Clinical research

Efficacy, safety and tolerability of β-adrenergic blockade with metoprolol CR/XL in elderly patients with heart failure

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Aim To study the efficacy and tolerability of β-blockade in elderly patients with heart failure in the MERIT-HF study.

Methods and results Cox proportional hazards model was used to calculate hazard ratios (HR) with 95% confidence intervals (CI). Risk reduction was defined as (1-HR). In patients ≥65 years total mortality was reduced by 37% (95% CI 17% to 52%; p = 0.0008), sudden death by 43% (95% CI 17% to 61%; p = 0.0032), and death from worsening heart failure by 61% (95% CI 32% to 77%; p = 0.0005). Hospitalisations for worsening heart failure was reduced by 36% (p = 0.0006). Elderly patients with severe heart failure (NYHA class III/IV with ejection fraction <0.25; n = 425), and patients above 75 years (n = 490) showed similar risk reductions. Metoprolol CR/XL was safe and well tolerated both during initiating therapy and during long-term follow-up.

Conclusions Metoprolol CR/XL was easily instituted, safe and well tolerated in elderly patients with systolic heart failure. The data suggest that these are the patients in whom treatment will have the greatest impact as shown by number of lives saved and number of hospitalisations avoided. The time has come to overcome the barriers that physicians perceive to β-blocker treatment, and to provide it to the large number of elderly patients with heart failure in need of this therapy.

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KEYWORDS Heart failure; β-Blockade; Prognosis; Tolerability; Elderly

Introduction

Heart failure is primarily a disorder of the elderly population, with 90% of all new cases occurring in patients above the age of 65 years.1,2 Its impact as a major and growing public health problem is evident by the estimated 1% prevalence in people older than 65 years, and 10% prevalence in patients above 75 years.1,2 Hospitalisation for heart failure is the most common cause in patients over 65 years of age, and the prediction is that the number of hospitalisations for heart failure will double in the next 10 years.1,3

Based on several large-scale clinical trials1–8 the current treatment guidelines for heart failure due to left
ventricular (LV) systolic dysfunction recommend β-blockers as routine treatment, that is a treatment that should be used in all patients who tolerate this medicine.2,9 Despite these recommendations, and strong clinical evidence supporting the use of β-blockers in heart failure, these agents are underutilised, particularly in the elderly.10,11 This is probably attributable largely to concern about the safety and tolerability of β-blockers in the elderly, as well as the lack of published data regarding their beneficial effects on mortality and hospitalisations in the elderly.

The Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HF) is the largest randomised clinical trial of β-blocker therapy in patients with heart failure due to LV systolic dysfunction.7,8 The MERIT-HF study had a pre-defined Data Analysis Plan, in which subgroup analyses were pre-specified, including an analysis of the elderly subgroup for safety reasons. Accordingly, and considering the large number of patients ≥65 years randomised in MERIT-HF (n = 1982), we performed an analysis to study the efficacy and tolerability of the β-blocker metoprolol succinate controlled release/extended release (CR/XL) in this elderly population. We also analysed separately the effect of metoprolol CR/XL in elderly patients with severe heart failure as defined by NYHA functional class III/IV with ejection fraction (EF) <0.25.5,12 Finally, some data are provided for the smaller group of patients aged 75 years or older.

Methods

Study design

The MERIT-HF was a prospective, placebo-controlled, double-blind clinical trial that randomised a total of 3991 patients. None was lost to follow-up. The study design and main results have been published earlier.7,8 The study had a planned mean follow-up time of 2.4 years, but was stopped early after recommendation from the Safety Committee. The mean follow-up time was one year. The present subgroup analysis focuses on patients ≥65 years of age at randomisation (n = 1982). Patients enrolled in MERIT-HF were 40–80 years of age, with EF ≤0.40 and in NYHA class II–IV heart failure for at least 3 months before enrollment (start of placebo run-in), with a heart rate at or above 68 beats/min (bpm) at enrollment, and receiving optimum standard therapy of diuretics and an ACE-inhibitor. If an ACE-inhibitor was not tolerated, other vasodilators, preferably angiotensin II receptor blockers were used. Digitalis could also be prescribed.

The recommended starting dose of metoprolol CR/XL/matching placebo was 25 mg once daily in NYHA class II patients and 12.5 mg in patients in NYHA class III and IV. It was recommended that the dose be doubled after each 2-week period until the target dose of 200 mg of metoprolol CR/XL once daily or matching placebo, or the highest tolerated dose, was reached.

The two primary outcome variables for the study were total mortality, and the combined endpoint of all-cause mortality or all-cause hospitalisation (time to first event). The pre-defined secondary endpoints were all-cause mortality or hospitalisation due to worsening heart failure (time to first event), cardiac death or non-fatal myocardial infarction, total number of hospitalisations due to cardiovascular causes; and to worsening heart failure, and withdrawal of study drug for any cause, and for worsening heart failure.

Statistical methods

Student’s t-test for continuous variables and Fishers Exact Test for categorical variables were used when analysing differences in baseline variables between the two age subgroups (≥65 years vs. <65 years). The Cox proportional hazards model was used to calculate hazard ratios (HR), for convenience expressed as relative risks, and 95% confidence intervals. When comparing absolute risk in the two placebo age groups (≥65 years vs. <65 years) adjustments for the following baseline variables were made: sex, EF, NYHA class, ischaemic aetiology, history of myocardial infarction, hypertension and diabetes mellitus, systolic blood pressure, heart rate, and smoking status. Absolute risk has been expressed as number of events per patient year of follow-up. When calculating patient years of follow-up for the different endpoints patients were censored at the time of the first event. Risk reduction was defined as (1-HR). P-values over 0.20 have been given as p > 0.20.

Results

Of the 1982 elderly patients, 992 were randomly assigned to receive placebo and 990 to receive metoprolol CR/XL; of the 2009 patients <65 years of age, 1009 were assigned to receive placebo and 1000 patients to receive metoprolol CR/XL (Table 1). The two randomisation groups were well balanced in both age groups. Compared with patients below 65 years of age (mean age 55.8 years; n = 2009), patients ≥65 years (mean age 71.8 years; n = 1982) had a higher prevalence of ischaemic aetiology (p < 0.0001), were more often in NYHA class III and IV (p < 0.0001), had slightly higher systolic blood pressure (p < 0.0001), lower diastolic blood pressure and heart rate (p < 0.0001), lower BMI (p < 0.0001), higher serum creatinine (p < 0.0001), and more patients were in atrial fibrillation (p < 0.0001). The elderly group also included a slightly higher proportion of women (p < 0.001). Similar differences as described above were observed between the two age groups with severe heart failure (defined as NYHA class III/IV and EF <0.25). For further characteristics in this subgroup, see below and Ref.12.

Fig. 1 illustrates with Kaplan–Meyer estimates survival curves for total and cause specific mortality in the two age groups, and Fig. 2 point estimates for relative risk and 95% CI for total mortality, cause specific mortality, and combined endpoints for the different subgroups analysed. Further details on these endpoints are given in Tables 4 and 5.

Primary outcome clinical events

Total mortality

The mortality in the placebo group was higher in those ≥65 years of age compared to those <65 years after adjustment for differences in baseline characteristics (excluding age): for total mortality the relative risk was 1.82 (95% CI 1.37 to 2.42; p < 0.0001); and for mortality from heart failure 4.18 (CI 2.21 to 7.92; p < 0.0001).
In patients ≥65 years there were 134 deaths (14.1% per patient year of follow-up) on placebo vs. 87 deaths (8.9%) on metoprolol CR/XL, a 37% risk reduction in total mortality (p = 0.0008). Corresponding figures in those below 65 years were 83 deaths (8.1% per patient year of follow-up) vs. 58 deaths (5.6%) corresponding to a 30% risk reduction in total mortality (p = 0.034).

All-cause mortality or all-cause hospitalisation (time to first event)
The combined endpoint of all-cause mortality or all-cause hospitalisation (time to first event) was reduced by 14% in patients ≥65 years (p = 0.030), and by 24% in patients below 65 years of age (p = 0.0007).

Secondary outcome clinical events

Cause-specific mortality
Sudden death was reduced by 43% in those ≥65 years (p = 0.0032), and by 38% in patients below 65 years (p = 0.019). In patients ≥65 years there were 45 deaths (4.7%) due to worsening heart failure in the placebo group, and 18 deaths (1.8%) in the metoprolol CR/XL group (risk reduction 61%; p = 0.0005). In patients below 65 years the risk for death from worsening heart failure was low in both randomisation groups, 13 deaths (1.3%) occurred in the placebo group and 12 deaths (1.2%) in the metoprolol CR/XL group.

Cause-specific combined endpoints
The combined endpoint of all-cause mortality or hospitalisation due to worsening heart failure (time to first event) was reduced by 30% in patients ≥65 years (p = 0.0002), and by 31% in patients below 65 years of age (p = 0.0008). In addition, there was also a reduction in the combined endpoint of cardiac death or non-fatal acute myocardial infarction in both age groups (Fig. 2).

Hospitalisations
Table 2 gives cause-specific data for number of patients hospitalised at least once and total number of hospitalisations in the two age groups. In patients ≥65 years there were 252 hospitalisations for worsening heart failure, and 127 hospitalisations for worsening heart failure and all-cause death.
failure in the placebo group vs. 161 hospitalisations in the metoprolol CR/XL group \( (p = 0.0006) \); in patients <65 years the corresponding figures were 199 and 156 \( (p = 0.004) \).

**Patients with severe heart failure (NYHA Class III/IV and EF <0.25)**

There were 425 patients \( \geq 65 \) years with severe heart failure in total (NYHA Class III/IV and EF <0.25; mean age 72 (4.1) years; mean ejection fraction 0.18 (0.04)) of whom 210 were randomised to placebo and 215 to metoprolol CR/XL. The risk for all-cause mortality or hospitalisation due to worsening heart failure in the placebo groups increased from 20.1% in all patients below 65 years of age to 48.5% in patients with severe heart failure \( \geq 65 \) years at randomisation, see Fig. 3.

In those \( \geq 65 \) years 48 deaths totally occurred on placebo and 32 deaths on metoprolol CR/XL (36% reduction; \( p = 0.051 \), Fig. 3); corresponding figures for those <65 years were 24 deaths vs. 13 deaths (47% reduction; \( p = 0.065 \)). The combined endpoint of all-cause mortality or hospitalisation due to worsening heart failure was reduced by 40% in those \( \geq 65 \) years \( (p = 0.031) \),
and by 49% in patients below 65 years of age ($p = 0.0011$).

**Patients aged 75 years or older**

There were 490 patients $\geq 75$ years of age in total (mean age 77 years (1.5); mean ejection fraction 0.27 (0.07)) of whom 247 were randomised to placebo and 243 to metoprolol CR/XL. Of these, 34 patients died in the placebo group and 24 in the metoprolol CR/XL group (relative risk 0.71; 95% CI 0.42–1.19); corresponding data for sudden death was 17 vs. 8 deaths (0.47; 0.20–1.10), and for death from heart failure 12 vs. 9 deaths (0.75; 0.32–1.77); for the combined endpoint of all-cause mortality or hospitalisation for worsening heart failure 67 vs. 53 patients (0.79; 95% CI 0.55–1.14). There were a total of 188 hospitalisations (all-cause) in the placebo group and 149 in the $\beta$-blocker group; corresponding figures for hospitalisation for worsening heart failure were 70 vs. 55 hospitalisations.

**Dose of study medicine, heart rate and blood pressure**

The mean daily dose of metoprolol CR/XL in patients $\geq 65$ years was 146 mg (81% $\geq 100$ mg, 54% on
200 mg) compared to 168 mg (90% ≥ 100 mg, 71% on 200 mg) in those below 65 years (p < 0.0001; corresponding placebo 172 vs. 178 mg). The corresponding doses of metoprolol CR/XL in those with severe heart failure (NYHA III/IV and EF < 0.25) were 140 mg (78% ≥ 100 mg, 50% on 200 mg) and 157 mg (84% ≥ 100 mg, 63% on 200 mg) in the two age groups, respectively (p < 0.0001; corresponding placebo 155 vs. 167 mg).

The mean metoprolol CR/XL dose in patients aged ≥ 75 years was 140 mg (76% ≥ 100 mg, 50% on 200 mg) once daily (164 mg on placebo).

The net decrease in heart rate with metoprolol CR/XL was comparable in the two age groups (10.7 bpm ≥ 65 years vs. 11.1 bpm < 65 at last follow-up visit). For patients receiving metoprolol CR/XL a net increase in systolic blood pressure of 2.1 mmHg (compared to placebo; p = 0.006) was recorded in the group ≥ 65 years of age, compared to +1.0 mmHg in those < 65 years (p = ns).

Safety and tolerability

Mortality and hospitalisations during up-titration of β-blockade

During the up-titration phase of the study until the 8 week visit 14 deaths and 112 hospitalisations occurred in the placebo group of patients ≥ 65 years, and 16 deaths and 90 hospitalisations in the group receiving metoprolol CR/XL. Corresponding figures in the subgroup of patients ≥ 65 years with advanced heart failure (NYHA III/IV and EF < 0.25) were 6 vs. 5 deaths and 32 vs. 27 hospitalisations; and in those ≥ 75 years 3 vs. 4 deaths and 31 vs. 24 hospitalisations.

Discontinuation of study medicine

The yearly discontinuation rate of study medicine (all-cause) by age and severity of heart failure is presented in Fig. 4. Overall, the proportion of patients who discontinued study medication was lower in the metoprolol CR/XL group compared to those on placebo regardless of patients’ age and severity of heart failure. Interestingly, the yearly discontinuation rate in the placebo group was doubled in patients ≥ 65 years of age with severe heart failure (NYHA III/IV and EF < 0.25) compared to all patients on placebo below 65 years (26.6% vs. 14.1%). In patients aged ≥ 75 years there were 52 discontinuations (all-cause) in the placebo group and 49 in the β-blocker group, and 10 vs. 9 patients discontinued because of worsening heart failure.

Table 3 presents the most commonly reported adverse events leading to discontinuation of study medicine in patients ≥ 65 years. More patients were withdrawn because of worsening heart failure, angina pectoris, and myocardial infarction in the placebo compared to the metoprolol CR/XL group. Adverse events like AV-block, depression, bronchospasm and aggravation of chronic obstructive pulmonary disease were remarkably similar on metoprolol CR/XL and placebo. Slightly more patients in the β-blocker group discontinued because of
bradycardia, hypotension, dizziness, fatigue and dyspnea. However, compared to placebo the net difference in discontinuation for any of these reasons was less than one patient per 100 treated during one year.

Discussion

The results of this analysis of MERIT-HF show that metoprolol CR/XL improved survival, reduced hospitalisations due to worsening heart failure, and was well tolerated and safe in elderly patients with chronic symptomatic systolic heart failure. Similar results on risk reductions and for tolerability and safety were observed for elderly patients with advanced heart failure, and for patients above the age of 75 years compared to all patients randomised.

Age-related changes in patients with heart failure

There is a series of age-related changes in the activity of the sympathetic nervous system, including an increase in plasma norepinephrine and in muscle sympathetic nerve activity, a decrease in chronotropic and inotropic responses to catecholamines, and a decrease in myocardial β-adrenergic receptor density. Furthermore, certain changes that occur with aging may alter the pharmacokinetics and pharmacodynamics of β-blockers in the elderly, with profound decreases in cardiac β-receptor responsiveness, decreased baro-receptor activity, and decreased hepatic and renal clearance. Thus the finding from this analysis of MERIT-HF that treatment with metoprolol CR/XL was safe, well tolerated and beneficial in elderly patients with heart failure due to LV systolic dysfunction is of paramount importance.

Complications of heart failure in the elderly and response to β-blockade

Cause-specific mortality

The risk of dying from heart failure increases steeply with age, which is also clearly illustrated in the figures from MERIT-HF. The risk of dying from heart failure was nearly four times higher in patients over the age of 65 years as compared with those below the age of 65 (see Fig. 1, lower panel, placebo group). It is noteworthy that treatment with metoprolol CR/XL almost completely abolished this increased risk of dying from heart failure in the elderly patients.

Regardless of age however, sudden death is the most common mode of death, occurring nearly twice as often as death from progressive heart failure in patients above the age of 65 years. It is noteworthy that the protective effect of the β-blocker on sudden death extended to those older than 65 years, as evident by a 43% reduction in sudden death in patients older than 65 years receiving metoprolol CR/XL.

Hospitalisations

The higher burden of heart failure in patients older than 65 years compared to those younger than 65 is also manifested by a 30% higher rate of hospitalisations for worsening heart failure in the elderly (placebo group), with multiple hospitalisations for worsening heart failure occurring more often in patients over 65 years compared to patients below 65 years. Not only did patients older than 65 years experience a significant reduction in

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo</th>
<th>Metoprolol CR/XL</th>
<th>Net Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Heart failure</td>
<td>62</td>
<td>7.2</td>
<td>41</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>12</td>
<td>1.4</td>
<td>6</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>11</td>
<td>1.3</td>
<td>6</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>6</td>
<td>0.7</td>
<td>10</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4</td>
<td>0.5</td>
<td>10</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>0.6</td>
<td>8</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>10</td>
<td>1.2</td>
<td>2</td>
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<tr>
<td>Dizziness</td>
<td>3</td>
<td>0.3</td>
<td>7</td>
</tr>
<tr>
<td>AV-block</td>
<td>5</td>
<td>0.6</td>
<td>4</td>
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<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td>8</td>
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<tr>
<td>Depression</td>
<td>3</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>2</td>
<td>0.2</td>
<td>2</td>
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<tr>
<td>COPD</td>
<td>2</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>All patients with any AE</td>
<td>132</td>
<td>15.3</td>
<td>121</td>
</tr>
</tbody>
</table>

*Bolded entries indicate significant changes.*

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Table 3: Tabulation of cause-specific adverse events leading to withdrawal of study medicine in the two randomization groups >65 years of age. Adverse events listed according to total number reported in the two randomization groups combined. Net difference (metoprolol CR/XL-placebo) refers to number (No.) of patients for 100 treated for the first year of treatment (% per first year)^

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*a*860 vs 890 patient years of follow-up until withdrawal of study medicine due to any adverse event or death in the placebo and metoprolol CR/XL group, respectively.

*b*One patient may have more than one reason for withdrawal.

*c*Refers to adverse events leading to withdrawal of study medicine.
### Table 4 Number of clinical events for cause-specific mortality, and combined endpoints in the two age groups*  

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>&lt;65 years</th>
<th>Metoprolol CR/XL</th>
<th>Risk reduction (95% CI)</th>
<th>p-value</th>
<th>&gt;65 years</th>
<th>Metoprolol CR/XL</th>
<th>Risk reduction (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause-specific mortality</strong></td>
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<td>Total</td>
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<td>Cardiovascular (CV)</td>
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<tr>
<td>Sudden death</td>
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<tr>
<td>Worsening heart failure</td>
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<td><strong>Combined endpoints</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality/all-cause hospitalisation</td>
<td>342 (40.1)</td>
<td>265 (80.2)</td>
<td>24 (11–35)</td>
<td>0.0007</td>
<td>425 (57.0)</td>
<td>376 (48.6)</td>
<td>14 (1–25)</td>
<td>0.03</td>
</tr>
<tr>
<td>All-cause mortality/hosp. due to worsening heart failure</td>
<td>193 (20.1)</td>
<td>134 (13.8)</td>
<td>31 (14–45)</td>
<td>0.0008</td>
<td>246 (28.0)</td>
<td>177 (19.5)</td>
<td>30 (16–43)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cardiac death/non-fatal acute MI</td>
<td>88 (8.6)</td>
<td>57 (5.5)</td>
<td>35 (10–54)</td>
<td>0.0094</td>
<td>137 (14.6)</td>
<td>82 (8.5)</td>
<td>42 (23–56)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval; hosp., hospitalisation; MI, myocardial infarction.  
*Only the first endpoint that occurred in each patient counted.

### Table 5 Number of clinical events for cause-specific mortality, and combined endpoints in the two age groups with severe heart failure (NYHA III/IV and ejection fraction <0.25)  

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>&lt;65 years</th>
<th>Metoprolol CR/XL</th>
<th>Risk reduction (95% CI)</th>
<th>p-value</th>
<th>&gt;65 years</th>
<th>Metoprolol CR/XL</th>
<th>Risk reduction (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause-specific mortality</strong></td>
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<td>Total</td>
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<td>Cardiovascular (CV)</td>
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<tr>
<td>Sudden death</td>
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<tr>
<td>Worsening heart failure</td>
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<td></td>
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<tr>
<td><strong>Combined endpoints</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality/all-cause hospitalisation</td>
<td>81 (59.6)</td>
<td>59 (39.1)</td>
<td>35 (7–52)</td>
<td>0.018</td>
<td>122 (86.5)</td>
<td>96 (64.0)</td>
<td>26 (3–43)</td>
<td>0.029</td>
</tr>
<tr>
<td>All-cause mortality/hosp. due to worsening heart failure</td>
<td>61 (40.1)</td>
<td>35 (20.5)</td>
<td>49 (23–67)</td>
<td>0.0011</td>
<td>83 (48.5)</td>
<td>53 (29.0)</td>
<td>40 (16–58)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Cardiac death/non-fatal acute MI</td>
<td>25 (13.8)</td>
<td>13 (7.0)</td>
<td>49 (0–74)</td>
<td>0.047</td>
<td>49 (25.5)</td>
<td>28 (14.1)</td>
<td>45 (12–65)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

CI, confidence interval; EF, ejection fraction; hosp., hospitalisation; MI, myocardial infarction.  
*Only the first endpoint that occurred in each patient was counted.
hospitalisation for worsening heart failure with β-blockade, but the magnitude of reduction was at least as good as that seen in those below 65 years (36% in those ≥65 years vs. 22% in those <65 years, respectively).

Elderly patients with advanced heart failure

Although compared to the entire cohort of elderly patients in MERIT-HF the elderly cohort with severe heart failure was smaller, the subgroup analysis of the elderly with severe heart failure showed risk reductions similar to those observed for all patients randomised.

Patients older than 75 years

MERIT-HF randomised close to 500 patients above the age of 75 years. The findings in this subgroup echoed the overall results in regards both to the good tolerability and estimates for reduction in mortality and hospitalisations.

Societal benefits of treating elderly patients with heart failure

Age and severity of heart failure are important for absolute mortality risk as illustrated by the observation that in patients ≥65 years with advanced heart failure every second patient died or was hospitalised for worsening heart failure, during one year of follow-up, compared to only one out of five patients below 65 years. However, regardless of absolute risk, in MERIT-HF relative risk was reduced by a similar extent, i.e., by 40% in those ≥65 years and 31% in those <65 years (see Figs. 1 and 2).

Considering the high event rate in elderly patients, and the marked reduction in the rate of hospitalisation for worsening heart failure observed in this study, β-blockade given to older patients should result in significant cost savings and reductions in the health care expenditures for the care of elderly patients with heart failure.

Absolute risk is of importance when considering the numbers needed to treat to save one life or avoid one hospitalisation. Based on observations in MERIT-HF, the number needed to treat for one year to save one life was 19 patients for those ≥65 years of age compared to 40 patients for the group <65 years of age. For the subgroup with severe heart failure, even fewer patients needed to be treated for one year to save one life, in total 11 patients for those ≥65 years of age vs. 16 patients for those <65 years. It is however important to emphasise that patients in NYHA class II to III represent the greatest number of patients with heart failure. It is in this population where the addition of a β-blocker to existing therapy will exert its largest public health benefit.

Safety and tolerability

More patients over 65 years of age were withdrawn from β-blocker treatment compared to those below 65 years, however, a similar pattern was seen in the placebo group with more elderly patients withdrawn from treatment compared to those <65 years. Thus discontinuation does not necessarily reflect clinically important adverse events caused by β-blockade, the drug may have been well-tolerated in many patients in whom it was nevertheless discontinued. However, β-adrenergic receptor blockade may cause a transient decrease in EF in some patients, which could also increase the symptomology of heart failure.

Metoprolol CR/XL was also tolerated well as judged by fewer drug withdrawals in comparison with placebo regardless of age and severity of heart failure, and also as judged from number of deaths and hospitalisations occurring during the up-titration phase of the study. The good tolerability may be due to both the careful up-titration program used, and the relative stability of the patients enrolled in the study. Patients with decompensated heart failure (pulmonary oedema, hypo-perfusion or hypo-tension) were not randomised until stabilised. Adverse events like AV-block, depression, bronchospasm and aggravation of chronic obstructive pulmonary disease were remarkably similar on placebo and metoprolol CR/XL. Interestingly, we found that systolic blood pressure increased by a few mmHg on metoprolol CR/XL compared to placebo in the elderly group, which, one may speculate, can indicate improved LV function on β-blockade during long-term treatment.

Limitations

To learn more about the benefits of β-blockade, we have in this report from MERIT-HF presented a number of analyses from elderly patients with systolic heart failure including subgroups of those with advanced heart failure, and also a subgroup including those above the age of 75 years at randomisation. Multiple testing has been performed and results in subgroups should therefore focus on consistency and 95% confidence intervals, rather than on p-values. We should expect some variation of the treatment effect around the overall estimate as we examine a large number of subgroups, due to smaller sample size in subgroups and due to chance. Thus, the best estimate of the treatment effect on total mortality and other clinical events for any subgroup is the estimate of the hazard ratio for the overall trial.

Conclusion

In conclusion the results of this analysis of MERIT-HF demonstrated that β-blockade with metoprolol CR/XL was safe and well tolerated in elderly patients with chronic symptomatic systolic heart failure. While physicians tend to be very cautious in these patients, the data suggest that these are the patients in whom treatment will have the greatest impact as seen by number of lives saved and number of hospitalisations avoided. An Editorial that accompanied the original publication of the MERIT-HF data concluded “it would be difficult to make an argument that β-blockers should be withheld from any patient meeting the general criteria for entry into clinical trials”. The results of the present analysis of the
large group of elderly patients included in MERIT-HF underlines the importance of this statement. It is time to overcome the barriers that physicians perceive to β-blocker treatment, and to provide it to the large number of elderly patients with heart failure in need of this therapy, this should both improve their quality and length of life.20

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References