Efficacy, safety and tolerability of metoprolol CR/XL in patients with diabetes and chronic heart failure: Experiences from MERIT-HF

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Background The objective of the current study was to examine the efficacy and tolerability of the β-blocker metoprolol succinate controlled release/extended release (CR/XL) in patients with diabetes in the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF).

Methods The Cox proportional hazards model was used to calculate hazard ratios (HR) for convenience expressed as relative risks (risk reduction = 1-HR), and 95% confidence intervals (CI).

Results The risk of hospitalization for heart failure was 76% higher in diabetics compared to non-diabetics (95% CI 38% to 123%). Metoprolol CR/XL was well tolerated and reduced the risk of hospitalization for heart failure by 37% in the diabetic group (95% CI 53% to 15%), and by 35% in the non-diabetic group (95% CI 48% to 19%). Pooling of mortality data from the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), MERIT-HF, and the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) showed similar survival benefits in patients with diabetes (25%; 95% CI 40% to 4%) and without diabetes (36%; 95% CI 44% to 27%); test of diabetes by treatment interaction was non-significant. Adverse events were reported more often on placebo than on metoprolol CR/XL.

Conclusions Patients with heart failure and diabetes have a much higher risk of hospitalization than patients without diabetes. Regardless of diabetic status, a highly significant reduction in hospitalizations for heart failure was observed with metoprolol CR/XL therapy, which was very well tolerated also by patients with diabetes. Furthermore, the pooled data showed a statistically significant survival benefit in patients with diabetes. (Am Heart J 2005;149:159–67.)

Randomized clinical trials with β-blockers have reported improved survival and reduced need for hospitalizations for worsening heart failure in patients with chronic symptomatic systolic heart failure.[1–4] However, many physicians are reluctant to prescribe β-blockers to the subgroup of patients with diabetes and heart failure. This probably is attributable largely to concern about the safety and tolerability of β-blockers in this subgroup, and also the lack of published data regarding their efficacy on mortality and hospitalizations in patients with diabetes. The aim of the present analyses was to examine the efficacy and tolerability of the β-blocker metoprolol succinate controlled release/extended release (CR/XL) in patients with diabetes in the Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF). We also performed a meta-analysis of the survival benefit of β-blockers in patients with diabetes in the Cardiac Insufficiency Bisoprolol Study II (CIBIS II), MERIT-

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HF, and the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS).

Methods

MERIT-HF was a prospective, double-blind, placebo-controlled trial that randomized 3991 patients. The study had a predefined *Data Analysis Plan*, in which subgroup analyses were pre-specified—including an analysis of patients with diabetes mellitus for safety reasons. The present analyses focus on the subgroup of patients with a history of diabetes (n = 985). A subgroup analysis of patients with diabetes and more severe heart failure defined as New York Heart Association (NYHA) class III/IV and ejection fraction (EF) <0.25 (n = 199) was also performed.

The study design and main results have been published previously.[2,3] An optimal allocation procedure (minimization method) was used at randomization, taking into account the history of diabetes and other characteristics described previously. The study was closed early after the 2nd interim analysis performed by the Independent Safety Committee, which showed a highly significant difference in total mortality favoring metoprolol CR/XL.[2] The mean follow-up time was 1 year.

Briefly, patients enrolled in MERIT-HF were men and women aged 40 to 80 years in NYHA classes II to IV with EF of ≤0.40, and who, at the time of enrollment, had a heart rate ≥68 beats per minute and were receiving optimum standard therapy with diuretics and an angiotensin-converting enzyme (ACE) inhibitor.

After a single, blind, placebo run-in phase of 2 weeks, patients were randomized to metoprolol CR/XL or placebo, with starting doses of 12.5 mg (NYHA classes III and IV) or 25 mg once daily. It was recommended that the dose be doubled every 2 weeks to a target dose of 200 mg once daily, or the highest tolerated dose.

The first 3 predefined outcomes in MERIT-HF were all-cause mortality, the combined end point of all-cause mortality plus all-cause hospitalization (time to first event), and all-cause mortality or hospitalization due to worsening heart failure (time to first event). Furthermore, the total number of hospitalizations due to cardiovascular causes and to worsening heart failure were predefined end points; withdrawal of study drug for any cause and worsening heart failure were also predefined end points. All serious adverse events (eg, death, hospitalization), and all adverse events leading to discontinuation of study drug were systematically recorded and reported (non-serious adverse events not leading to withdrawal of study drug did not have to be reported). For the present paper, all available documents were also evaluated for information indicative of impaired glycemic control.

Statistical analysis

The Student *t* test for continuous variables and Fisher's exact test for categorical variables were used when analyzing differences in baseline characteristics between patients with and without diabetes. The Cox proportional hazards model was used to calculate hazard ratios (HR), for convenience expressed as relative risks, and 95% confidence intervals (CI). Adjustment was performed for the following variables: sex, EF, NYHA class, ischemic etiology, history of myocardial infarction, hypertension, systolic blood pressure, heart rate, and smoking status. Absolute risk has been expressed as number of events per patient year of follow-up. Risk reduction was defined as 1-HR. The total number of hospitalizations was analyzed with the Monte Carlo method. *P* values of <.05 (2-sided) were considered significant.

Pooling of all-cause mortality data for patients with and without diabetes from CIBIS II,[5] MERIT-HF, and COPERNICUS[6] was performed with a meta-analysis technique based on the 95% CIs of the relative risks in the studies.

Results

Of the 985 patients with a history of diabetes, 490 were randomized to placebo and 495 to metoprolol CR/XL; 3006 had no history of diabetes, 1511 were randomized to placebo and 1495 to metoprolol CR/XL. Baseline characteristics in the 2 randomization subgroups (placebo and metoprolol CR/XL) were very similar regardless of diabetes status (Table I). However, as expected, there were a number of differences in baseline characteristics between patients with and without diabetes (Table I).

There were 199 patients with diabetes and more severe heart failure (NYHA III/IV and EF <0.25); of these, 106 patients were randomized to placebo and 93 to metoprolol CR/XL. Similar differences in baseline characteristics between patients with and without diabetes were found in those with severe heart failure, as in those for all patients randomized with and without diabetes (data not shown). Mean EF at baseline in patients with severe heart failure was 0.19. For further data on baseline characteristics in patients with severe heart failure, see Goldstein et al.[7]

Total mortality

Diabetes versus non-diabetes. Mortality risk was slightly higher in the diabetic subgroup compared to the non-diabetic subgroup (placebo vs placebo 8%; 95% CI −20% to 47%; $P > .2$; Figure 1). For those with severe heart failure, a similar trend was observed (26%; 95% CI −24% to 210%; $P > .2$).

Risk reduction with metoprolol CR/XL. A consistent trend for a survival benefit favoring metoprolol CR/XL was observed in patients with diabetes: for all-cause mortality, with 61 deaths (12.7% per patient-year of follow-up) in the placebo group and 50 deaths (10.1%) in the metoprolol CR/XL group, risk reduction was 18% (95% CI 44% to −19%; $P > .2$; Figure 2); and for cardiovascular mortality (56 vs 44 deaths), including sudden death (30 vs 22 deaths), and deaths from worsening heart failure (20 vs 14 deaths), respectively (for results on mortality in the non-diabetic group, see end of the Results section). In patients with diabetes and severe heart failure, there were 24 deaths in the placebo group and 14 in the metoprolol CR/XL group (risk reduction 29%; 95% CI 65% to −41%; $P > .2$).

Table I. Baseline characteristics of patients with and without diabetes

Characteristics	Diabetes		No diabetes		Diabetes vs. no diabetes *P* value
	Placebo (n = 490)	Metoprolol CR/XL (n = 495)	Placebo (n = 1511)	Metoprolol CR/XL (n = 1495)	
Mean age (y)	64.7	64.6	63.4	63.6	<.01
Caucasian (%)	92	91	95	95	<.01
Female sex (%)	27	28	21	21	<.0001
Ischemic etiology (%)	75	72	63	63	<.0001
NYHA class (%)					<.0001
II	32	36	44	42	
III	63	60	52	54	
IV	4.5	4.0	3.6	3.3	
Ejection fraction (mean)	0.28	0.28	0.28	0.28	>.2
Systolic blood pressure (mm Hg)	132	132	129	129	<.0001
Diastolic blood pressure (mm Hg)	77	79	78	78	>.2
Heart rate (beats/min)	84	84	82	82	<.001
Body mass index (kg/m^2)	28.5	28.6	26.9	26.8	<.0001
Serum creatinine (μmol/L)	112	112	105	106	<.0001
Smoking status					<.0001
Previous smoker (%)	60	57	53	54	
Current smoker (%)	7	12	17	15	
Medical history					
Previous MI (%)	54	53	47	46	<.001
Hypertension (%)	57	56	39	40	<.0001
Angina pectoris (%)	46	42	38	39	<.01
PTCA or CABG (%)	31	28	23	25	<.01
Intermittent claudication (%)	16	13	9	8	<.0001
Previous stroke (%)	9	10	7	8	<.05
Atrial fibrillation (%)	16	15	16	16	>.2
Medications					
Diuretics (%)	94	94	89	90	<.0001
ACE inhibitor (%)	89	90	90	89	>.2
ACE-I or AII-blocker (%)	96	95	96	95	>.2
Digitalis (%)	71	70	62	61	<.0001
Acetylsalicylic acid (%)	51	49	44	45	<.01
Statin (%)	27	26	23	21	<.01
Oral antidiabetic (%)	55	53	-	-	NA
Insulin (%)	35	34	-	-	NA
Symptoms					
Peripheral edema (%)	21	22	13	13	<.0001
Jugular venous distension (%)	18	17	13	13	<.001
Pulmonary rales (%)	13	14	10	10	<.01
Third heart sound (%)	23	24	23	23	>.2

NYHA, New York Heart Association; *PTCA,* percutaneous transluminal coronary angioplasty; *CABG,* coronary artery bypass graft; *ACE-I,* angiotensin-converting enzyme inhibitor; *AII-blocker,* angiotensin II blocker; *MI,* myocardial infarction; *NA,* not applicable.

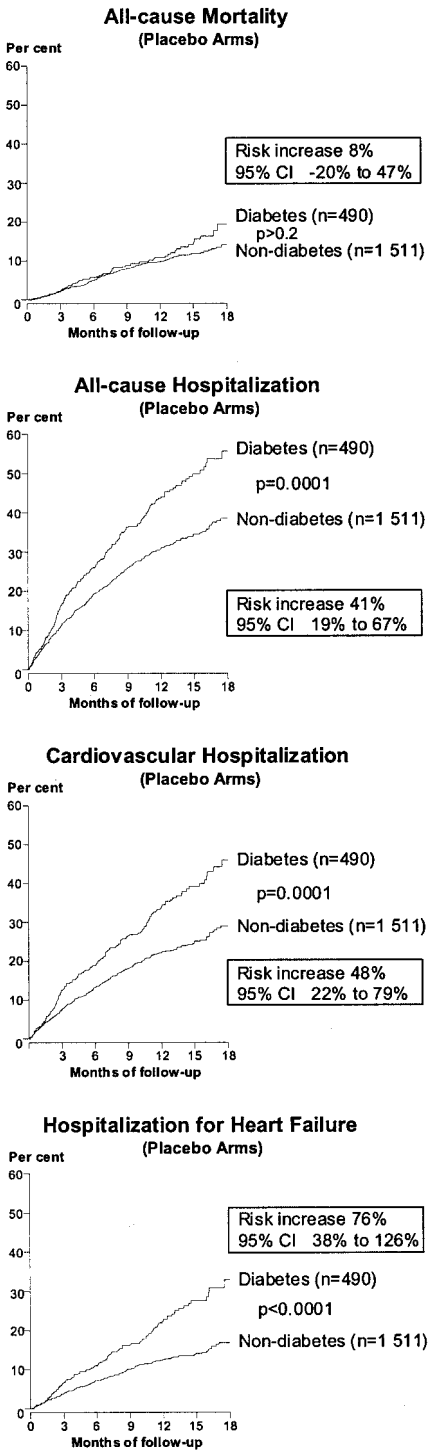
Hospitalizations

Diabetes versus non-diabetes. The risk of hospitalization was significantly higher in patients with diabetes compared to those without diabetes (placebo vs placebo, time to first event; Figure 1): for all-cause hospitalization, the increase in risk was 41% (19% to 67%; $P = .0001$); for a cardiovascular hospitalization, 48% (22% to 79%; $P = .0001$); and for a hospitalization for worsening heart failure, 76% (38% to 126%; $P < .0001$).

The highest absolute risk to be hospitalized for worsening heart failure was observed in diabetic patients with severe heart failure (NYHA III/IV and EF<0.25) on placebo (50.4% per patient year of follow-up, Figure 3, *lower panel*).

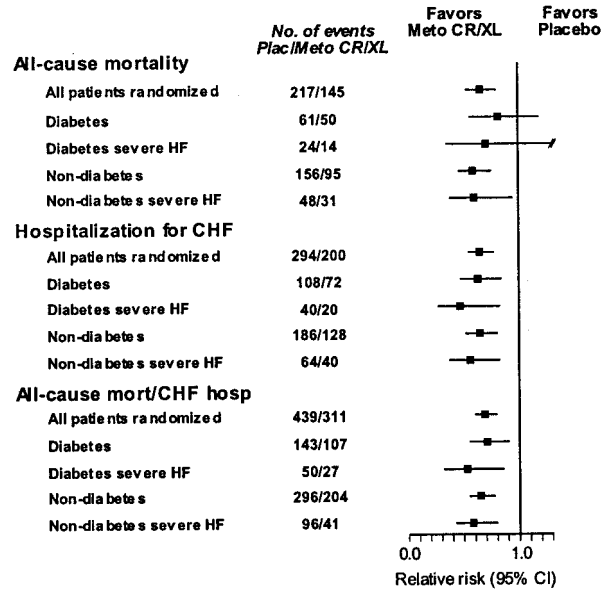
Risk reduction with metoprolol CR/XL. In the diabetic group, 108 patients in the placebo group were hospitalized for worsening heart failure compared with 72 patients in the metoprolol CR/XL group (risk reduction 37%; 95% CI 53% to 15%; $P = .0026$; Figure 2 and 3, and Table II). The corresponding risk reduction in the non-diabetic group was 35% (95% CI 48% to 19%; $P = .0002$). Similar reductions were observed for total number of hospitalizations for heart failure (Table II).

Figure 1



Kaplan-Meier estimates of cumulative percentage of all-cause mortality (*top panel*), all-cause hospitalization (*second panel*), cardiovascular hospitalization (*third panel*), and hospitalization from worsening heart failure (*bottom panel*) in patients with and without diabetes.

Figure 2



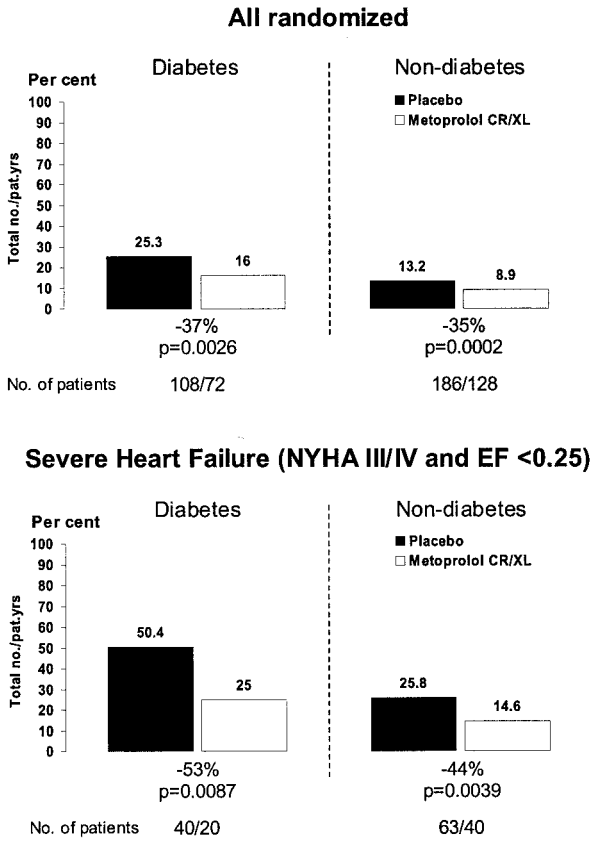
Point estimates for hazard ratios and 95% confidence intervals for all-cause mortality, hospitalizations due to heart failure, and combined end point of all-cause mortality or hospitalization due to worsening heart failure (time to first event) separately given for all patients randomized and for the 2 subgroups with and without diabetes, respectively. Data are also given for patients with severe heart failure (NYHA III/IV and EF of <0.25) with and without diabetes. Number of patients suffering an event (death or hospitalization, respectively) is also given for all groups illustrated.

In the diabetic group with severe heart failure, 40 patients in the placebo group were hospitalized for worsening heart failure compared with 20 patients in the metoprolol CR/XL group (risk reduction 53%; 95% CI 73% to 17%; $P = .0087$ (Figure 2 and 3, and Table III). The corresponding risk reduction in the non-diabetic group was 44% (95% CI 63% to 17%; $P = .0039$). Similar reductions were observed for total number of hospitalizations for heart failure (Table III).

Combined end points

Figure 2 illustrates highly significant reductions in the combined end point of all-cause mortality plus hospitalizations for worsening heart failure (time to first event) in all subgroups analyzed. As concerns all-cause mortality or all-cause hospitalization, 231 and 206 patients in the diabetic group ($P = .16$), and 536 and 435 patients in the non-diabetic group ($P = .0001$), respectively, had an event; corresponding figures for those with severe heart failure were 60 and 44 patients in the diabetic group ($P = .19$), and 143 and

Figure 3



Bar diagrams illustrating absolute risk (by randomization group and normalized for patient years of follow-up) and relative risk reduction for number of patients hospitalized for worsening heart failure with and without diabetes. The *lower panel* gives data for the 2 diabetic subgroups with severe heart failure defined as NYHA III/IV and EF of <0.25.

111 patients in the non-diabetic group ($P = .0050$), respectively.

Safety and tolerability

Hospitalizations and deaths occurring during the titration phase. During the titration phase, up to the 3-month visit there were 10 hospitalizations in the diabetic group on placebo and 5 on metoprolol CR/XL, and 21 versus 14 deaths, respectively. Corresponding figures in the non-diabetic subgroup were 20 versus 14, and 51 versus 38, respectively.

Adverse events. Adverse events were more often reported in the diabetic group than in the non-diabetic group and, regardless of diabetic status, were more often reported on placebo than on metoprolol CR/XL (Table IV). No difference in adverse events indicating impaired glycemic control was observed between metoprolol CR/XL and placebo in the diabetic subgroup.

Adverse events leading to discontinuation of study medicine

Regardless of diabetic status and severity of heart failure, more patients on placebo than on metoprolol CR/XL discontinued study treatment (Figure 4). The absolute figures for discontinuation rates were very similar on metoprolol CR/XL in all subgroups, regardless of diabetic status and severity of heart failure.

In the diabetic group, 31 patients on placebo discontinued study drug because of heart failure compared with 18 patients in the metoprolol CR/XL group (risk reduction 44%; $P = .045$). In patients with diabetes and severe heart failure, 12 and 4 patients ($P = .06$), respectively, stopped study drug because of worsening heart failure.

The mean dose of metoprolol CR/XL at the last follow-up visit was 162 mg in patients with diabetes and 156 mg in patients without diabetes; corresponding figures in those with severe heart failure (NYHA III/IV and EF<0.25) were 171 mg and 163 mg, respectively.

Pooling of mortality data from CIBIS II, MERIT-HF, and COPERNICUS

In CIBIS II, the relative risk in the diabetes subgroup was 0.81 (95% CI 0.51 to 1.28), and in the non-diabetes subgroup 0.66 (0.54 to 1.19)[5]; corresponding figures in MERIT-HF were 0.82 (0.56 to 1.19) and 0.69 (0.46 to 0.76), and for COPERNICUS 0.65 in both subgroups[6] (Figure 5). Pooling of the mortality data from CIBIS II, MERIT-HF, and COPERNICUS showed similar survival benefits in patients with and without diabetes: the relative risk for all-cause mortality in patients with diabetes was 0.76 (95% CI 0.60 to 0.96), and in those without diabetes it was 0.64 (0.56 to 0.73); test of diabetes by treatment interaction was non-significant.

Discussion

The results of the present analysis show that patients with heart failure and diabetes, compared with patients with heart failure but without diabetes, more often had a history of myocardial infarction and revascularization procedures, more often had hypertension and intermittent claudication, and had more severe heart failure as judged from NYHA class and symptoms and signs such as dyspnea, rales, peripheral edema, and jugular venous distension.

Patients with diabetes also had a much higher risk of hospitalization for heart failure, a much higher risk for adverse events, and a much higher risk of stopping study drug because of adverse events than did patients without diabetes. The risk was especially high in pa-

Table II. Cause-specific data for number of patients hospitalized at least once and total number of hospitalizations in all patients randomized with and without diabetes

	Diabetes			No diabetes		
Hospitalizations	**Placebo (n = 490)**	**Metoprolol CR/XL (n = 495)**	***P***	**Placebo (n= 1511)**	**Metoprolol CR/XL (n = 1495)**	***P***
All causes						
No. of patients with any hospitalization (n, rate, %)	209 (57.9)	190 (50.7)	.17	459 (37.1)	391 (30.6)	.010
Total no. of hospitalizations(n)	390	343	.18	759	678	.011
Cardiovascular causes						
No. of patients with any hospitalization (n, rate, %)	163 (41.4)	134 (32.4)	.034	331 (25.0)	260 (19.2)	.0019
Total no. of hospitalizations (n)	279	221	.026	494	428	.0029
Worsening heart failure						
No. of patients with any hospitalization (n, rate, %)	108 (25.4)	72 (16.0)	.0024	186 (13.2)	128 (8.9)	.0008
Total no. of hospitalizations (n)	180	124	.0022	271	193	.0008

Rate, Per patient-year of follow-up.

Table III. Cause-specific data for number of patients hospitalized at least once and total number of hospitalizations in all patients with severe heart failure (NYHA III/IV and ejection fraction of <0.25) with and without diabetes

	Diabetes			No diabetes		
Hospitalizations	**Placebo (n = 106)**	**Metoprolol CR/XL (n = 93)**	***P***	**Placebo (n = 290)**	**Metoprolol CR/XL (n = 306)**	***P***
All causes						
No. of patients with any hospitalization (n, rate, %)	53 (76.7)	41 (62.9)	NS	123 (59.1)	100 (42.7)	.014
Total no. of hospitalizations (n)	126	72	NS	237	201	.012
Cardiovascular causes						
No. of patients with any hospitalization (n, rate, %)	49 (65.9)	30 (39.8)	.034	96 (42.3)	69 (27.1)	.0070
Total no. of hospitalizations (n)	101	47	.026	168	136	.0094
Worsening heart failure						
No. of patients with any hospitalization (n, rate, %)	40 (50.4)	20 (25.0)	.0024	63 (25.8)	40 (14.6)	.0053
Total no. of hospitalizations (n)	75	27	.0022	112	78	.0051

Rate, Per patient-year of follow-up.

tients with diabetes and advanced heart failure on placebo: their risk for a hospitalization for heart failure was nearly 4 times higher than that of all patients without diabetes on placebo (50.4% vs 13.2% per year, respectively, Figure 3). Regardless of diabetic status and severity of heart failure, however, there was a highly significant reduction in hospitalizations for heart failure with metoprolol CR/XL therapy, which was very well tolerated by patients with diabetes.

Pooled data from CIBIS II, MERIT-HF and COPERNICUS

In individual trials with β-blockers, reduction of mortality in patients with diabetes may not be apparent because these patients constitute a minority of those randomized (Figure 5), thereby limiting the number of deaths available for analysis. Although 95% CIs for the hazard ratios were widely overlapping between patients with and without diabetes in MERIT-HF, and no statistically significant interaction was observed, the question arises whether β-blockade more effectively reduces the risk of dying in patients without diabetes compared with patients with diabetes. To shed light on this question, data for mortality reduction by diabetic status have been analyzed for MERIT-HF, CIBIS II, and COPERNICUS combined (Figure 5). The pooled data show a statistically significant survival benefit in patients with diabetes also.

Hospitalizations

The risk for hospitalization for heart failure was 76% higher in patients with diabetes compared with those without diabetes (placebo groups). However, the risk reduction with metoprolol CR/XL was similar in pa-

Table IV. Adverse events in the two randomization groups with and without diabetes

	Diabetes		No diabetes	
Adverse event*	**Placebo % (n)**	**Metoprolol CR/XL % (n)**	**Placebo % (n)**	**Metoprolol CR/XL % (n)**
Heart failure	17.5 (84)	13.6 (67)	9.8 (147)	6.6 (99)
Hyperglycemic reaction	4.2 (20)	4.9 (24)	–	–
Angina pectoris	5.0 (24)	2.8 (14)	4.1 (62)	3.8 (57)
Myocardial infarction	3.3 (16)	4.3 (21)	2.2 (32)	1.7 (25)
Atrial fibrillation	3.8 (18)	1.6 (8)	2.4 (36)	1.7 (25)
Dyspnea	1.3 (6)	1.8 (9)	1.3 (20)	1.3 (20)
Hypotension	1.5 (7)	1.6 (8)	0.4 (6)	0.9 (14)
Dizziness	1.0 (5)	1.2 (6)	0.7 (11)	1.1 (16)
Bradycardia	0.6 (3)	1.4 (7)	0.4 (6)	1.5 (22)
AV-block	1.0 (5)	0.8 (4)	0.3 (5)	0.2 (3)
Pulmonary edema	0.6 (3)	0.8 (4)	0.4 (6)	0.3 (4)
Hypoglycemic reaction†	0.6 (3)	0.8 (4)	–	–
Diabetic ulcer	0.8 (4)	0.8 (4)	–	–
Fatigue	0.4 (2)	0.2 (1)	0.8 (12)	1.3 (19)
Depression	0.4 (2)	0.2 (1)	0.5 (7)	0.2 (3)
Impotence	0.2 (1)	0.2 (1)	0.1 (2)	0.3 (5)
Bronchospasm	0.4 (2)	0.2 (1)	0.4 (6)	0.3 (4)
Chronic obstructive pulmonary disease	0 (0)	0.2 (1)	0.5 (7)	0.3 (5)
New-onset diabetes	–	–	0.3 (4)	0.2 (3)
Any adverse event leading to discontinuation	17.1 (74)	11.7 (53)	10.7 (160)	9.5 (143)
All patients with any adverse event	56.8 (272)	48.8 (241)	41.0 (614)	36.0 (544)

*One patient may have >1 adverse event.
†All in patients on insulin.

tients with diabetics (37%) compared with those without diabetics (35%). Because of the increased absolute risk in patients with diabetes, fewer patients with diabetes have to be treated to avoid 1 hospitalization for heart failure compared with patients without diabetes: treatment of 9 patients with diabetes for 1 year avoided 1 hospitalization for heart failure; the corresponding figure in patients without diabetes was 23 patients.

A highly significant reduction in number of patients being hospitalized for worsening heart failure in those with severe heart failure also was observed; the risk reduction in the diabetic group was 53% compared with 44% in the non-diabetic group. In this subgroup, 4 and 9 patients in the diabetic and non-diabetic group, respectively, had to be treated for 1 year to avoid 1 hospitalization.

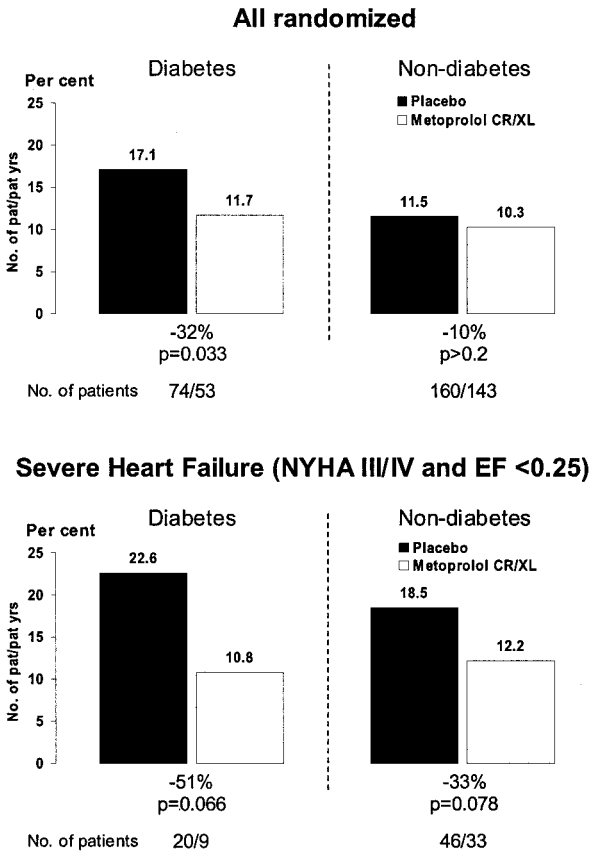
Safety and tolerability

Metoprolol CR/XL was well tolerated by patients with heart failure and diabetes both during the titration phase and long-term, as judged from number of patients hospitalized for worsening heart failure and number of adverse events reported. Investigators were able to up-titrate metoprolol CR/XL to doses similar to those in the non-diabetic subgroup. No difference in adverse events indicating impaired glycemic control was observed between metoprolol CR/XL and placebo in the diabetic subgroup. The excellent tolerability profile of metoprolol CR/XL may be due to the careful up-titration procedure used, and to the high degree of β_1-selectivity, even at higher doses, of this extended-release formulation.[8]

Limitations

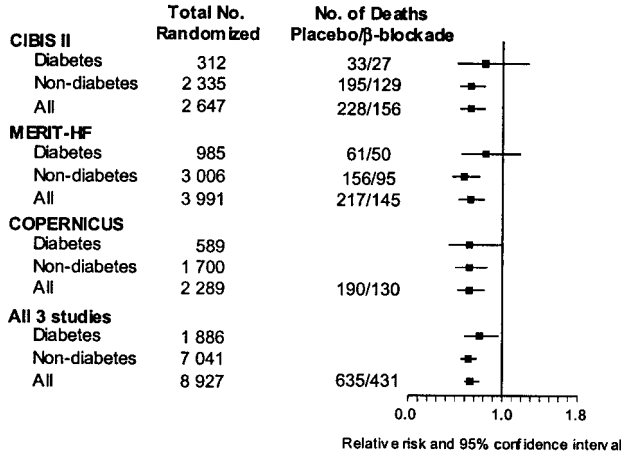
The point estimate for the mortality reduction in the meta-analysis was somewhat lower for patients with diabetes compared with those without diabetes: 24% and 36%, respectively. In the subgroup of patients with severe heart failure in MERIT-HF (NYHA III/IV and EF <0.25), the mortality reduction was 29% and 40% in patients with diabetes and those without, respectively. However, just as we must be extremely cautious in over-interpreting positive effects in subgroups, even those that are predefined, we must also be cautious in focusing on subgroups with an apparent lesser degree of effect. We should examine subgroups to obtain a general sense of consistency.[9] We should expect some variation of the treatment effect around the overall estimate as we examine a large number of subgroups. The overall reduction in total mortality was remarkably similar in CIBIS II, MERIT-HF,

Figure 4



Bar diagrams illustrating the yearly discontinuation rate of study medicine due to adverse events by randomization group for all patients with and without diabetes. The *lower panel* gives data for those with severe heart failure (NYHA III/IV and EF of <0.25).

Figure 5



Point estimates for hazard ratios and 95% confidence intervals for all-cause mortality for all patients randomized in CIBIS II, MERIT-HF, and COPERNICUS and for subgroups of patients with and without diabetes, respectively.

and COPERNICUS (34% to 35%; Figure 5). Thus, the best estimate of the treatment effect on total mortality for any subgroup is the estimate of the hazard ratio for the overall trial.[9]

Non-serious adverse events not leading to withdrawal of study drug did not have to be reported in MERIT-HF. We do not believe, however, that the pattern as regards these latter events is different from that which we observed for all other adverse events.

Clinical implications

Diabetes mellitus, and in particular type 2 diabetes, has become progressively more common.[10-12] Factors explaining this increase in prevalence include not only adoption of stricter criteria but also an actual increase due to aging of the population, as well as an increase in body fat and a decrease in physical activity in our society.[13,14] Diabetes mellitus is closely linked to accelerated coronary atherosclerosis and related complications such as myocardial infarction and heart failure.[10,11,13] Proper treatment of risk factors, and meticulous metabolic control of diabetes, may considerably improve the prognosis for patients with diabetes and myocardial infarction,[15] and possibly prevent its occurrence.[16,17] Nevertheless, even with the best preventive strategies and treatment of established cardiovascular risk factors, a considerable proportion of patients with diabetes will develop heart failure.[1-4,10,11,13]

The findings of this study confirm the markedly increased risk of morbidity conferred by diabetes in patients with heart failure secondary to left ventricular systolic dysfunction. In particular, the risk of hospitalization for heart failure was profoundly increased (76%) in patients with diabetes compared with those without diabetes. The significant reduction in number of patients with diabetes hospitalized for heart failure during treatment with metoprolol CR/XL (37% in all patients and 53% in those with severe heart failure) illustrate the beneficial effect of β-blockers in patients with heart failure and diabetes.

Furthermore, our analysis of the combined data from the CIBIS II, MERIT-HF, and COPERNICUS clearly demonstrates the reduction of total mortality conferred by β-blockers in patients with diabetes and heart failure.

Conclusions

Our analysis showed that the benefit of treatment with metoprolol CR/XL in heart failure extends to pa-

tients with diabetes, including those with diabetes and severe heart failure. Metoprolol CR/XL was very well tolerated in this population, with no evidence of the risks traditionally attributed to β-blockade such as hypo- and hyperglycemia. It is time to remove existing barriers for the use of β-blocker treatment in patients with heart failure and diabetes and to provide it to the large number of diabetic patients in need of this therapy, which should improve their quality of life by decreasing hospitalizations for heart failure, and also increase survival.

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