

Tolerability of β -Blocker Initiation and Titration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)

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on behalf of the MERIT-HF Investigators

Background— β -Blockade improves survival when administered over a long period of time to patients with heart failure. However, the time course of any possible deterioration during the titration phase has not been reported.

Methods and Results—We looked at evidence of clinical deterioration in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) by analyzing events and symptoms during the first 90 days. During titration, the Kaplan-Meier curves for the combined end point of all-cause mortality/all-cause hospitalization were similar in all patients randomized, with no significant difference in favor of placebo at any visit or in any of the analyzed subgroups (New York Heart Association class II, III/IV, or III/IV with ejection fraction <0.25 , heart rate ≤ 76 bpm, and systolic blood pressure ≤ 120 mm Hg). The curves started to diverge in favor of β -blockade after 60 days. Low heart rate was the main factor that limited titration. In New York Heart Association class III/IV, 5.9% of the patients receiving placebo discontinued study medicine during the first 90 days compared with 8.1% of those receiving metoprolol CR/XL ($P=0.037$ unadjusted, $P=NS$ adjusted); corresponding figures in those with New York Heart Association class III/IV and ejection fraction <0.25 were 7.1% and 8.0% ($P=NS$). From day 90 until the end of the study, more patients in the placebo group discontinued study medicine in all subgroups. There was no change in diuretic or ACE inhibitor dosing with β -blocker titration. Most patients reported no change in symptoms of breathlessness or fatigue during the titration phase.

Conclusions—When carefully titrated, metoprolol CR/XL can be given safely to the overwhelming majority of patients with stable mild to moderate heart failure, with minimal side effects or deterioration. (*Circulation*. 2002;105:1182-1188.)

Key Words: heart failure ■ receptors, adrenergic, beta ■ drugs

Beta-blockade improves survival, reduces hospitalizations for heart failure, and improves left ventricular function when given over a long period of time to patients with heart failure.¹⁻⁵ However, there has been concern that β -blockade may lead to worsening heart failure when the therapy is initiated. Faced with the potential for causing adverse events, many physicians are reluctant to start these agents. To minimize the risks, it is recommended that the drugs be started at low doses and slowly titrated to effective doses. However, the frequency of increased symptoms during titration, identification of the patients at greatest risk, and the time course of any possible deterioration have not been reported for any of the large β -blocker trials.

The Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) was a randomized,

double-blind, placebo-controlled study of the controlled-release/extended-release formulation of metoprolol succinate in 3991 patients with heart failure, most classified as New York Heart Association (NYHA) class II and III.^{1,2} The investigators of MERIT-HF collected data about hospitalizations and causes of study drug discontinuation at every visit. In addition, the success of drug titration was recorded, including the reasons for delayed titration. Furthermore, symptoms of breathlessness and fatigue, as well as the need for modification of doses of diuretics and ACE inhibitors, were assessed. With these data, clinical deterioration during the titration period can be evaluated in a sensitive manner. Such information is not accessible by mere review of major end points. We therefore used the MERIT-HF data to determine which patients were at risk for deterioration and for what period after β -blocker initiation.

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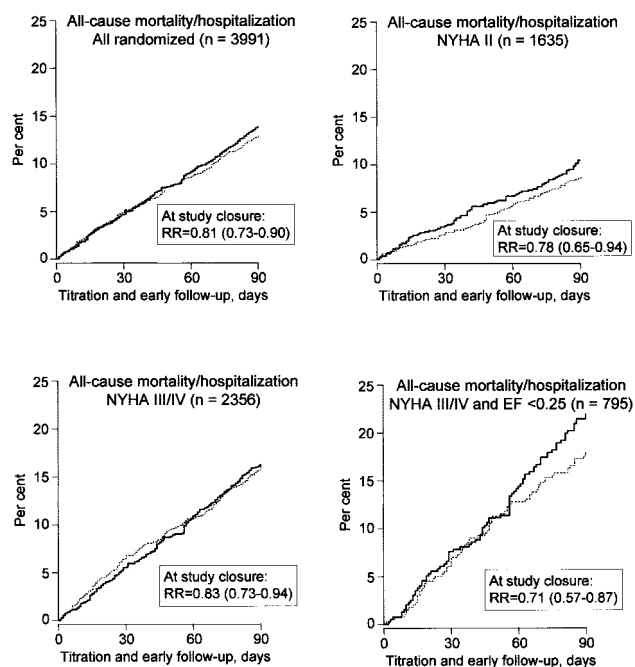


Figure 1. Kaplan-Meier estimates for combined end point of total mortality/all-cause hospitalization during first 90 days of follow-up in all patients randomized and in NYHA class II, NYHA class III/IV, and NYHA class III/IV with ejection fraction (EF) <0.25 . Relative risk and 95% CIs at study closure are given. Solid lines indicate placebo; dashed lines, metoprolol CR/XL.

Methods

Inclusion and Exclusion Criteria

The major inclusion criteria for MERIT-HF were symptomatic heart failure for at least 3 months and a left ventricular ejection fraction ≤ 0.40 in men and women aged 40 to 80 years. Resting heart rate was ≥ 68 bpm and systolic blood pressure (SBP) was ≥ 100 mm Hg at the start of placebo run-in. Patients were required to be in stable clinical condition during the 2-week placebo run-in phase before randomization.

Treatment and Measurements

Patients were treated with metoprolol CR/XL or placebo administered once daily. The initial dose was recommended to be 25 mg/d in NYHA class II patients and 12.5 mg/d in patients with NYHA functional class III or IV. It was recommended that the dose be doubled after each 2-week period until the target daily dose of 200 mg of metoprolol CR/XL or placebo was reached. This regimen could be modified according to the judgment of the investigator.

Because of a highly significant reduction in mortality, the study was closed early on the recommendation of the Independent Safety Committee.¹ The mean follow-up period was 1 year.

Delayed Titration

Delayed titration is one way to assess subtle side effects of study drug initiation. Patients who began the study at 25 mg/d were scheduled to be taking 50 mg/d at the week 4 visit, 100 mg/d at the week 6 visit, and 200 mg/d at the week 8 visit. If a patient was not taking the expected dose, the investigator was asked whether the cause for delay was bradycardia, low blood pressure, worsening heart failure, or another reason. For patients who started at 12.5 mg/d, these doses were scheduled to be reached 1 visit later. The analysis of reasons that patients were taking a lower dose than expected does not include those in whom the drug was discontinued.

Diuretic Dosing

An increase in diuretic dosing was analyzed as an indication of an investigator's assessment of fluid retention or slight worsening of heart failure. Furosemide was the most common diuretic prescribed (2837 patients at randomization), and these data are presented. The patterns were similar for other diuretics.

ACE Inhibitor Dosing

Because it is believed that β -blockers might lead to hypotension, we investigated changes in doses of prescribed ACE inhibitor. Concern about hypotension by the study investigators would be indicated by decreases in doses of ACE inhibitors. Enalapril was the most frequently prescribed ACE inhibitor (1197 patients at randomization), and these data are presented. The patterns were similar for other ACE inhibitors.

Symptoms of Breathlessness and Fatigue

At each visit, patients were asked whether breathlessness occurred at rest/lying flat, when washing and dressing, when walking on a flat level at their own pace, when walking with someone of their own age on a flat level, or when walking upstairs, uphill, or quickly. Patients were also asked whether fatigue did not occur or occurred with heavy, moderate, or slight exertion or at rest. The levels of breathlessness and fatigue were compared with baseline and are reported as improved, worse, or the same.

Subgroups

To ascertain whether certain groups of patients might respond differently, we evaluated patients by NYHA class and those in the lowest tertiles of heart rate (≤ 76 bpm) and SBP (≤ 120 mm Hg). These groups were determined by values obtained at randomization and thus reflect some patients whose heart rates and blood pressure were below entry criteria. Because there were few NYHA class IV patients, to assess patients with more severe congestive heart failure, we analyzed patients in NYHA class III or IV and with ejection fraction <0.25 .

Statistics

The statistical plan of MERIT-HF determined that ≥ 180 events in any subgroup would yield a power of $\geq 70\%$ to detect a 30% increase in risk. In the present post hoc analysis of tolerability during the titration phase, we have used the Cox proportional hazards model to calculate relative risk, 95% CIs, and *P* values for the 90-day data. When analyzing discontinuations, we have reported unadjusted probability values, as well as values adjusted for multiplicity of testing.

Results

Deaths and Hospitalizations During the Titration Phase

The time to death or first hospitalization (during titration) is shown in Figure 1 for all patients and for those in various subgroups. In NYHA class III and IV patients, there was no difference in early mortality between those who received placebo and those who received active drug. The Kaplan-Meier curve of hospitalizations and deaths shows fewer events in the metoprolol CR/XL group after ≈ 2 months. Similar patterns were seen in patients with NYHA class III and IV symptoms and an ejection fraction <0.25 . There were no significant differences in favor of placebo in any subgroup at any follow-up visit before 90 days. At the 90-day time point, relative risk was 0.95 for all patients, 0.81 for NYHA class II, 1.01 for NYHA class III or IV, and 0.79 for NYHA class III or IV with ejection fraction <0.25 . There was no adverse effect of metoprolol CR/XL in groups defined by

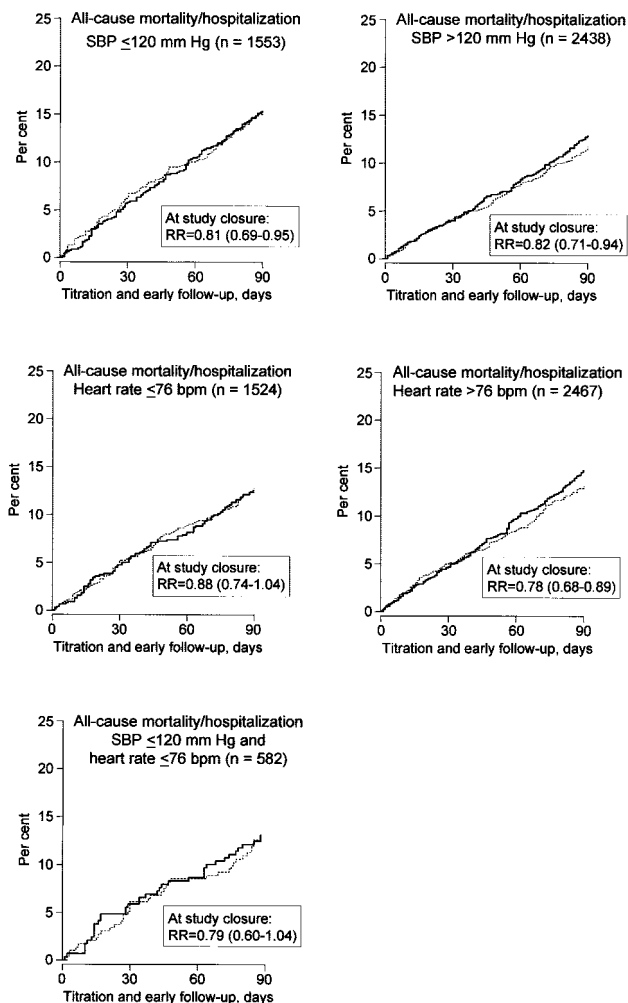


Figure 2. Kaplan-Meier estimates for combined end point of total mortality/all-cause hospitalization during first 90 days of follow-up for subgroups of patients with baseline SBP ≤120 mm Hg, SBP >120 mm Hg, heart rate ≤76 bpm, heart rate >76 bpm, and heart rate ≤76 bpm and SBP ≤120 mm Hg. Relative risk and 95% CIs at study closure are given. Solid lines indicate placebo; dashed lines, metoprolol CR/XL.

baseline heart rate or SBP (Figure 2). At the 90-day time point, relative risk was 0.97 for patients with baseline SBP ≤120 mm Hg, 1.03 for SBP >120 mm Hg, 0.99 for heart rate ≤76 bpm, 0.93 for heart rate >76 bpm, and 0.90 for those with SBP ≤120 mm Hg and heart rate ≤76 bpm (all $P=NS$).

Permanent Early Discontinuations

Figures 3 and 4 illustrate all-cause discontinuation from randomized treatment in all patients and in the different subgroups during the first 18 months. (Illustrations for a period longer than 90 days have been given because the crossover in several subgroups occurred after the 90 day time-point.) In NYHA class III or IV patients, 5.9% of the patients in the placebo group (69 of 1176) discontinued study medicine during the first 90 days after randomization; the corresponding figure in the metoprolol CR/XL subgroup was 8.1% (95 of 1180; $P=0.037$ unadjusted, $P=NS$ adjusted). However, from day 90 until end of study, more patients in

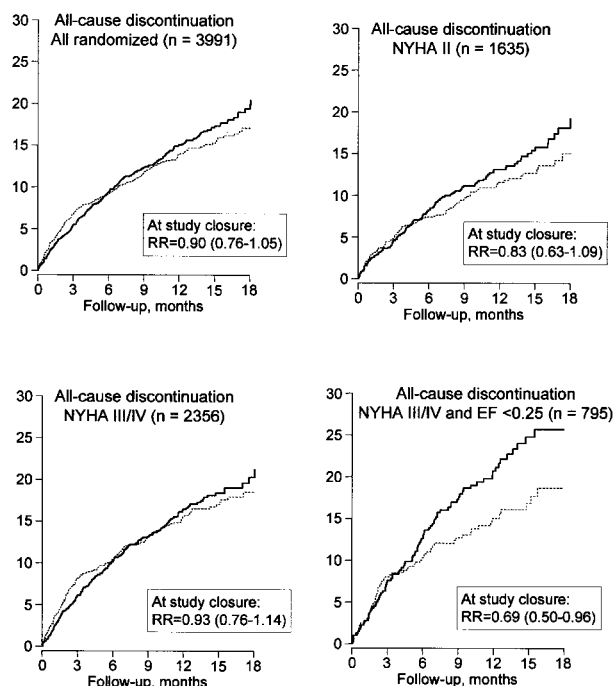


Figure 3. Kaplan-Meier estimates for drug discontinuation during first 18 months of follow-up in all patients randomized and in patients in NYHA class II, NYHA class III/IV, and NYHA class III/IV with ejection fraction (EF) <0.25. Relative risk and 95% CIs at study closure are given. Solid lines indicate placebo; dashed lines, metoprolol CR/XL.

NYHA class III or IV discontinued study medicine in the placebo group ($n=126$) than in the β -blocker group ($n=90$).

In the placebo group of patients with severe heart failure (NYHA class III or IV and ejection fraction <0.25), 7.1% (28 of 396) discontinued study medicine during the first 90 days; the corresponding figure in the metoprolol CR/XL subgroup was 8.0% (32 of 399; $P=NS$). From day 90 until end of study, 58 patients taking placebo and 30 taking metoprolol CR/XL discontinued the study drug. Among patients taking placebo, 4.3% (56 of 1304) with SBP >120 mm Hg discontinued study medicine during the first 90 days compared with 6.6% (90 of 1359) in the metoprolol CR/XL subgroup ($P=0.007$ unadjusted, $P=NS$ adjusted). Subsequently, more patients were discontinued from placebo. Among patients taking placebo, 4.6% (29 of 626) with heart rate ≤76 bpm discontinued study medicine during the first 90 days compared with 7.3% (44 of 604; $P=NS$) in the metoprolol CR/XL group. Subsequently, more patients were discontinued from placebo.

There were no significant differences in discontinuation of study medicine at the 90-day time point in any of the other blood pressure or heart rate subgroups. There was no statistically significant excess of discontinuations in the metoprolol CR/XL group at end of study for any blood pressure or heart rate subgroup, although numerically, more patients were discontinued from metoprolol CR/XL than from placebo in patients with baseline heart rates ≤76 bpm (93 versus 83 discontinuations, $P=0.32$; Figure 4). Discontinuations for the subgroup of patients with SBP ≤120 mm Hg and heart

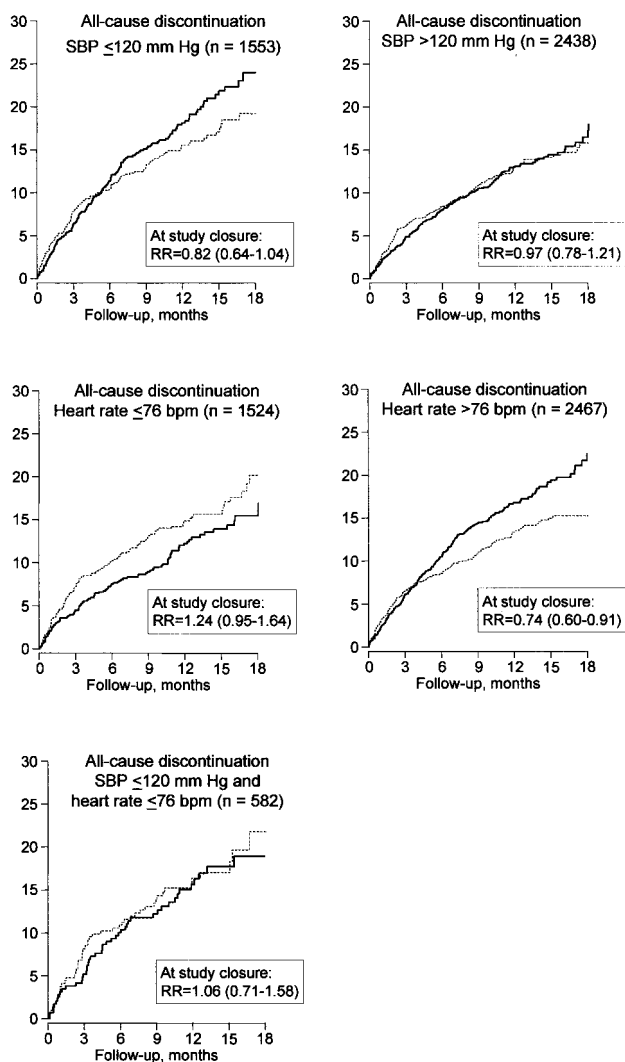


Figure 4. Kaplan-Meier estimates for drug discontinuation during first 18 months of follow-up for subgroups of patients with baseline SBP ≤ 120 mm Hg, SBP > 120 mm Hg, heart rate ≤ 76 bpm, heart rate > 76 bpm, and heart rate ≤ 76 bpm and SBP ≤ 120 mm Hg. Relative risk and 95% CIs at study closure are given. Solid lines indicate placebo; dashed lines, metoprolol CR/XL.

rate ≤ 76 bpm at baseline were similar in the placebo and metoprolol CR/XL randomization subgroups (Figure 4).

Delayed Titration

Patients whose therapy was begun at 25 mg of metoprolol CR/XL daily had less severe heart failure, as indicated by NYHA class, mortality, and ejection fraction (data not shown). This was to be expected, because the protocol suggested that NYHA class II patients should be initiated at a dose of 25 mg/d and class III and IV patients at a dose of 12.5 mg/d.

Figure 5 shows the reason for delayed titration in patients categorized by initial dose. By week 4, almost all patients who had initially received 25 mg/d had tolerated 50 mg of the drug daily. By week 8, the majority of these patients were receiving the targeted 200 mg/d dose; 9.1% of patients had not been fully titrated because of low heart rate in the metoprolol CR/XL group compared with 2.4% in the placebo

group. Increasing symptoms of congestive heart failure were reported in 5.2% of patients given metoprolol CR/XL compared with 4.6% of patients in the placebo group. There was no difference in the incidence of delayed titration for low blood pressure (3.9% versus 3.8%). Other causes for delayed titration (mainly stated as “NYHA III” or “NYHA IV”) were observed for 11.7% of the patients in the metoprolol CR/XL group compared with 10.8% in the placebo group.

Most of the patients whose study medication was initiated at a dose of 12.5 mg/d were also titrated successfully to 100 or 200 mg/d (Figure 5). Again, low heart rate was the most common limiting factor; it was the cause of incomplete titration in 11.3% of patients taking β -blocker at 3 months versus 3.3% of those taking placebo. At the 3-month visit, 7.6% of patients taking metoprolol CR/XL had delayed titration due to low blood pressure compared with 5.9% of placebo patients. At the same visit, 8.7% of patients randomized to metoprolol CR/XL were not taking the target dose because of heart failure, compared with 5.4% of patients randomized to placebo. The distribution of heart rates of patients whose titration was limited for low heart rate is given in the Table; very few patients had a resting heart rate < 50 bpm, and heart rate was > 60 bpm in many of these patients.

Symptoms of Breathlessness and Fatigue

Most patients reported no change in symptoms during titration (Figure 6). For those with more severe heart failure (NYHA class III or IV patients with ejection fraction < 0.25), more patients in the β -blocker group reported improved symptoms of breathlessness and fatigue (and fewer reported deterioration) at the last follow-up visit ($P=0.036$ and $P=0.005$, respectively).

Diuretic Dosing

There was no deleterious effect of metoprolol CR/XL on diuretic dosing during the titration (Figure 7). The mean furosemide dose tended to increase during titration, but this occurred equally in patients who received metoprolol and those who received placebo. Similar patterns were seen in patients receiving other diuretics. NYHA class III and IV patients tended to have a greater increase in furosemide dose than NYHA class II patients, with no effect of metoprolol CR/XL. In NYHA class III or IV patients with ejection fraction < 0.25 , the mean furosemide dose at the 3-month visit had increased 10.4 mg in the placebo group and 1.7 mg in the metoprolol CR/XL group ($P=0.031$). At the conclusion of the study, the mean dose had increased 17.3 mg in the placebo group and 2.0 mg in the metoprolol CR/XL group ($P=0.0002$).

ACE Inhibitor Dosing

The mean daily enalapril dose (in those receiving this ACE inhibitor) was 14.3 mg in both randomization groups at baseline. After 90 days, the dose was 14.5 and 15.0 mg/d in the placebo and metoprolol CR/XL groups, respectively. Doses in subgroups were similar to those in all randomized patients both at baseline and during follow-up.

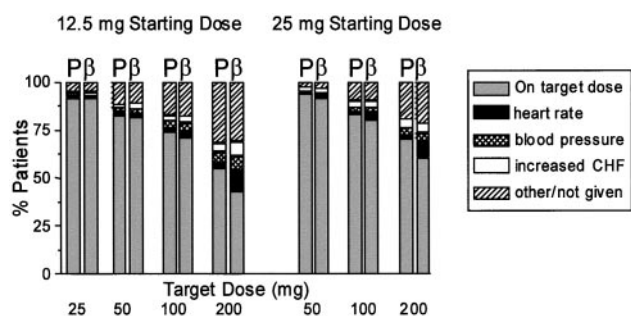


Figure 5. Percentage of patients taking study drug who received targeted dose is indicated for each titration visit, as is reason given for not receiving targeted dose. Metoprolol CR/XL is indicated by β and placebo by P. Low heart rate was the most common reason stated for lower dose than expected in patients receiving metoprolol CR/XL. CHF indicates congestive heart failure.

Discussion

This analysis of MERIT-HF demonstrates the tolerability of metoprolol CR/XL initiation in patients with heart failure. It is the first attempt to evaluate a large-scale β -blocker study to determine the pattern and incidence of clinical deterioration (of any magnitude) in the weeks after initiation of these agents. The rarity of worsening symptoms, adverse events, delayed titration, and adjustment of concomitant medications provides reassurance that β -blockers can be used safely in the general population of patients with stable mild to moderate heart failure. However, improvement does not occur immediately, and the present study supports the need to watch these patients carefully during titration.

Distribution of Heart Rates in Patients With "Low Heart Rate" Stated as the Reason for Lower-Than-Expected Dose of Study Medicine During Titration and at Last Follow-Up Visit

Visit/Group	Heart Rate (mean \pm SD)	Heart Rate, n	
		<50 bpm	<60 bpm
2 Weeks			
Metoprolol CR/XL (n=32)	66 \pm 9	0	6
Placebo (n=27)	68 \pm 10	1	3
4 Weeks			
Metoprolol CR/XL (n=53)	62 \pm 10	5	21
Placebo (n=40)	71 \pm 10	0	5
6 Weeks			
Metoprolol CR/XL (n=92)	61 \pm 9	3	40
Placebo (n=44)	69 \pm 11	0	8
8 Weeks			
Metoprolol CR/XL (n=159)	59 \pm 9	16	79
Placebo (n=51)	69 \pm 13	1	11
3 Months			
Metoprolol CR/XL (n=191)	59 \pm 10	23	99
Placebo (n=43)	66 \pm 9	2	7
Last visit			
Metoprolol CR/XL (n=182)	62 \pm 10	14	67
Placebo (n=38)	68 \pm 14	3	12

Adverse Effects in Previous Studies

A consistent finding in previous studies that evaluated β -blocker use in heart failure was an overall frequency of adverse events that was lower in patients who received active drug than in those who received placebo. Fewer hospitalizations and less deterioration have been reported for metoprolol CR/XL, carvedilol, and bisoprolol.²⁻⁵ However, there has been concern that symptoms may worsen in many patients during initiation of these drugs. Improvement in cardiac function has been shown to occur after 1 month.⁶

The common use of active-drug run-in periods has been an important limitation of many previous studies. In the US carvedilol program, 5.6% of patients did not complete 2 weeks of active run-in for carvedilol, with 1.4% experiencing worsening heart failure and 0.6% dying.³ In another carvedilol study, 6% of patients were withdrawn during the open-label run-in period; 2% of the patients experienced worsening heart failure, and 2% were withdrawn because of hypotension.⁷ In the Metoprolol in Dilated Cardiomyopathy trial of immediate-release metoprolol tartrate, 4% of patients discontinued the study during the run-in period of 5 mg twice daily for 2 to 5 days.⁸ The problem with evaluating tolerance during a run-in period is the impossibility of determining which side effects are secondary to the drug and which are due to other reasons. These findings, however, raised concerns that the benefits of β -blockade are only applicable to people who tolerate the initial dose, with a relatively large number of patients appearing to be intolerant of the drug.

To address the impact of β -blockers in the overall patient population relevant to clinical practice, MERIT-HF did not include a run-in period for active therapy. (There was a 2-week placebo run-in period.) Nevertheless, little deterioration was evident. The risk of any deterioration caused by β -blockade appears greatest during the first 4 to 8 weeks of drug treatment initiation. By 8 weeks, mortality/hospitalization rates started to trend in favor of β -blockade for all patients randomized, as well as for those with more severe heart failure. At the 3-month visit, the mean dose of furosemide in those with more severe heart failure had increased more in the placebo group than in the β -blocker group.

Patients included in MERIT-HF were clinically stable, and few NYHA class IV patients were enrolled. Therefore, the data cannot be extrapolated to patients in a clinically unstable situation or to NYHA class IV patients. NYHA class IV patients are clearly more likely to experience adverse events.⁹ Nevertheless, the sickest patients in MERIT-HF showed excellent tolerability to β -blockade. Furthermore, patients in NYHA class II to III represent the greatest number of patients with heart failure. It is in this population that the addition of β -blockers to existing therapy will exert its largest public health benefit.

Applicability to Other β -Blockers

It is possible that different β -blockers may cause different incidences of adverse events. For example, the vasodilation associated with carvedilol might lead to more intolerance secondary to hypotension. In the present study, blood pressure was not a clinical problem. However, in the US carvedilol studies, dizziness was reported in 33% with active drug

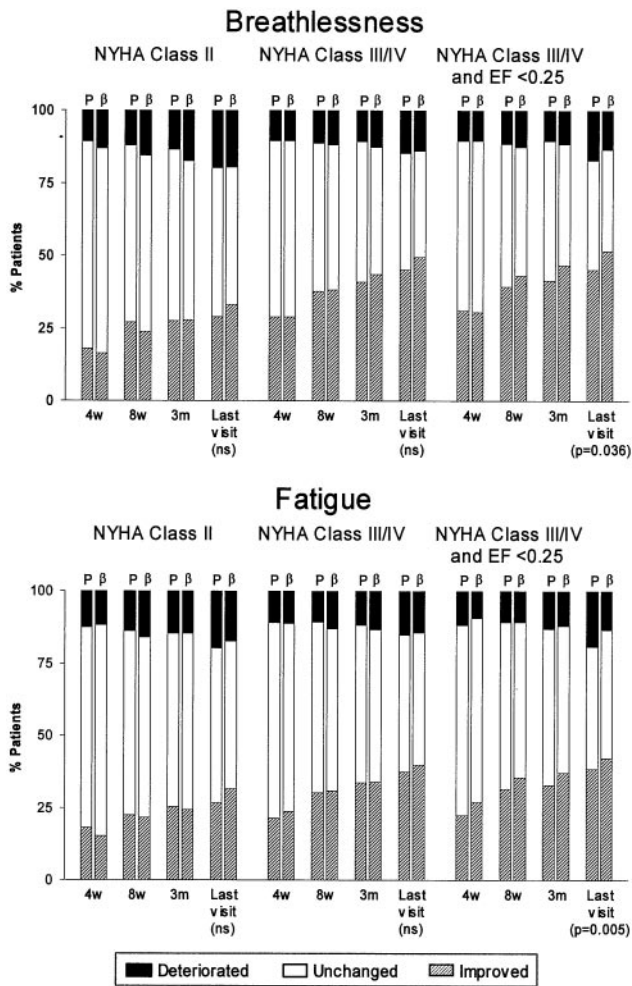


Figure 6. Percentage of patients (by NYHA class) reporting improved, unchanged, or deteriorated symptoms of breathlessness (top) and fatigue (bottom). Metoprolol CR/XL is indicated by β and placebo by P. EF indicates ejection fraction.

and 20% with placebo. Similarly, hypotension was reported in 9% of the carvedilol group and 4% of the placebo patients.³

The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) reported no increased permanent withdrawal rate with β -blockade during the initiation period.⁵ It is possible that the vasodilation caused by carvedilol might improve tolerance in some individuals. Nevertheless, the COPERNICUS data appear consistent with the MERIT-HF data in a similar group of patients (NYHA class III or IV and ejection fraction <0.25). The frequency of delayed titration in COPERNICUS has not been reported.

Discontinuation and Delayed Titration in Subgroups

Few patients were withdrawn from the study during initiation. In NYHA class II patients, active drug was withdrawn in fewer patients receiving active drug. Compared with placebo, an excess of <3% of NYHA class III and IV patients were discontinued from active drug during titration. In NYHA class III and IV patients with an ejection fraction <0.25, there was less than a 1% excess discontinuation. During long-term maintenance therapy, more patients were discontinued from placebo than from active drug in all NYHA classes. Subgroup

analyses can be difficult to interpret, and it is not known whether these small differential findings are due to chance effects. Furthermore, discontinuation does not necessarily reflect clinically important adverse events. With heart rate being the most common reason given for discontinuation, the drug may have been well tolerated in many patients in whom it was nevertheless discontinued.

Low heart rate was the most common reason stated by the investigators for delayed titration. Drug discontinuations were also more common in patients with the lowest heart rates. Previous studies have reported bradyarrhythmias in patients given β -blockers. For example, symptomatic bradycardia was seen in 3% of patients in an open-label carvedilol study.⁹ In another carvedilol study, 9% of patients receiving carvedilol had bradycardia noted as an adverse event, with 0.9% discontinued from the drug for this reason.³ In MERIT-HF, the net difference between metoprolol CR/XL and placebo for discontinuation of study medicine because of bradycardia was 0.6% for 1 year of follow-up.² In the Cardiac Insufficiency Bisoprolol Study II (CIBIS-2), 2 cases of heart block and 2 cases of bradycardia led to drug withdrawal.⁴

Because titration was at the investigators' discretion in MERIT-HF, low heart rate did not necessarily represent an adverse event. Whereas it is possible that a decrease in heart rate could cause adverse effects, physicians' concerns about relatively low heart rates might also limit β -blocker use. Thus, although 11 patients were removed from active drug for bradycardia (compared with 5 given placebo),² it is difficult to discern whether discontinuation was necessary. The Table shows normal heart rates in many patients with delayed titration due to "low heart rate." As previously reported, patients with lower heart rates benefited from long-term administration of metoprolol CR/XL.

Conclusions

β -Blockade prolongs life and improves symptoms in patients with heart failure. The results of MERIT-HF also show that it

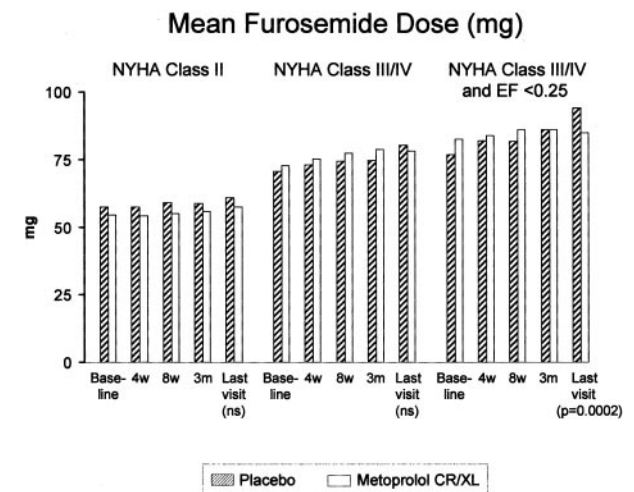


Figure 7. Daily dose of furosemide (for patients receiving furosemide) by NYHA class and treatment group. Diuretic dose increased throughout the study and was greater in more symptomatic patients. During titration, there was no difference between patients who received β -blockade and those who received placebo. EF indicates ejection fraction.

can be initiated safely in the overwhelming majority of patients with stable mild to moderate heart failure, with minimal side effects or deterioration. Sicker patients need to be monitored carefully, because titration began with low doses in MERIT-HF and proceeded cautiously. When given in this manner, extended-release metoprolol succinate is both safe and effective. β -Blockade should be prescribed for the overwhelming majority of patients with stable mild to moderate heart failure.

Acknowledgments

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