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Dose of Metoprolol CR/XL and Clinical Outcomes in Patients With Heart Failure

Analysis of the Experience in Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF)

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OBJECTIVES We performed a post-hoc subgroup analysis in the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) with the aim of reporting on the heart rate (HR) response during the titration phase and clinical outcomes from the three-month follow-up visit to end of study in two dosage subgroups: one that had reached more than 100 mg of metoprolol CR/XL once daily (high-dose group; n = 1,202; mean 192 mg) and one that had reached 100 mg or less (low-dose group; n = 412; mean 76 mg).

BACKGROUND Clinicians have questioned whether patients need to reach the target beta-blocker dose to receive benefit.

METHODS Outcome (Cox-adjusted) was compared with all placebo patients with dose available at the three-month visit (n = 1,845).

RESULTS Data indicated somewhat higher risk in the low-dose group compared with the high-dose group. Heart rate was reduced to a similar degree in the two dose groups, indicating higher sensitivity for beta-blockade in the low-dose group. The reduction in total mortality with metoprolol CR/XL compared with placebo was similar: 38% (95% confidence interval [CI], 16 to 55) in high-dose group (p = 0.0022) and also 38% (95% CI, 11 to 57) in the low-dose group (p = 0.010).

CONCLUSIONS Risk reduction was similar in the high- and low-dose subgroups, which, at least partly, may be the result of similar beta-blockade as judged from the HR response. The results support the idea of an individualized dose-titration regimen, which is guided by patient tolerability and the HR response. Further research is needed to shed light on why some patients respond with a marked HR reduction and reduced mortality risk on a relatively small dose of a beta-blocker. (J Am Coll Cardiol 2002;40:491–8) © 2002 by the American College of Cardiology Foundation

Randomized survival trials have reported improved survival and reduced need for hospitalizations for worsening heart failure (HF) with beta-adrenergic blocking agents in a broad spectrum of patients with New York Heart Association (NYHA) functional class II to IV HF and left ventricular systolic dysfunction (1–4). The Cardiac Insufficiency Bisoprolol Study (CIBIS-II), Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) and Carvedilol Prospective Randomized Cumulative Survival study (COPERNICUS) all showed a 34% to 35% reduction in total mortality with bisoprolol in CIBIS-II, with metoprolol controlled-release/extended-release (CR/XL) in MERIT-HF and with carvedilol in COPERNICUS. In these trials treatment was initiated with a low beta-blocker dose with careful titration to a predefined maximum target dose or to the highest tolerated dose. None of the trials was designed as a dose response study. The beta-blocker dose could, however, be modified according to the judgment of the investigators and according to guidelines as defined in the study protocols for the different trials performed (1–5). Thus, not all patients reached the maximum target beta-blocker dose, and clinicians have questioned whether patients do, in fact, need to reach the maximum dose to receive benefit.

In order to study outcomes in relation to the achieved dose of one of the agents investigated, metoprolol CR/XL, a controlled release/extended release formulation of the $beta_1$-selective beta-blocker metoprolol succinate, the outcome in two subgroups from MERIT-HF were analyzed post-hoc: one subgroup included patients who had reached more than 100 mg of metoprolol CR/XL at the end of the titration phase (three-month visit) and the other subgroup

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Abbreviations and Acronyms

CI	= confidence interval
CIBIS II	= Cardiac Insufficiency Bisoprolol Study
COPERNICUS	= Carvedilol Prospective Randomized Cumulative Survival study
CR/XL	= controlled-release/extended-release
HF	= heart failure
HR	= heart rate
MERIT-HF	= Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure
NYHA	= New York Heart Association

of patients who had reached 100 mg or less. This report focuses on the heart rate (HR) response during the titration phase, achieved plasma concentration of metoprolol succinate and clinical outcomes from the three-month follow-up visit to end of study in the two dosage subgroups.

METHODS

The MERIT-HF trial randomized a total of 3,991 patients (2,3,5). The present analysis deals with the subgroup of patients with dose of study medicine >0 mg at the end of the titration phase (three-month visit; n = 3,651). A total of 340 patients, 156 randomized to placebo and 184 to metoprolol CR/XL, are not included in the present analysis; of these, 75 had died within 90 days after the date of randomization (40 patients randomized to placebo and 35 to metoprolol CR/XL); 116 versus 149 patients were alive at 90 days, but had dose missing; of these, 23 versus 13 died later in the placebo and metoprolol CR/XL groups, respectively.

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). In addition to the two primary end points, other predefined end points were sudden death and death from worsening HF and also the combined end points (time to first event) of total mortality or hospitalization due to worsening HF and of 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 HF and withdrawal of study drug for any cause, and for worsening HF.

Inclusion and exclusion criteria for MERIT-HF have been published earlier (2,3,5). Briefly, patients had symptomatic HF in NYHA functional class II to IV and ejection fraction ≤0.40 and were on optimum standard therapy with diuretics and an angiotensin-converting enzyme inhibitor.

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 mg 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 maximum target dose of 200 mg once daily or the highest tolerated dose. The titration schedule could be modified according to the discretion of the investigator and according to written guidelines in the study protocol, published earlier (5).

Metoprolol plasma concentration. At the three-month visit, a blood sample was drawn for the analysis of plasma concentration of metoprolol succinate. Blood samples were kept frozen at −20°C until analysis, which was performed at Bioanalytical Chemistry, AstraZeneca, Mölndal, Sweden. Metoprolol concentrations were determined by mass spectrometry (6). Minimum detectable concentration was about 10 nmol/l with a relative standard deviation of <10% at a concentration of 10 nmol/l.

Statistical methods. The present analysis is post-hoc. It should also be noted that the comparison of placebo with the two metoprolol CR/XL dose groups does not represent a true comparison of randomization subgroups. This is because the placebo group and two metoprolol CR/XL dose groups are defined according to postrandomization events: being alive at the time of the three-month visit and with a dose of study medicine >0 mg. In order to adjust for a possible difference in risk between subgroups when analyzing relative risk, we have applied a Cox proportional hazard regression analysis taking into account the following baseline risk factors: age, gender, NYHA class, ejection fraction, history of hypertension, acute myocardial infarction and diabetes mellitus, etiology of HF (ischemic or nonischemic) and smoking. Furthermore, the following postrandomization events were included in the analysis: starting dose of study medicine (12.5 mg or 25 mg) and number of hospitalizations before the three-month visit. However, there are probably other confounders present, which are unknown and, therefore, cannot be accounted for. Thus, in the Cox analyses of mortality and hospitalizations, we have chosen to compare both the low-dose beta-blocker subgroup and the high-dose beta-blocker subgroup with all placebo patients with dose available at the three-month follow-up visit (n = 1,845). Estimates of relative risk and their 95% confidence intervals (CI) have been obtained from the fitted models.

RESULTS

Baseline characteristics for the different subgroups are given in Table 1. Compared with the high-dose metoprolol CR/XL subgroup, the low-dose subgroup was slightly older (65.9 years vs. 62.5 years) and had somewhat more patients in NYHA functional class III/IV (67% vs. 53%). Baseline blood pressure was somewhat lower in the low-dose subgroup. A history of ischemic etiology of HF was slightly more common in the low-dose group, concomitantly with a slightly higher incidence of a history of myocardial infarction.

HR response during titration. In the low-dose metoprolol CR/XL group, 65% of the patients started on 12.5 mg; the corresponding figure in the high-dose group was 43%. Mean metoprolol CR/XL dose after three months was 76

Table 1. Entry Characteristics in Relation to Dose of Study Medicine Achieved at the Three-Month Follow-Up Visit (≤100 mg: Low Dose and >100 mg: High Dose)

Characteristics	Both Dose Groups		Metoprolol CR/XL	
	Placebo (n = 1,845)	Metoprolol CR/XL (n = 1,806)	Low-Dose Group (n = 604)	High-Dose Group (n = 1,202)
Mean age (yrs)	63.6	63.7	65.9	62.5
Gender (% females)	22.8	22.4	21.5	22.8
Caucasian (%)	94	94	93	94
Ischemic etiology (%)	65	65	70	62
NYHA functional class (%) II	42	42	33	47
III	55	55	62	51
IV	3.3	3.3	5.0	2.4
Ejection fraction	0.28	0.28	0.27	0.28
SBP (mm Hg)	130	130	127	131
DBP (mm Hg)	78	79	76	80
Heart rate (beats/min)	83	83	81	83
Height (cm)	172	172	172	172
Weight (kg)	81.0	80.7	78.3	81.9
BMI (kg/m^2)	27.3	27.3	26.5	27.7
S-creatinine (μmol/l)	106	107	112	104
Current smoker (%)	15	14	11	16
Medical history				
Previous MI (%)	49	47	54	44
Hypertension (%)	44	44	43	45
Diabetes mellitus (%)	24	25	23	26
Medications				
Diuretics (%)	90	90	90	90
Furosemide (mg)	64	66	73	62
ACEI (%)	90	89	87	90
AII blocker (%)	7.0	7.0	9.1	6.0
ACEI or AII blocker (%)	97	96	96	96
Digitalis (%)	64	63	63	63
Symptoms				
Peripheral pitting edema	14	15	15	15
Jugular venous distension	13	13	13	13
Pulmonary rales	11	11	11	11
Third heart sound	23	23	22	24

ACEI = angiotensin-converting enzyme inhibitor; AII = angiotensin II blocker; BMI = body mass index; CR/XL = controlled-release/extended release; DBP = diastolic blood pressure; MI = myocardial infarction; NYHA = New York Heart Association; SBP = systolic blood pressure.

mg in the low-dose group (9% on 25 mg, 30% on 50 mg, 56% on 100 mg, other ≤100 mg 5%) versus 192 mg in the high-dose group (16% on 150 mg, 84% on 200 mg). The median plasma concentration of metoprolol succinate corresponded well with beta-blocker dose given: 95 nmol/l (low-dose) versus 247 nmol/l (high-dose), respectively at the three-month follow-up visit.

Figure 1 illustrates HR in relation to achieved beta-blocker dose during the titration phase and up to the three-month visit. After two weeks the mean dose of metoprolol CR/XL was 17 mg in the low-dose group, and HR was reduced to 75 beats/min. After four weeks 32 mg, after six weeks 64 mg and after eight weeks and three months, the same mean metoprolol CR/XL dose was reached, 76 mg, also with the same mean HR of 67 beats/min at the eight-week and three-month visits. After two weeks a mean dose of 21 mg was achieved in the high-dose group and after three months 192 mg. Thus, HR after three months was 67 beats/min in both low-dose and high-dose groups—a mean reduction in HR from baseline of 13.7 versus 15.9 beats/min, respectively. This corresponds to a mean HR reduction per mg metoprolol CR/XL of 0.21 beats/min/mg in the low-dose group and 0.08 beats/min/mg in the high-dose group ($p < 0.0001$). In the placebo arm, HR after three months was reduced by 2.8 beats/min.

Clinical outcomes. Total mortality in the placebo group (n = 1,845) from the date of the three-month visit to end of follow-up was 10.8% per patient year of follow-up, compared with 6.8% in the two beta-blocker subgroups combined (n = 1,806; Table 2, Fig. 2), corresponding to a relative risk reduction of 38% (95% CI, 20 to 53; $p = 0.0003$, Table 3, Fig. 3). Mortality tended to be higher in the low-dose metoprolol CR/XL subgroup compared with the high-dose subgroup (8.0% vs. 6.2% per patient year of follow-up; relative risk 1.30, 95% CI, 0.87 to 1.96), but relative risk reduction (Cox-adjusted) with metoprolol CR/XL compared with placebo (n = 1,845) was similar: 38% (95% CI, 11 to 57) in low-dose subgroup ($p = 0.010$) and 38% (95% CI, 16 to 55) in the high-dose subgroup

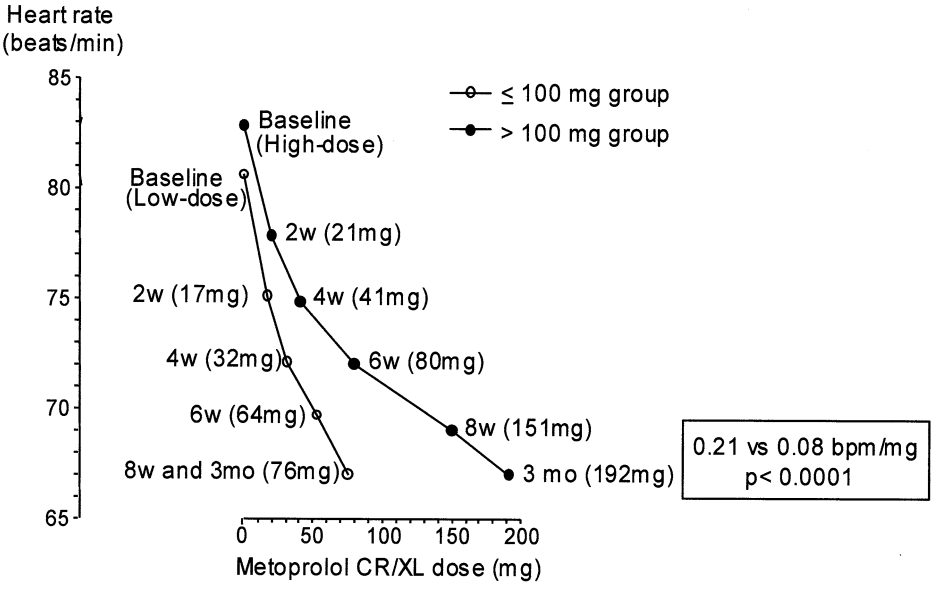

Figure 1. Illustration of the relation between achieved dose of metoprolol controlled-release/extended-release (CR/XL) and heart rate during the titration phase and up to the three-month (mo) visit in the low-dose **(open circles)** and high-dose metoprolol CR/XL subgroups **(solid circles)**. Mean dose of metoprolol CR/XL and mean heart rate in the low-dose subgroup was the same at the eight-week (w) visit and the three-month visit. At the three-month visit, the reduction in heart rate per milligram metoprolol CR/XL was significantly higher in the low-dose metoprolol CR/XL subgroup (0.21 beats/min [bpm]/mg) compared with the high-dose metoprolol CR/XL subgroup (0.08 beats/min/mg, $p < 0.0001$).

($p = 0.0022$; Table 3 and Figs. 2 to 4). Test of etiology (ischemia vs. nonischemia) by treatment interaction was nonsignificant ($p = 0.19$ for total mortality in the low-dose group, unadjusted, and $p = 0.90$ in the high-dose group). All-cause mortality or all-cause hospitalization (time to first event) was also reduced to a similar extent in the two dose groups: low-dose 22% (95% CI, 7 to 34; $p = 0.0056$) and high-dose 29% (95% CI, 18 to 39; $p < 0.0001$, Table 3). Relative risk for all other prespecified end points was also rather similar for the two beta-blocker subgroups (Tables 2 and 3, Figs. 2 to 4).

Reasons for lower than expected dose of study drug. Table 4 presents reasons for lower than expected dose at the three-month visit as stated by the investigators. Low HR was the most common reason for lower than expected beta-blocker dose at the three-month visit: stated as reason for 10.4% of patients in the metoprolol CR/XL subgroup compared with 2.3% in the placebo subgroup. At the

Table 2. Number of Patients With Events in Both Dose Groups Combined and in the Low- and High-Dose Groups, Respectively

	Both Dose Groups		Metoprolol CR/XL	
End Point	Placebo (n = 1,845)	Meto CR/XL (n = 1,806)	Low-Dose Group (n = 604)	High-Dose Group (n = 1,202)
Cause-specific mortality				
Total	154	97	38	59
Cardiovascular	144	84	32	52
Sudden death	96	54	18	36
Worsening heart failure	40	21	10	11
Combined end points*				
All-cause mortality or all-cause hospitalization*	579	445	175	270
All-cause mortality or hospitalization due to worsening heart failure*	335	185	81	104
Cardiac death or nonfatal acute MI*	162	92	36	56
Hospitalizations				
All-cause	499	407	163	244
Cardiovascular cause	365	266	116	150
Worsening heart failure	224	113	57	56

*Only one event counted in each patient (the first occurring).
Meto CR/XL = metoprolol controlled-release/extended-release; MI = myocardial infarction.

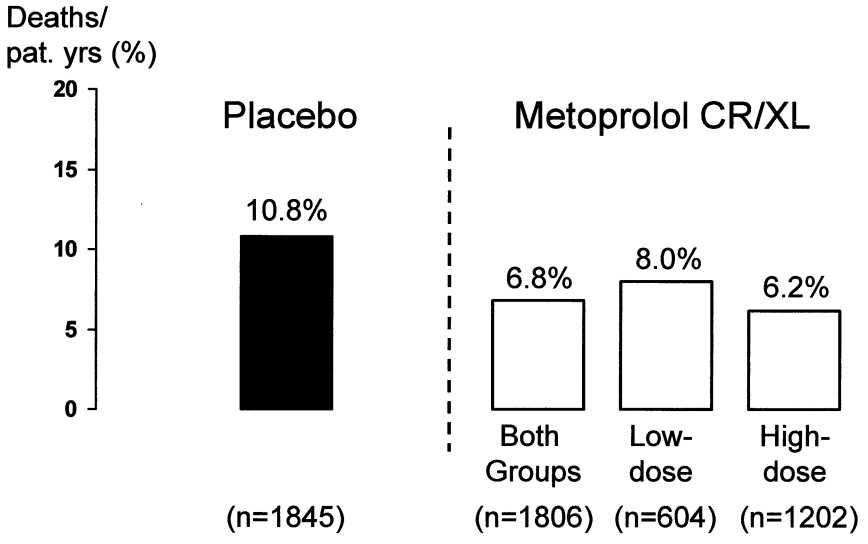

Figure 2. Total mortality defined as deaths per patient years (pat. yrs) in the placebo group and in the different metoprolol controlled-release/extended-release (CR/XL) subgroups after date of the three-month visit to end of follow-up.

three-month visit, bradycardia, defined as HR below 50 beats/min, occurred in 3.6% of the patients in the beta-blocker group and in 0.3% in the placebo group. For further information on reasons for lower than expected dose at the three-month visit, see reference 7.

Withdrawal of study drug. All-cause discontinuation of placebo (n = 1,845) after the three-month visit to end of follow-up was 15.0% per patient year of follow-up (203 discontinuations); the corresponding figure in the two beta-blocker groups combined (n = 1,806) was 10.3% (141 discontinuations; risk reduction for all-cause discontinuation 31%, 95% CI, 15 to 45; p = 0.0006).

DISCUSSION

The results of this post-hoc subgroup analysis in relation to dose of study medicine at the end of the titration phase (three-month visit) in MERIT-HF showed that the majority of patients tolerated the target dose of 200 mg metoprolol CR/XL. One-third of the patients on study medicine

Table 3. Relative Risk Reduction and 95% CI for the Comparison of the Two Dose Groups Combined (Cox Adjusted Estimates, see Statistical Methods) and for the Comparison of the Low-Dose Metoprolol CR/XL Group With All Placebo and High-Dose Metoprolol CR/XL Group Versus All Placebo, Respectively

End Point	All Meto CR/XL (n = 1,806) Risk Reduction (95% CI) %	vs. All Placebo (n = 1,845) p Value	Low-Dose Meto CR/XL (n = 604) Risk Reduction (95% CI) %	vs. All Placebo (n = 1,845) p Value	High-Dose Meto CR/XL (n = 1,202) Risk Reduction (95% CI) %	vs. All Placebo (n = 1,845) p Value
Mortality						
Total	38 (20 to 52)	0.0003	38 (11 to 57)	0.010	38 (16 to 55)	0.0022
Cardiovascular	43 (25 to 56)	0.0001	46 (20 to 63)	0.0021	41 (19 to 57)	0.0013
Sudden death	45 (23 to 60)	0.0005	50 (16 to 70)	0.0087	41 (13 to 60)	0.0072
Worsening CHF	48 (12 to 69)	0.015	53 (4 to 77)	0.038	47 (−5 to 73)	0.070
Combined*						
All-cause mortality/all-cause hosp.	27 (17 to 35)	< 0.0001	22 (7 to 34)	0.0056	29 (18 to 39)	< 0.0001
All-cause mortality/hosp. due to worsening CHF	49 (39 to 58)	< 0.0001	42 (25 to 55)	< 0.0001	53 (41 to 62)	< 0.0001
Cardiac death/nonfatal acute MI	44 (27 to 56)	< 0.0001	44 (19 to 61)	0.0022	44 (24 to 59)	0.0002
Hospitalizations						
All-cause	22 (12 to 32)	0.0002	15 (−5 to 32)	0.14	25 (11 to 38)	0.0014
CV cause	31 (20 to 42)	< 0.0001	19 (−2 to 37)	0.08	38 (23 to 50)	< 0.0001
Worsening CHF	54 (42 to 63)	< 0.0001	40 (17 to 57)	0.0019	62 (49 to 72)	< 0.0001

*Only one event counted in each patient (the first occurring).

CHF = chronic heart failure; CI = confidence interval; CV = cardiovascular; hosp. = hospitalization; Meto CR/XL = metoprolol controlled-release/extended-release; MI = myocardial infarction.

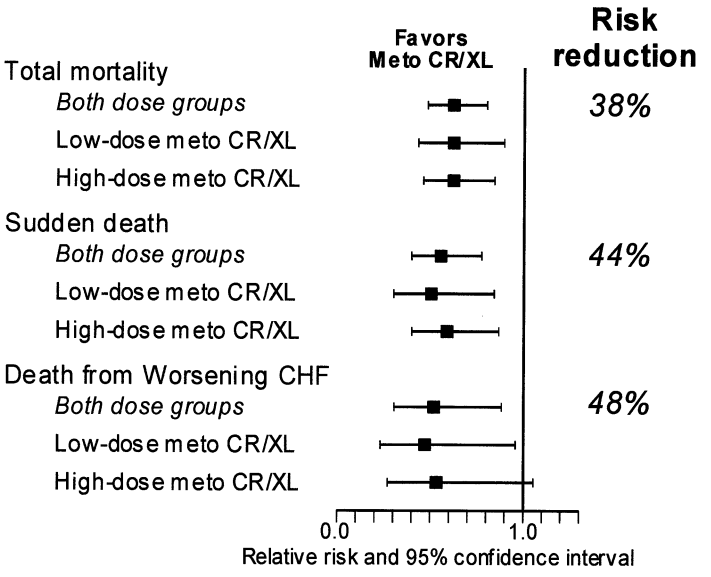

Figure 3. Relative risk and 95% confidence intervals for total mortality, sudden death and death from worsening heart failure in both beta-blocker subgroups combined and in the low-dose and high-dose metoprolol controlled-release/extended-release (meto CR/XL) subgroups (Cox-adjusted estimates, see Statistical Methods section). CHF = chronic heart failure.

achieved ≤100 mg of metoprolol CR/XL (mean, 76 mg) at the end of the titration phase. Very interestingly, both the low-dose and the high-dose beta-blocker subgroups reached the same mean HR after three months of 67 beats/min, a finding of central importance for the understanding of the results, indicating similar effects on HR in the two metoprolol CR/XL subgroups in spite of the large difference in dose given and plasma concentration of metoprolol succinate achieved. The similar risk reduction, which our data indicate, may, therefore, at least partly, be the result of similar beta-blockade in the low- and high-dose subgroups.

Effect on clinical events. Data from the two beta-blocker dose subgroups combined showed that, from the three-month visit to end of follow-up, total mortality was reduced by 38%, sudden death by 45% and hospitalizations for worsening HF by 54%. The reduction in total mortality—38%—is slightly higher than the 34% reported for the complete follow-up time (2,3), and the slightly higher figure is explained by the fact that there was very little difference in mortality during the titration phase (the first three months after randomization). The data showed the same reduction in total mortality—38%—in the low-dose and high-dose beta-blocker subgroups. Data for the other prespecified end points also showed a similar reduction in relative risk in the low-dose and high-dose beta-blocker subgroups.

Weak points of the present analysis. The present analysis has two weak points: it is post-hoc and also a comparison of nonrandomized subgroups; the groups are defined by post-randomization events: being alive at the three-month visit and receiving a dose of study medicine above 0 mg. The estimates of relative risk for cause-specific mortality, for combined end points and for number of patients hospitalized was performed with correction for differences in baseline risk factors and also for some postrandomization risk factors between the beta-blocker subgroups and the placebo group. We cannot exclude that confounding factors not revealed by these risk factors affected risk in the different subgroups analyzed. However, we believe that the point estimates along with the 95% CIs give a rough estimate of the benefits of beta-blockade in the two different subgroups. The data indicate that, in many patients, up-titration was stopped due to "low HR" in patients with no symptoms of bradycardia (7). It is not possible to know if the outcome in the low-dose group would have been different if the patients had been titrated to a higher dose. When interpreting this data, one should keep in mind that MERIT-HF was not designed as a dose-response study.

Comments on earlier performed dose-response studies. For obvious reasons survival trials are very rarely designed as dose-response studies. In one small six-month study (Multicenter Oral Carvedilol Heart Failure Assessment), 345 patients with mild to moderate HF were randomized to receive treatment with placebo and three different dose levels of carvedilol, 6.25 mg twice a day (low-dose group), 12.5 mg twice a day (medium-dose group) or 25 mg twice a day (high-dose group) (8). The primary efficacy parameter was submaximal exercise. Carvedilol had no detectable effect on exercise capacity. However, carvedilol was associated with dose-related improvements in ejection fraction. All together, 13 deaths occurred in the placebo group and 12 deaths in the three carvedilol dose groups; 17 hospitalizations occurred in the 84 patients randomized to placebo, 9 in the 83 patients randomized to low-dose, 11 in the 89 patients randomized to medium-dose and 9 in the 89 patients randomized to high-dose carvedilol. Thus, because of the low number of patients randomized, the study had no power to analyze any dose-dependent effect on clinical events in a meaningful way.

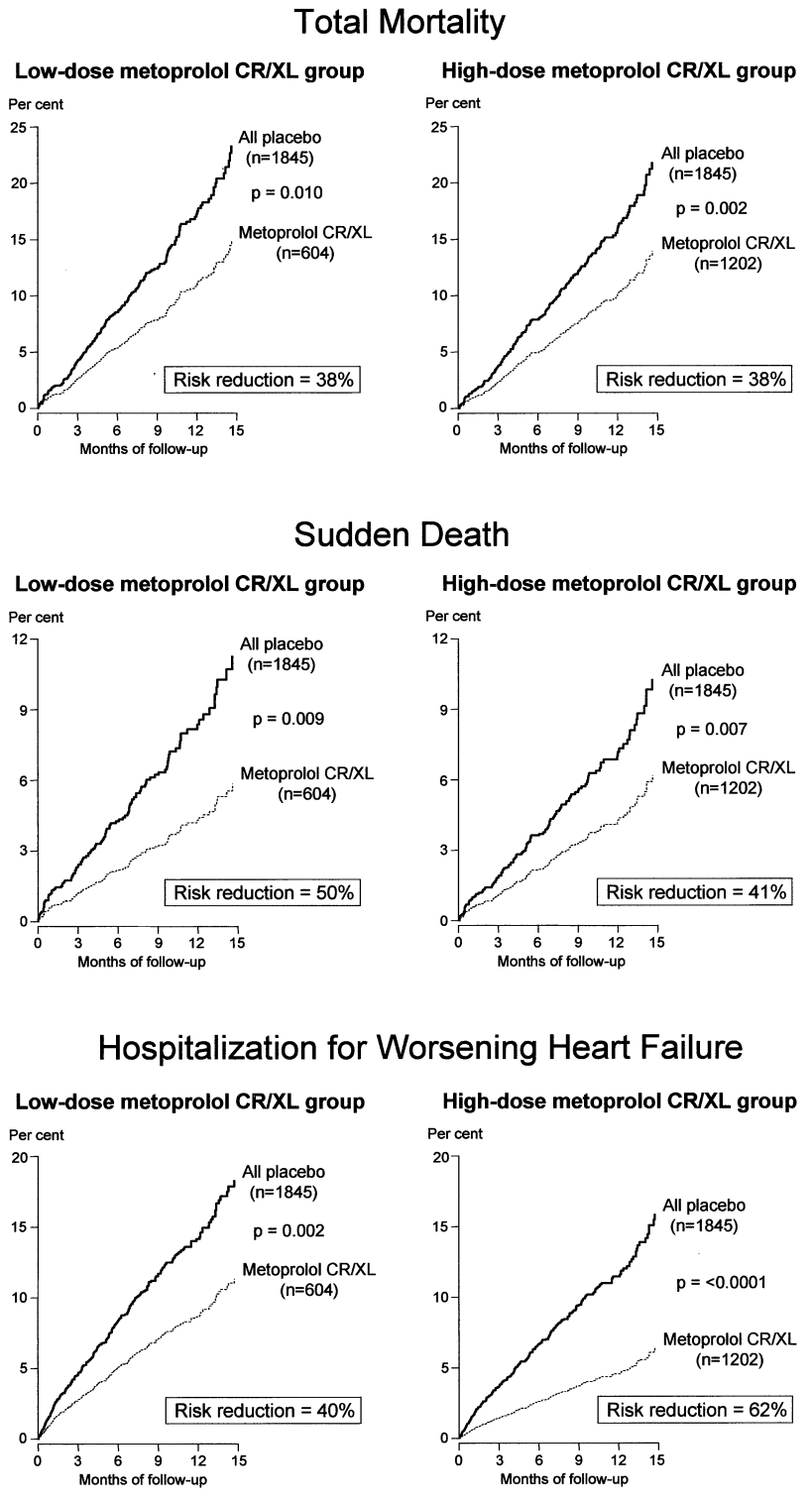

Figure 4. Cumulative percentages of all-cause mortality **(top),** sudden death **(middle)** and hospitalizations for worsening heart failure **(bottom).** Low-dose metoprolol controlled-release/extended-release (CR/XL) subgroup is illustrated in the **left hand panel** and high-dose metoprolol CR/XL group in the **right hand panel** (Cox-adjusted estimates. Estimates of risk have been obtained from the fitted models explaining why the graphs for the placebo groups have a different appearance in the low- and high-dose subgroups; see Statistical Methods section).

Sensitivity to beta$_1$-receptor blockade. The difference in dose between the low- and high-dose beta-blocker subgroups does not seem to be due to differences in body size or body mass index, which were quite comparable in the two dosage subgroups. Nor do the data on plasma concentration of metoprolol succinate in the two dosage subgroups indicate any difference in pharmacokinetics between the two subgroups. Taken together, the data on the HR response

Table 4. Reason for Lower Than Expected Dose of Study Medicine at the Three-Month Visit in the Two Randomization Groups

Reason	Placebo (n = 1,805) %	Metoprolol CR/XL (n = 1,845) (%)
Low heart rate	2.3	10.4
Low blood pressure	4.5	5.4
Symptoms of worsening heart failure	4.6	6.7

CR/XL = controlled-release/extended-release.

during the titration phase and plasma concentration of metoprolol succinate at the three-month visit suggest that the patients in the low-dose group were more sensitive to beta-blockade than the patients in the high-dose group and that physicians titrated the beta-blocker, at least partly, based on the HR response. One might speculate that the increased sensitivity to $beta_1$-receptor blockade in the low-dose group is caused by a downregulation and desensitization of myocardial $beta_1$-receptors due to more advanced HF of the patients in the low-dose subgroup compared with the high-dose subgroup (9–11).

Reasons for lower than expected dose. An analysis of the reasons for lower than expected dose at the three-month visit revealed that "low HR" was the most common reason stated in the beta-blocker group. However, the prevalence of bradycardia defined as HR <50 beats/min was low. This indicates that physicians titrated, at least partly, to avoid bradycardia. Those at risk for bradycardia in clinical practice are mainly patients with sick sinus node and atrioventricular block. Such patients were probably excluded by the protocol, which listed patients with HRs below 68 beats/min at enrollment, and patients with atrioventricular block as specific exclusion criteria.

Tolerability. Discontinuation of study medicine occurred less often on metoprolol CR/XL than on placebo after the three-month visit. For patients still on study medicine at the end of the titration phase, metoprolol CR/XL is very well tolerated during long-term maintenance HF therapy.

Conclusions. In summary, the low-dose group included high-risk patients, and HR was reduced more per each milligram of metoprolol CR/XL in the low-dose group compared with the high-dose group, 0.21 versus 0.08 beats/min/mg, a highly significant difference. The HR response indicates a similar degree of beta-blockade in the two beta-blocker subgroups despite the large difference in beta-blocker dose given and plasma concentration of metoprolol CR/XL achieved. The similar risk reduction, which our data indicate, may, therefore, at least partly, be the result of similar beta-blockade in the low- and high-dose subgroups. Prognosis clearly seems to be improved for the group of higher risk patients where the investigators made the judgment not to increase the dose to the maximum target dose of 200 mg metoprolol CR/XL. The maximum target dose of 200 mg metoprolol CR/XL, reached by most patients with heart failure in MERIT-HF, should, however, not be reduced but strived for in all patients who tolerate this dose. The results support the idea of an individualized dose-titration regimen, which is guided by patient tolerability and the HR response. Further research is needed to shed light on why some patients respond with a marked HR reduction and reduced mortality risk on a relatively small dose of a beta-blocker.

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