once daily or the highest tolerated dose. The titration schedule could be modified according to written guidelines (6) and according to the discretion of the investigator.

In addition to the two primary end points, other predefined combined end points (time to first event) were total mortality or hospitalization due to worsening heart failure and cardiac death or nonfatal acute myocardial infarction. Further predefined end points were the total number of hospitalizations due to cardiovascular causes, and due to worsening heart failure, withdrawal of study drug for any cause, and for worsening heart failure. The follow-up procedures and statistical analysis for the MERIT-HF study are described in previous reports (3,4,6). Briefly, analyses were by intention-to-treat. The main analyses utilized the log-rank test for the comparison of the two randomization groups, and the Cox proportional hazards survival model to calculate relative risk and 95% CIs.

In one additional analysis, mortality data for the subgroups of patients with severe heart failure (NYHA functional class III/IV and ejection fraction <0.25) from the CIBIS II and MERIT-HF studies were pooled (Mantel-Haenzel method for pooling) with the COPERNICUS trial data. Results from the Beta-blocker Evaluation of Survival Trial (BEST) were not included in this pooling (7). This was because the beta-blocker used in this trial, bucindolol, markedly differs from the other beta-blockers investigated (metoprolol CR/XL, bisoprolol, carvedilol) in leading to a much more pronounced beta-blockade, especially of $beta_2$-receptors. This may be deleterious for patients with severe heart failure in need of endogenous circulating norepinephrine support (7).

RESULTS

Of the 3,991 patients enrolled in MERIT-HF, 795 patients represented a subgroup of the total patient population in

Table 1. Entry Characteristics in the Two Randomization Subgroups With Severe Heart Failure: Data Are Also Given for All Other Patients Randomized

Characteristics	Metoprolol CR/XL (n = 399)	Placebo (n = 396)	All Other (n = 3,196)
Mean age (yrs)	64.7	64.6	63.6
Gender, (%) women	24	22	22
Caucasian (%)	91	91	95
Ischemic etiology of heart failure (%)	64	65	66
NYHA functional class (%)			
II	0	0	51
III	90	91	47
IV	10	9	2
Ejection fraction (mean)	0.19	0.19	0.30
Systolic blood pressure (mean)	125	124	131
Diastolic blood pressure (mean)	77	77	79
Heart rate (mean)	85	85	82
Medical history			
Previous MI (%)	47	49	48
Time since last MI <1 year (%)	6	6	8
Hypertension (%)	40	41	45
Diabetes mellitus (%)	23	27	25
Medications			
Diuretics (%)	97	95	89
ACE inhibitor (%)	87	86	90
AII blocker (%)	10	10	6
ACE inhibitor or AII blocker (%)	95	95	96
Digitalis (%)	67	74	62
Symptoms			
Peripheral pitting edema	20	21	14
Jugular venous distension	18	19	13
Pulmonary rales	14	11	11
Third heart sound	37	33	20

ACE = angiotensin-converting enzyme; AII = angiotensin II; CR/XL = controlled release/extended release; MI = myocardial infarction; NYHA = New York Heart Association.

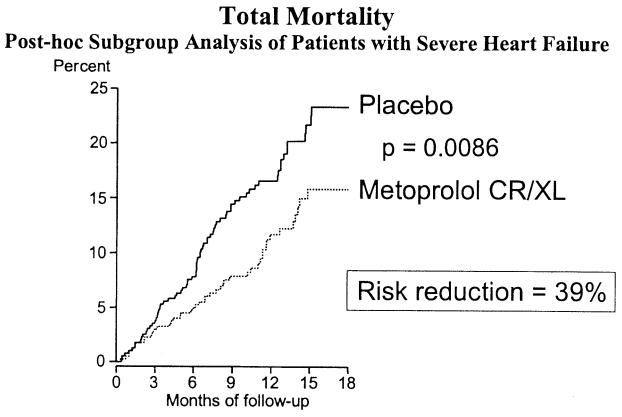
NYHA functional class III/IV with ejection fraction <0.25, and they are the subject of this analysis. Of those patients, 399 were randomized to metoprolol CR/XL and 396 to placebo. Baseline characteristics in the two randomization subgroups were very similar, which may be due to the optimal allocation procedure that was used at randomization (Table 1). Table 1 also gives baseline data for all patients not classified as belonging to the severe heart failure subgroup (n = 3,196). Compared with all other patients randomized, patients in the severe heart failure group were slightly older, had a lower mean ejection fraction and were more likely to have physical signs of heart failure. Furthermore, systolic blood pressure was lower and heart rate was higher in the severe heart failure subgroup (Table 1).

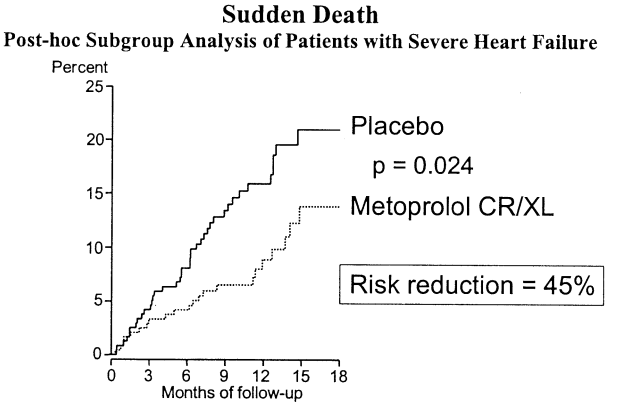
There were 45 deaths (11.7% per patient year of follow-up) in the metoprolol CR/XL group and 72 (19.1%) in the

Table 2. Effect of Metoprolol CR/XL and Placebo Treatment on Cause-Specific Mortality and on the Combined End Points in the Subgroups With Severe Heart Failure

End Point	Metoprolol CR/XL (n = 399)	Placebo (n = 396)	Risk Reduction (95% CI) (%)	p Value
Cause-specific mortality				
Total	45	72	39 (11–58)	0.0086
Cardiovascular	40	70	44 (18–62)	0.0028
Worsening heart failure	13	28	55 (13–77)	0.015
Sudden death	22	39	45 (7–67)	0.024
Combined end points				
All-cause mortality or all-cause hospitalization*	155	203	29 (13–43)	0.0012
All-cause mortality or hospitalization due to worsening heart failure*	88	144	44 (27–57)	< 0.0001
Cardiac death or nonfatal acute MI*	41	74	46 (21–63)	0.0014

*n = time to first event.
CI = confidence interval; CR/XL = controlled release/extended release; MI = myocardial infarction.





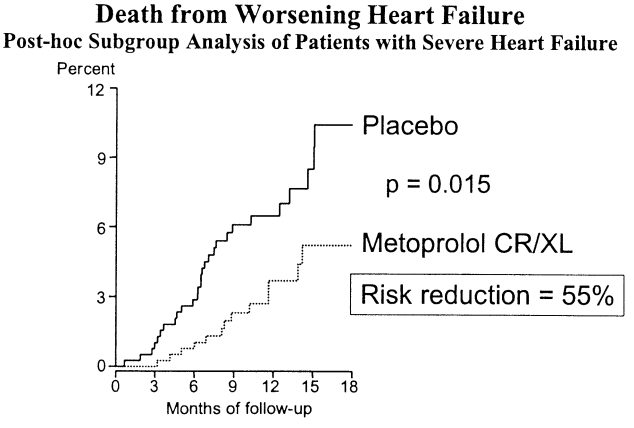
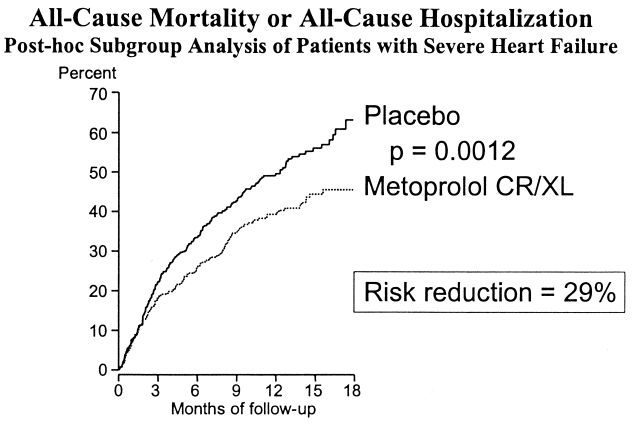
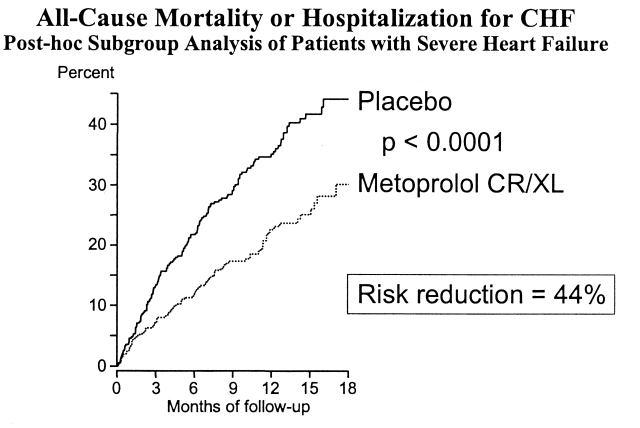


Figure 1. Kaplan-Meier curves of cumulative percentage of all-cause mortality **(top)**, sudden deaths **(middle)** and deaths from worsening heart failure **(bottom)**. CR/XL = controlled release/extended release.





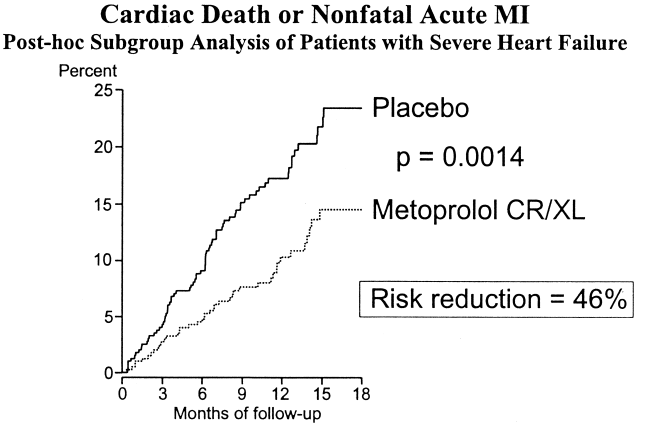


Figure 2. Kaplan-Meier curves of cumulative percentage of the combined end points (time to first event) of all-cause mortality or all-cause hospitalization **(top)**, all-cause mortality or hospitalization for worsening chronic heart failure (CHF) **(middle)** and for cardiac death or nonfatal acute myocardial infarction (MI) **(bottom)**. CR/XL = controlled release/extended release.

placebo group (Table 2). Metoprolol CR/XL decreased total mortality by 39% (Fig. 1 top, and Table 2), sudden death by 45% (Fig. 1 middle) and death due to worsening heart failure by 55% (Fig. 1 bottom). Metoprolol CR/XL also decreased the combined end points of all-cause mortality or all-cause hospitalization (time to first event) by 29% (Fig. 2 top and Table 2), all-cause mortality or hospitalization for worsening heart failure by 44% (Fig. 2 middle), and cardiac death or nonfatal myocardial infarction by 46% (Fig. 2 bottom).

Metoprolol CR/XL also reduced the total number of hospitalizations (all-cause) by 27% (0.709 vs. 0.965 per patient year of follow-up; $p = 0.0037$). During the up-titration phase of the study, the cumulative number of patients hospitalized (all-cause) were: 17 versus 21 after two weeks; 28 versus 30 after four weeks; 39 versus 40 after six weeks; 46 versus 56 after eight weeks; and 76 versus 102

Table 3. Cause-Specific Data for Number of Patients Hospitalized at Least Once and Total Number of Hospitalizations in the Two Randomization Groups With Severe Heart Failure

Hospitalizations	Metoprolol CR/XL (n = 399)	Placebo (n = 396)	p Value
Due to all causes			
No. of patients with any hospitalization (n, [rate]*)	141 (0.468)	176 (0.635)	0.0088
Total no. of hospitalizations (n)	273 (0.709)	363 (0.965)	0.0037
Due to cardiovascular causes			
No. of patients with any hospitalization (n, [rate])	99 (0.299)	143 (0.461)	0.0005
Total no. of hospitalizations (n)	183 (0.475)	269 (0.715)	0.0005
Due to worsening heart failure			
No. of patients with any hospitalization (n, [rate])	60 (0.169)	103 (0.319)	< 0.0001
Total no. of hospitalizations (n)	105 (0.273)	187 (0.497)	< 0.0001

*Per patient year of follow-up.
CR/XL = controlled release/extended release.

after three months in the metoprolol CR/XL and placebo groups, respectively. The total number of hospitalizations for cardiovascular causes was reduced by 34% (0.475 vs. 0.715 per patient year of follow-up; p = 0.0005), and for worsening heart failure by 45% (0.273 vs. 0.497; p < 0.0001; Table 3 and Fig. 3 upper).

Physicians classified NYHA functional class at baseline and at the last visit in the study. Improvement was recorded in 46.2% versus 36.7% of the patients in the metoprolol CR/XL and placebo groups, respectively (40.4% vs. 32.6% improved one class; 5.8% vs. 4.1% improved two classes); 49.5% versus 55.9% were unchanged; 4.3% versus 7.4% deteriorated one class. These data show a more favorable change in NYHA functional class in the metoprolol CR/XL group compared with the placebo group (p = 0.0031). The mean dose of study medicine in the severe heart failure subgroup at the last available visit was 148 mg in the metoprolol CR/XL group and 161 mg in the placebo group. The drug was well tolerated. There were 31% fewer withdrawals due to all causes (p = 0.027; Fig. 3) and 49% fewer due to worsening heart failure (p = 0.012) in the metoprolol CR/XL group compared with the placebo group. During the up-titration phase of the study, the cumulative numbers of patients withdrawn for worsening heart failure were as follows: 3 versus 3 after two weeks; 3 versus 4 after four weeks; 6 vs. 6 after six weeks; 8 vs. 7 after eight weeks; and 11 versus 15 after three months in the metoprolol CR/XL and placebo groups, respectively.

DISCUSSION

This subgroup analysis of the MERIT-HF study examined the effect of metoprolol CR/XL in patients with severe heart failure in NYHA functional class III/IV with ejection fraction <0.25. The beneficial effects observed in the total MERIT-HF trial are also observed in this subgroup with severe heart failure. In the MERIT-HF study, total mortality was decreased by 34%, sudden death by 41%, and death due to worsening heart failure by 49% (3); this compared to 39%, 45% and 55%, respectively, in this severe heart failure subgroup. Beneficial effects on hospitalizations and NYHA functional class similar to the overall results of the MERIT-HF study were also observed in the severe heart failure subgroup.

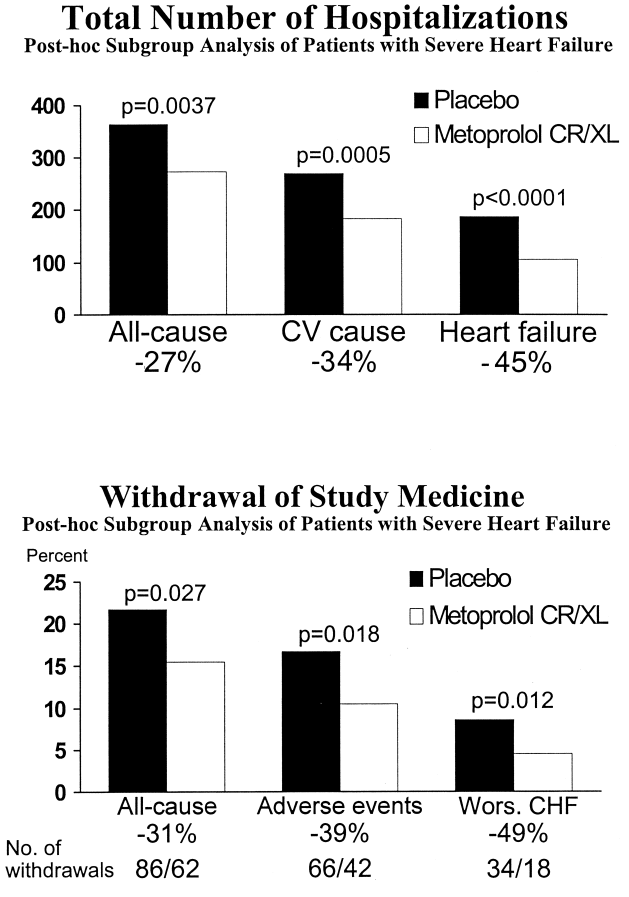


Figure 3. (Upper) Total number of hospitalizations all-cause due to cardiovascular (CV) causes and due to worsening heart failure in the two randomization groups. Percentage figures are normalized for patient years of follow-up. **(Lower)** Total number of patients with permanent withdrawal of study drug due to any cause, due to any adverse event and due to worsening heart failure in the two randomization groups. Percentage figures are normalized for patient years of follow-up. CHF = chronic heart failure; CR/XL = controlled release/extended release.

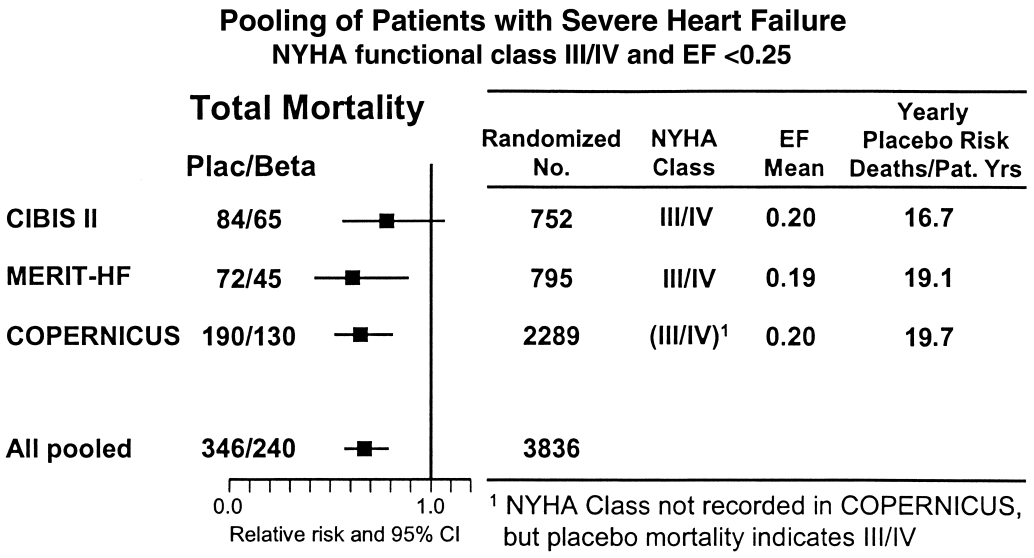


Figure 4. Point estimates for hazard ratios and 95% confidence intervals for total mortality for subgroups of patients with severe heart failure (New York Heart Association [NYHA] functional class III/IV and ejection fraction [EF] <0.25) in the CIBIS II study and the MERIT-HF study. Data for the COPERNICUS trial are also given together with pooled data. Number of deaths and number of patients in each randomization group, mean EF and yearly placebo (Plac) risk defined as deaths/patient years of follow-up are also given by study and for the pooled data. CI = confidence interval; n = 3,836.

The characteristics of this subgroup differed from the total study population by design, with much lower ejection fraction, more advanced symptomatology and higher placebo mortality. Nevertheless, even in this severe heart failure population, the drug was well tolerated without any evidence of increased withdrawal of drug due to worsening heart failure, and there was no evidence that metoprolol CR/XL therapy resulted in more frequent hospitalizations at any time during follow-up.

Comparison with the COPERNICUS trial and the CIBIS II study. The present results are based on a post hoc analysis, but the decrease in mortality is similar to that observed in the COPERNICUS trial, in which carvedilol was investigated. The COPERNICUS trial enrolled 2,289 patients who had symptoms at rest or with minimal exertion despite optimal therapy with ACE inhibitors and diuretic therapy; ejection fraction was <0.25 (mean 0.20). Similar to previous observations in randomized clinical trials with beta-blockers, carvedilol was well tolerated. In the COPERNICUS trial, total mortality was reduced by 35%, with a placebo mortality of 19.7% per patient year of follow-up (compared to 39% and 19.1%, respectively, in the severe heart failure group of the MERIT-HF study; Fig. 4). A subgroup analysis of the CIBIS II study of patients with ejection fraction <0.25 also revealed a rather similar mortality benefit as that observed in the COPERNICUS trial (point estimate for hazard ratio 0.78 [0.56 to 1.07], Philippe Lechat, personal communication, 2000; Fig. 4). The combined experience of all three studies including patients with severe heart failure covers more than 3,800 patients with a highly significant reduction in total mortality (Fig. 4).

Tolerability. It has been known for some time that patients with more severe heart failure have higher levels of circulating norepinephrine and, therefore, are more likely to experience the ravages of heightened sympathetic activation and lowered vagal tone (8). It is possible that these patients with increased sympathetic stimulation and lower vagal tone may be more dependent upon the inotropic effects of endogenous circulating norepinephrine. Beta-adrenergic receptor blockade may cause a transient decrease in ejection fraction in some patients, which could also increase the symptomatology of heart failure (9). However, metoprolol CR/XL was well tolerated as judged by 49% fewer drug withdrawals for worsening heart failure in comparison with placebo, and also as judged from hospitalizations both when initiating treatment and long-term. The good tolerability may be due to both the careful up-titration program used, and the relative stability of the patients enrolled in the study. Patients with unstable decompensated heart failure (pulmonary edema, hypoperfusion or hypotension) were not randomized until stabilized.

Conclusions. This subgroup analysis of the MERIT-HF study indicates that the benefits observed in the total study are echoed in this severe heart failure group. Metoprolol CR/XL was safe and well tolerated. Study results do not support the common belief that beta-blocker treatment of patients with advanced heart failure results in adverse effects. In fact, both their overall benefit and their excellent tolerability are confirmed in this substudy, which corroborates the results of the COPERNICUS trial, and the subgroup analysis of the patients with severe heart failure in the CIBIS II study. In comparison to the overall results of the MERIT-HF study, in which treatment of 27 patients for one year resulted in one life saved, this analysis of the

severe heart failure patients indicates that treatment of 13 patients for one year would result in one life saved. It is, however, important to emphasize that patients in NYHA functional class II to III represent the greatest number of patients with heart failure. It is in this population where the addition of beta-blockers to existing therapy will exert its largest public health benefit. The benefit of metoprolol CR/XL therapy in heart failure, therefore, is best represented by the overall effect in patients with NYHA functional class II to IV in the total MERIT-HF study.

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