What Resting Heart Rate Should One Aim For When Treating Patients With Heart Failure With a Beta-Blocker?

Experiences From the Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF)

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OBJECTIVES
The goal of this study was to explore the question: what resting heart rate (HR) should one aim for when treating patients with heart failure with a beta-blocker?

BACKGROUND
The interaction of pretreatment and achieved resting HR with the risk-reducing effect of beta-blocker treatment needs further evaluation.

METHODS
Cardiovascular risk and risk reduction were analyzed in five subgroups defined by quintiles (Q) of pretreatment resting HR in the Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF).

RESULTS
Mean baseline HR in the 5 Qs were 71, 76, 81, 87, and 98 beats/min; achieved HR 63, 66, 68, 72, and 75 beats/min; and net change —8, —10, —11, —13, and —14 beats/min, respectively. Baseline HR was related to a number of baseline characteristics. Cardiovascular risk was no different in Q1 to Q4 (placebo groups) but increased in Q5 (HR above 90 beats/min). No relationship was observed between the risk-reducing effect of metoprolol controlled release/extended release (CR/XL) and baseline HR in the five Qs of baseline HR, or achieved HR, or change in HR during follow-up, respectively.

CONCLUSIONS
Metoprolol CR/XL significantly reduced mortality and hospitalizations independent of resting baseline HR, achieved HR, and change in HR. Achieved HR and change in HR during follow-up were closely related to baseline HR; therefore, it was not possible to answer the question posed. Instead, one has to apply a very simple rule: aim for the target beta-blocker dose used in clinical trials, and strive for the highest tolerated dose in all patients with heart failure, regardless of baseline and achieved HR.

Several studies have demonstrated an association between resting heart rate (HR) and long-term cardiovascular risk independent of other major cardiovascular risk factors in epidemiologic studies (1–4) among patients with hypertension (5) and after myocardial infarction (6–8). However, the interaction of pretreatment resting and achieved HR with the risk-reducing effect of beta-blocker treatment in heart failure needs further evaluation.

The main aim of the present analysis of the Metoprolol Controlled Release/Extended Release Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) (9) was to try to answer the question: what resting HR should one aim for when treating patients with heart failure with a beta-blocker? For this purpose, patients were divided into five subgroups defined by quintiles (Q) of baseline resting HR. We report on: 1) baseline characteristics in the five HR subgroups; 2) risk for death and hospitalizations in the five HR subgroups; 3) achieved HR and net change in HR during follow-up in the five metoprolol controlled release/extended release (CR/XL) subgroups defined by Qs of baseline resting HR; and 4) relative risk reduction with metoprolol CR/XL in the five HR subgroups in relation to baseline HR, achieved HR, and change in HR during follow-up.

METHODS
Study design. The MERIT-HF study was a prospective, randomized, placebo-controlled clinical trial that random-
ized 3,991 patients (9). The present subgroup analysis focuses on subgroups of patients arbitrarily defined by Qs of baseline resting HR, giving a fair amount of events in each HR subgroup. The study design and main results of MERIT-HF study have been published previously (9).

Briefly, patients enrolled in the MERIT-HF study were 40 to 80 years of age, with an ejection fraction ≥0.40 and in New York Heart Association (NYHA) functional class II to IV heart failure for at least three months before enrollment, with an HR at or above 68 beats/min at the enrollment visit. Baseline HR was taken as the mean of the two HRs recorded at the enrollment visit (start of a two-week placebo run-in) and the randomization visit, and may, therefore, be lower than 68 beats/min. Patients were receiving optimum standard therapy with diuretics and an angiotensin-converting enzyme inhibitor. After the single-blind placebo run-in phase, patients were randomized to metoprolol CR/XL or placebo with starting doses of 12.5 mg (recommended for patients in NYHA functional class III and IV) or 25 mg once daily. It was recommended to double the dose every two weeks to a target dose of 200 mg once daily, or the highest tolerated dose (9).

**Statistical methods.** Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables were used when analyzing the relationship between a number of baseline characteristics and resting baseline HR. The test of treatment by HR interaction used the p value of the Wald statistic of the interaction term in a Cox regression model. The risk defined as the number of patients per year of follow-up (placebo group) was very similar in Q1 to Q4. Therefore, in a secondary analysis, Q1 to Q4 were merged into one group when analyzing the difference in risk between Q1 to Q4 and Q5 utilizing Cox proportional regression analysis, taking into account the following variables: age; gender; ejection fraction; NYHA functional class; ischemic etiology; history of myocardial infarction, hypertension, and diabetes mellitus; and systolic blood pressure. Cox proportional regression analysis was also performed within each Q to determine the risk-reducing effect of beta-blocker treatment independent of baseline differences (adjusting for the following baseline variables: age; gender; ejection fraction; NYHA functional class; ischemic etiology; history of myocardial infarction, hypertension, and diabetes mellitus; systolic blood pressure; and HR). When analyzing outcome in relation to achieved HR and change in HR during follow-up, respectively, outcome was analyzed from the date of the three-month visit to study closure. All data were analyzed as intention to treat.

**RESULTS**

**Baseline HR as an independent risk factor for outcome.** In the placebo group, baseline HR as a continuous variable came out as a highly significant independent risk factor for all-cause mortality (p = 0.003; 217 deaths) for cardiovascular mortality (p = 0.006; 203 deaths), and also for the number of patients hospitalized for worsening heart failure (p < 0.0001; 294 hospitalizations). No such statistically significant relationship was observed between baseline HR and outcome in the beta-blocker group.

**Baseline characteristics by Qs of baseline HR.** Baseline HRs in the 5 Qs were: 71 beats/min in Q1, 76 beats/min in Q2, 81 beats/min in Q3, 87 beats/min in Q4, and 98 beats/min in Q5, respectively (Table 1). All patients in Q5 had a baseline HR over 90 beats/min. Baseline HR was related to a number of other baseline characteristics (Table 1). With increasing HR, patients were more often in NYHA functional class III and IV (52% in Q1 vs. 68% in Q5), more often had non-ischemic etiology of heart failure (25% vs. 45%), a history of diabetes (20% vs. 28%), atrial fibrillation (14% vs. 21%), higher diastolic blood pressure (76 vs. 80 mm Hg), and were more often treated with diuretics (86% vs. 93%) and antidiabetic drugs (10% vs. 16%). With increasing baseline HR, the proportion of women also increased (18% vs. 25%), there was a decline in age (mean age 66.1 years in Q1 vs. 61.7 years in Q5), and also in ejection fraction (29% vs. 26%), fewer patients had a history of myocardial infarction (60% vs. 36%), and fewer patients were receiving aspirin (51% vs. 40%) and statins (30% vs. 16%), respectively. Symptoms like peripheral edema, jugular venous distension, and lung rales increased with increasing baseline HR (Table 1).

**Risk in the placebo HR subgroups during follow-up.** Figure 1 (left panel) is a bar diagram that illustrates risk defined as number of deaths per patient-years of follow-up in the five placebo HR subgroups. An inspection of the diagram reveals that the mortality risk was quite similar in Q1 to Q4. In the following analyses, Q1 to Q4 were, therefore, merged into one group (Q1 to Q4). Relative risk in Q5 was significantly higher compared with Q1 to Q4 for total mortality (1.51; 95% confidence interval 1.12 to 2.05); for deaths from heart failure (1.90; 95% confidence interval 1.09 to 3.33); but not for sudden death (1.27; 95% confidence interval 0.85 to 1.91).

Similar data for the number of patients hospitalized are illustrated in Figure 1 (right panel). Risk for hospitalizations was very similar in Q1 to Q4. Relative risk in Q5 was significantly higher compared with Q1 to Q4 for all-cause hospitalizations (1.40; 95% confidence interval 1.18 to 1.68); for cardiovascular hospitalizations (1.55; 95% confidence interval 1.27 to 1.90); and also for hospitalization due to worsening heart failure (1.78; 95% confidence interval 1.38 to 2.29).
Table 1. Baseline Clinical Characteristics in the Five Heart Rate Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Q1 (n = 802)</th>
<th>Q2 (n = 772)</th>
<th>Q3 (n = 833)</th>
<th>Q4 (n = 770)</th>
<th>Q5 (n = 814)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (mean, beats/min)</td>
<td>70.6 ± 2.3</td>
<td>76.0 ± 1.3</td>
<td>80.9 ± 1.5</td>
<td>86.8 ± 2.0</td>
<td>98.1 ± 7.2</td>
</tr>
<tr>
<td>Heart rate (range, beats/min)</td>
<td>58.0–73.3</td>
<td>73.7–78.5</td>
<td>78.7–83.3</td>
<td>83.5–90.3</td>
<td>90.7–141.7</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>66.1 ± 9.1</td>
<td>64.8 ± 9.4</td>
<td>63.0 ± 9.8</td>
<td>63.2 ± 9.7</td>
<td>61.7 ± 9.8</td>
</tr>
<tr>
<td>Females (%)</td>
<td>18</td>
<td>22</td>
<td>22</td>
<td>25</td>
<td>26</td>
</tr>
<tr>
<td>Caucasian (%)</td>
<td>95</td>
<td>94</td>
<td>94</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 ± 8.8</td>
<td>172 ± 8.7</td>
<td>172 ± 8.8</td>
<td>171 ± 8.6</td>
<td>171 ± 8.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.7 ± 15.2</td>
<td>80.9 ± 16.3</td>
<td>81.1 ± 16.0</td>
<td>80.7 ± 16.4</td>
<td>80.9 ± 16.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.8 ± 4.1</td>
<td>27.3 ± 4.7</td>
<td>27.3 ± 4.5</td>
<td>27.4 ± 4.9</td>
<td>27.5 ± 5.1</td>
</tr>
<tr>
<td>NYHA functional class II/III/IV (%)</td>
<td>49/50/2</td>
<td>42/54/3</td>
<td>42/55/4</td>
<td>41/55/4</td>
<td>32/63/5</td>
</tr>
<tr>
<td>Nonischemic etiology (%)</td>
<td>25.4</td>
<td>30.2</td>
<td>32.9</td>
<td>39.9</td>
<td>45.0</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>29 ± 7</td>
<td>28 ± 7</td>
<td>28 ± 7</td>
<td>28 ± 7</td>
<td>26 ± 7</td>
</tr>
</tbody>
</table>

Smoking habits
- Never: 26.2%
- Daily: 12.1%
- History of diabetes (%): 19.5%
- History of hypertension (%): 42.8%
- History of MI (%): 59.6%
- Atrial fibrillation (%): 13.5%
- Medications (%)
  - Diuretics: 86.3%
  - ACE inhibitors: 88.0%
  - AII blocker: 8.0%
  - Digitalis: 60.0%
  - Aspirin: 50.9%
  - Statin: 29.8%
  - Oral antidiabetic: 9.6%
  - Systolic BP (mm Hg): 129 ± 26
  - Diastolic BP (mm Hg): 76 ± 8.8
  - S-creatinine (µmol/l): 109 ± 31
  - Peripheral edema: 13.5%
  - Jugular venous distension: 10.1%
  - Angiontensin II; BMI; BP; LV; left ventricular; MI; myocardial infarction; NA; NYHA; New York Heart Association; Q; quintile.

**Dose of study medicine in the five Qs of baseline HR.** The mean dose of metoprolol CR/XL at last follow-up visit in the 5 Qs of baseline HR were: 146 mg (Q1), 149 mg (Q2), 163 mg (Q3), 167 mg (Q4), and 166 mg (Q5), respectively (Fig. 2). Over 80% of the patients in each Q reached at least 100 mg of metoprolol CR/XL once daily, and 54% in Q1 reached the target dose of 200 mg once daily compared with 69% in Q5. The reasons for lower than target dose in the beta-blocker group (as stated by the investigator) in the 5 Qs are given in Table 2; low HR was stated as the reason for 19.4% in Q1 compared with 4.0% in Q5 (corresponding figures in the placebo group 4.1% vs. 0.6%, respectively). The reasons “low blood pressure” and “increasing symptoms of chronic heart failure” occurred in the relatively similar proportion in the different five Qs, and were no different from placebo (Table 2).

**DISCONTINUATION.** Although discontinuation of metoprolol CR/XL tended to be slightly higher than on placebo in Q1 (52 cases on placebo and 69 on metoprolol CR/XL; p = NS), it was lower on metoprolol CR/XL compared with placebo among those with the highest baseline HR (Q5): 89 versus 51 cases (0.59; 95% confidence interval 0.42 to 0.83; p = 0.003).

In the first Q, eight patients stopped treatment because of bradycardia in the metoprolol CR/XL group; corresponding data in the other Qs were five patients (Q2), two patients (Q3), and one patient (Q4). None of the patients in Q5 stopped treatment because of bradycardia in the metoprolol CR/XL group. Corresponding data in the placebo group were two patients (Q1), no patient (Q2 to Q4), and three patients (Q5), respectively.

**Achieved HR in the five Qs of baseline HR.** Figure 2 presents baseline HR, achieved HR, and change in HR at the last follow-up visit in the five Qs defined by Q of baseline HR. Achieved HR at the last follow-up visit was 63 beats/min in Q1, 66 in Q2, 68 in Q3, 72 in Q4, and 75 beats/min in Q5. Heart rates in the 5 Qs were reduced by 7, 12, 15, and 22 beats/min, respectively. However, HR was also reduced in the placebo group, especially in Q5 with 8 beats/min leading to a net reduction of 14 beats/min in Q5, which should be compared with 8, 10, 11, and 13
beats/min in Q1 to Q4, respectively. The percent net reduction in HR in the metoprolol CR/XL subgroups in the 5 Qs were: 10.3% in Q1, 13.9% in Q2, 15.5% in Q3, 17.5% in Q4, and 22.6% in Q5, respectively.

All analyses here refer to all patients randomized including those with atrial fibrillation. In order to analyze data in more homogenous subgroups of patients, we also analyzed only those in sinus rhythm as well as a subgroup of those in sinus rhythm with ischemic etiology only. Baseline HR was actually the same in these two subgroups as in all patients randomized (71, 76, 81, 87, and 98 beats/min in both subgroups), and percent reduction in HR with metoprolol CR/XL was very similar compared with all patients randomized (12.0%, 14.7%, 15.7%, 17.3%, and 23.2% and 11.1%, 14.4%, 15.6%, 17.2%, and 22.4%, respectively).

Risk reduction with metoprolol CR/XL in relation to baseline and achieved HR. Tests of baseline resting HR (as a continuous variable) by treatment interaction was non-significant both for total mortality and number of patients hospitalized for worsening heart failure.

TOTAL MORTALITY IN RELATION TO HR IN THE FIVE Qs. No significant relationship was observed between baseline HR and point estimates for a change in risk for total mortality with metoprolol CR/XL in the five Qs of baseline HR (Fig. 3, upper panel, Cox-adjusted, see section on
Statistical methods for details). An analysis of achieved HR in relation to change in risk for total mortality in the same five subgroups defined by Q of baseline HR revealed very similar risk reductions in Q1 with 63 beats/min in achieved HR compared with Q5 with 75 beats/min in achieved HR (Fig. 3, lower panel). Again, a similar pattern was observed when net change in HR (metoprolol CR/XL minus placebo) or percent net reduction in HR with metoprolol CR/XL was plotted against point estimates for change in risk for total mortality with metoprolol CR/XL in the five Qs (Fig. 4, left panels): Q1 with an 8 beats/min net reduction in HR had a similar risk reduction for total mortality as Q5 with a 15 beats/min reduction (the percent net reduction in HR with metoprolol CR/XL in these two groups was 10% and 23%, respectively. No relationship was observed between change in risk in hospitalizations for heart failure with metoprolol CR/XL and baseline resting HR (Fig. 5, upper panel). The risk of being hospitalized for heart failure was not lowest in those who lowest achieved HR (Fig. 5, lower panel). On the contrary, although 95% confidence intervals were widely overlapping between the different Qs, the point estimate for risk reduction tended to be higher in Q5 with an achieved HR of 75 beats/min (68% relative risk reduction) compared with Q1 with an achieved HR of 63 beats/min (51%). This is probably explained by the higher placebo risk in those with highest baseline HR (Fig. 1, lower right hand panel).

There was no relationship between change in HR (net change or percent net reduction) and risk reduction for hospitalizations for worsening heart failure in Q1 to Q4 (Fig. 4, right hand panels). Risk reduction for hospitalization for worsening heart failure tended to be somewhat larger (p = NS) in Q5 (68% risk reduction) compared with Q1 (51%), but this was probably more related to the higher risk in the placebo group in Q5 (see comments in the preceding text) than to the higher percent reduction in HR with metoprolol CR/XL.

**DISCUSSION**

The results of the present study showed that metoprolol CR/XL significantly reduced the relative risk for mortality and hospitalizations independently of resting baseline HR. Furthermore, results showed very similar risk reduction in the subgroup that achieved the lowest HR during follow-up (Q1 63 beats/min) compared with the subgroup that only reduced HR to 75 beats/min (Q5). A similar pattern was observed when net change in HR during follow-up was plotted against point estimates for change in risk for total mortality: Q1 with an 8 beats/min net reduction in HR had a similar risk reduction for total mortality as Q5 with a 15 beats/min reduction (the percent net reduction in HR with metoprolol CR/XL in these two groups was 10% and 23%, respectively.

<table>
<thead>
<tr>
<th>Quintile (Q)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
</tr>
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<tr>
<td>Meto CR/XL dose (mg)</td>
<td>146</td>
<td>149</td>
<td>163</td>
<td>167</td>
<td>166</td>
</tr>
<tr>
<td>Net reduction (bpm)</td>
<td>8</td>
<td>10</td>
<td>11</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>% reduction (bpm)</td>
<td>10</td>
<td>14</td>
<td>16</td>
<td>18</td>
<td>23</td>
</tr>
</tbody>
</table>

**Figure 2.** Baseline heart rate (open circles) and achieved heart rate at last follow-up visit (solid circles) in the five quintiles (Q) of baseline heart rate. Mean metoprolol CR/XL dose, net reduction in heart rate (baseline minus achieved), and percent net reduction in heart rate with metoprolol CR/XL also given for the different subgroups. bpm = beats/min; Meto CR/XL = metoprolol controlled release/extended release.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
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<tr>
<td>Low heart rate Placebo (%)</td>
<td>4.1</td>
<td>4.0</td>
<td>1.1</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Metoprolol CR/XL (%)</td>
<td>19.4</td>
<td>14.1</td>
<td>7.2</td>
<td>7.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Low blood pressure Placebo (%)</td>
<td>4.1</td>
<td>4.3</td>
<td>2.5</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Metoprolol CR/XL (%)</td>
<td>6.1</td>
<td>6.0</td>
<td>7.4</td>
<td>5.8</td>
<td>5.2</td>
</tr>
<tr>
<td>Increasing symptoms of CHF Placebo (%)</td>
<td>5.0</td>
<td>5.8</td>
<td>5.3</td>
<td>7.5</td>
<td>8.0</td>
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<tr>
<td>Metoprolol CR/XL (%)</td>
<td>9.7</td>
<td>5.5</td>
<td>5.3</td>
<td>5.5</td>
<td>10.3</td>
</tr>
<tr>
<td>Other reason* Placebo (%)</td>
<td>14.1</td>
<td>16.2</td>
<td>12.4</td>
<td>14.9</td>
<td>14.0</td>
</tr>
<tr>
<td>Metoprolol CR/XL (%)</td>
<td>21.5</td>
<td>21.0</td>
<td>14.4</td>
<td>15.2</td>
<td>15.8</td>
</tr>
</tbody>
</table>

*Most often stated as “low ejection fraction at baseline” or “New York Heart Association functional class III or IV at baseline,” probably indicating an unwillingness on behalf of the investigator to increase the dose for unspecified reasons.

CHF = chronic heart failure; CR/XL = controlled release/extended release; Q = quintile.
respectively). This means that the question initially posed, “what resting HR should one aim for when treating patients with heart failure with a beta-blocker?,” cannot be answered. Achieved HR and reduction in HR during follow-up are too dependent on baseline HR for a meaningful analysis of this issue (for further comments, see the following text).

There was no interaction between baseline HR and the benefit of bisoprolol on mortality and hospitalizations in the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) (10). In the present study, the benefit in absolute terms tended to be somewhat higher (p<.005 NS) in the group with baseline resting HR above 90 beats/min. This subgroup also had the highest placebo risk, which may explain the tendency for somewhat higher relative risk reduction in this subgroup compared with patients with baseline resting HR below 90 beats/min.

The risk defined as the number of events per patient-year of follow-up (Fig. 1) was very similar in Q1 to Q4, that is, in patients with baseline resting HR below 90 beats/min, and only increased in patients with HR above 90 beats/min. Thus, the results from the present analysis in patients with heart failure differ somewhat from previous epidemiologic studies (2–4), studies among patients with hypertension (5), and post-infarction patients (6–8), where risk appears to increase gradually with increasing HR. One explanation for this finding may be that baseline HR in this group of patients with systolic heart failure interacted with a number of other baseline characteristics, including myocardial dysfunction (see the following text and Table 1), which, one might speculate, should occur less commonly in the other groups.

An interesting finding was the differences in baseline variables across the five HR subgroups; in those with highest HRs, there were more females, diabetics, and patients using diuretics, and more patients in NYHA functional class III and IV with lower ejection fraction, and fewer patients with ischemic etiology, and, accordingly, fewer patients using aspirin and statins. Thus, a higher HR is not only a marker of myocardial dysfunction, but also reflects other demographic variables.

The pathophysiologic explanations of the relationship between a high HR and mortality and morbidity is not clearly defined, but might be related to an autonomic imbalance with a shift toward a dominant sympathetic activity and reduced vagal activity, causing increased myocardial metabolic rate with chronic ischemia and hypoxia at the cellular level. This is manifested through increased plasma norepinephrine and myocardial norepinephrine spillover and increased HR (11). The increase in HR and plasma catecholamines correlate with reduced HR variability (12,13), which is related to reduced vagal tone and a poor prognosis. Activation of the sympathoadrenal system causes vasoconstriction and toxic effects on the myocardium, resulting in progressive impairment of left ventricular function and arrhythmias.

Tolerability. Metoprolol CR/XL was well tolerated, although patients were more likely to be discontinued from the drug in Q1 (baseline resting HR below 73 beats/min) than in Q5 (HR above 90 beats/min), presumably because of physicians’ concerns about low HRs. Some patients may have been withdrawn more easily because of anticipated adverse effects of a low HR, rather than symptomatic bradycardia or other adverse events. The lack of symptoms in patients in the MERIT-HF study in whom beta-blocker was not up-titrated because of low HR has been previously discussed (14).

Study limitations. The analyses presented in this investigation are performed post hoc. Differences in a large number of baseline variables were observed between those with lower HRs compared with those with higher HRs. Although the Cox analyses were adjusted for a number of these baseline variables, we cannot exclude that other unidentified confounders were present. Furthermore, inclu-
tion criteria stipulated an HR $\geq$ 68 beats/min at enrollment. Thus, heart failure patients with low HRs before treatment were not studied. We studied only resting HR, not exercise HR.

**Clinical implications.** The main aim of the present analysis of the MERIT-HF study was to try to answer the question: what resting HR should one aim for when treating patients with heart failure with a beta-blocker? For this purpose patients were divided into five subgroups defined by Q of baseline resting HR. Results showed that achieved HR, net reduction in HR, and percent net reduction in HR with metoprolol CR/XL all were too dependent on baseline HR for a meaningful analysis of the question posed. Instead of targeting a special HR after instituting a beta-blocker in patients with heart failure, regardless of baseline and achieved HR. The percent reduction in HR from baseline should be at least 10% in those with lowest HR before treatment, being over 20% in those patients with HR over 90 beats/min before treatment. The data on clinical outcome in the different Qs of baseline HR should not be interpreted as indicating that clinical outcome is independent of the HR response. In all Qs, investigators aimed for the highest tolerated dose, and this should also be the rule in clinical practice.

Absolute risk is of importance when considering numbers to treat to save one life. On the basis of observations in the MERIT-HF study, the number needed to treat for one year to save one life was 33 for those in Q1 to Q4 (HR below 90 beats/min) compared with 20 patients to treat one year to save one life for the group with the highest HR and highest risk (baseline HR above 90 beats/min). It is, however,
important to emphasize that patients in Q1 to Q4 represent the greatest number of patients with heart failure. It is in this population where the addition of a beta-blocker to existing therapy will exert its largest public health benefit.

Conclusions. We conclude that the results of the present analysis of MERIT-HF data showed that, in patients with chronic systolic heart failure, the risk for death and hospitalizations was similar in the first four Qs of baseline HR (placebo group, all with baseline resting HR below 90 beats/min), but increased in Q5 (baseline HR above 90 beats/min). Metoprolol CR/XL significantly reduced mortality and hospitalizations independent of baseline resting HR. The benefit in absolute terms appeared to be somewhat higher (p = NS) in the group with highest HR, which was also the group with the highest placebo risk. Data showed that achieved HR and change in HR during follow-up were closely related to baseline HR. It is not possible to define a special target HR for all patients with heart failure treated with a beta-blocker. Instead, one has to apply a very simple rule: aim for the target beta-blocker dose used in clinical trials or the highest tolerated dose in all patients with heart failure, regardless of baseline and achieved HR. Regardless of HR, investigators in the MERIT-HF study aimed for the highest tolerated dose, and this should also be the rule in clinical practice.

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REFERENCES


