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Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis

Dipak Kotecha,1,2 Luis Manzano,3 Henry Krum,2 Giuseppe Rosano,4,5 Jane Holmes,6 Douglas G Altman,6 Peter D Collins,7 Milton Packer,8 John Wikstrand,9 Andrew J S Coats,10,11 John G F Cleland,7 Paulus Kirchhof,1 Thomas G von Lueder,12 Alan S Rigby,13 Bert Andersson,9 Gregory YH Lip,1 Dirk J van Veldhuisen,14 Marcelo C Shibata,15 Hans Wedel,16 Michael Böhm,17 Marcus D Flather18 on behalf of the Beta-Blockers in Heart Failure Collaborative Group

ABSTRACT
OBJECTIVES
To determine the efficacy and tolerability of β blockers in a broad age range of women and men with heart failure with reduced ejection fraction (HFrEF) by pooling individual patient data from placebo controlled randomised trials.

DESIGN
Prospectively designed meta-analysis of individual patient data from patients aged 40-85 in sinus rhythm at baseline, with left ventricular ejection fraction <0.45.

PARTICIPANTS
13 833 patients from 11 trials; median age 64; 24% women.

MAIN OUTCOME MEASURES
The primary outcome was all cause mortality; the major secondary outcome was admission to hospital for heart failure. Analysis was by intention to treat with an adjusted one stage Cox proportional hazards model.

RESULTS
Compared with placebo, β blockers were effective in reducing mortality across all ages; hazard ratios were 0.66 (95% confidence interval 0.53 to 0.83) for the first quarter of age distribution (median age 50); 0.71 (0.58 to 0.87) for the second quarter (median age 60); 0.65 (0.53 to 0.78) for the third quarter (median age 68); and 0.77 (0.64 to 0.92) for the fourth quarter (median age 75). There was no significant interaction when age was modelled continuously (P=0.1), and the absolute reduction in mortality was 4.3% over a median follow-up of 1.3 years (number needed to treat 23). Admission to hospital for heart failure was significantly reduced by β blockers, although this effect was attenuated at older ages (interaction P=0.05). There was no evidence of an interaction between treatment effect and sex in any age group. Drug discontinuation was similar regardless of treatment allocation, age, or sex (14.4% in those given β blockers, 15.6% in those receiving placebo).

CONCLUSION
Irrespective of age or sex, patients with HFrEF in sinus rhythm should receive β blockers to reduce the risk of death and admission to hospital.

REGISTRATION
PROSPERO CRD42014010012; Clinicaltrials.gov NCT00832442.

Introduction
β blockers reduce morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction and are a cornerstone of modern evidence based treatment. Current heart failure guidelines do not differentiate treatment on the basis of age or sex, although initiation and maintenance of treatment is suboptimal both in older people and women.1-3 With increasing age, patients are more likely to be women (with less marked reduction in left ventricular ejection fraction). This interaction, along with relatively low numbers of older patients in randomised controlled trials, has created uncertainty about the optimum management of elderly patients with heart failure and reduced ejection fraction (HFrEF), both in women and men. Moreover, there are theoretical concerns about altered pharmacokinetics in older people that might affect the dose required or the tolerability of treatment.4 5 Although subgroup data and the results from SENIORS (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure) suggest that the efficacy of β blockers is retained in older patients,6-8 low uptake and poor maintenance of treatment continue to be a clinical reality.

The Beta-blockers in Heart Failure Collaborative Group was set up to combine individual patient data from major randomised controlled trials in heart failure and provide clear direction on clinically relevant subsets of patients in which there is uncertainty about the balance of safety and efficacy of β blockers.9 10 Meta-analysis of individual patient data allows more robust examination of treatment effects in subgroups and enables of time to event analyses adjusted for baseline covariates, making it ideal for the appropriate pooling of original data.11 We have
previously shown that morbidity and mortality are not improved by β blockers in patients with HFrEF and concomitant atrial fibrillation, in contrast with patients in sinus rhythm, who had substantial reductions in admission to hospital and all cause mortality.12

In this analysis, we explored the interactions of β blocker efficacy and tolerability with age and sex, using the largest and most robust dataset of pooled data from randomised trials. Our aim was to inform clinicians on the appropriate use of these important therapeutic agents for patients with HFrEF in sinus rhythm.

Methods

The Beta-blockers in Heart Failure Collaborative Group (BB-meta-HF) is a multinational effort, combining individual data from the major randomised controlled trials investigating the use of β blockers in heart failure. The group consists of the leading investigators of these trials and international experts, with the support of the four pharmaceutical companies that conducted the original trials (Astra Zeneca, GlaxoSmithKline, Merck Serono, and Menarini). This report was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses of individual participant data (PRISMA-IPD) guidelines31 and prospectively registered with Clinicaltrials.gov (NCT00832444) and the PROSPERO database of systematic reviews (CRD42014010012).30 Detailed rationale and methods have previously been published.9,12

Eligibility, search strategy, and data collection

Published or unpublished randomised controlled trials were identified through computer aided searches (for example, Medline and Current Contents), scrutiny of reference lists of trials, trials registries, meeting abstracts, and review articles as well as discussion with group members and pharmaceutical manufacturers. We included randomised controlled trials that reported mortality as a primary outcome or part of a composite outcome comparing β blockers versus placebo. Only unconfounded head to head trials were eligible, with recruitment of over 300 patients and planned follow-up of more than six months to make the project technically feasible and clinically relevant. The search results, individual study demographics and a standardised data request form to obtain individual patient data from each trial have been published.9

The 11 included studies account for 95.7% of eligible participants recruited in randomised controlled trials based on a systematic literature review: the Australia/New Zealand Heart Failure Study (ANZ),14 the Beta-Blocker Evaluation Survival Trial (BEST),15 the Carvedilol Post-Infarct Survival Control in LV Dysfunction Study (CAPRICORN),16 the Carvedilol Hibernating Reversible Ischaemia Trial: Marker of Success Study (CHRISTMAS),17 the Cardiac Insufficiency Bisoprolol Study (CIBIS I),18 the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II),19 the Carvedilol Prospective Randomised Cumulative Survival Study (COPERNICUS),20 the Metoprolol in Idiopathic Dilated Cardiomyopathy Study (MDC),21 the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF),22,23 the SENIORS Study,24 and the US Carvedilol Heart Failure Study (US-HF).25 All included studies had low overall risk of bias, as determined with the Cochrane Collaboration’s risk of bias tool.25

Patient involvement

We have insufficient evidence to comment on whether patients were actively involved in the design or management of these 11 trials.

Outcomes

We extracted data from original source files, and additional follow-up mortality outcomes were available in seven studies.8,14-16,20,25,26 Our primary outcome was all cause mortality, including all reported deaths from each component study. Major secondary outcomes were all cause mortality during the trial period, all reported cardiovascular deaths, admission to hospital for heart failure, cardiovascular admission to hospital, fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, and composites of mortality and hospital admission. One smaller study (1.4% of patients) did not provide data on hospital admission or other adverse clinical events,21 though all studies contributed to the primary outcome (fig 1). Safety outcomes focused on discontinuation of study drug treatment because of adverse events (hypotension, bradycardia, exacerbation of heart failure, renal impairment, and respiratory dysfunction). We defined tolerability as the dose achieved as a percentage of maximum target dose, according to the particular β blocker and specific trial design.

Population

Individual patient data were available for 18 637 patients. For this analysis, restriction to patients with HFrEF was prespecified as a left ventricular ejection fraction cut off of <0.45, chosen to reflect the era in
which these trials were undertaken, and the cardiac imaging distinction that separates patients with moderate and severe left ventricular dysfunction from those with mild or “intermediate” reduction in left ventricular ejection fraction. In light of our previous findings regarding the lack of prognostic benefit of β blockers in patients with atrial fibrillation, we evaluated only those in sinus rhythm at baseline. To improve the robustness of the age analysis across the combined dataset, we also excluded the 4% of patients at the extremes of age (outside the age range of 40–85). One patient in the placebo arm was recorded as alive during study visits but had a missing final follow-up date and was excluded from analysis. Age was primarily assessed as a continuous variable, with prespecified division into quarters. Sex was explored as a secondary interaction variable across the age quarters of the age distribution.

Statistical analysis
Data are presented as percentages or medians and interquartile range (IQR; displayed as 25th-75th centiles). Estimated glomerular filtration rate was calculated with the modification of diet in renal disease (MDRD) formula, normalised to a body surface area of 1.73 m². All analyses followed the principle of intention to treat. Outcomes were analysed with a stratified Cox proportional hazards regression model. This is a one stage fixed effects approach and assumes that all trials are estimating a common treatment effect with baseline hazards that vary across studies. Hazard ratios and 95% confidence intervals are presented, along with corresponding P values. We prespecified adjustment in Cox models for age, sex, previous myocardial infarct, and baseline NYHA (New York Heart Association) class (II/III v IV), left ventricular ejection fraction, heart rate, systolic blood pressure, diuretic therapy, and angiotensin converting enzyme inhibitors (ACEi) or β blockers compared with placebo across the age range of age, modelled as a continuous variable. No statistical interaction with age was identified (P=0.1 for interaction). Table 2 displays the hazard ratio and figure 3 the Kaplan-Meier plots for each age quarter, confirming efficacy for the primary outcome in all quarters, including the oldest patients. Similar absolute risk reductions with β blockers were noted in all age quarters (table D in appendix). β blockers were effective in both women and men, in the whole group, and within specific age quarters (table 2 and fig 4). All sensitivity analysis for the primary outcome identified similar results to the main statistical model (table E in appendix).

Secondary outcomes
There was attenuation of the benefits of β blockers on cardiovascular death by age (P=0.04 for interaction) but there remained a significant reduction in events even in the oldest age group (table 3). Similar findings were seen with hospital admission for heart failure (fig 3 and table D in appendix), cardiovascular hospital admission and composite clinical outcomes. Fatal and non-fatal myocardial infarct or stroke were not reduced with β blockers in the whole group nor in any age quartile (table 2). For all of the secondary outcomes, the effect in women and men were similar, with no interaction identified according to gender (table 2 and fig 4).
Table 1 | Baseline characteristics* in patients with heart failure with reduced ejection fraction and sinus rhythm by quarter of age distribution. Figures are number (percentage) unless stated otherwise

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quarter 1 (youngest) (n=3458)</th>
<th>Quarter 2 (n=3590)</th>
<th>Quarter 3 (n=3327)</th>
<th>Quarter 4 (oldest) (n=3458)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) age (years)</td>
<td>50 (46-53)</td>
<td>60 (58-62)</td>
<td>68 (66-70)</td>
<td>75 (73-78)</td>
</tr>
<tr>
<td>Women</td>
<td>639 (18%)</td>
<td>764 (21%)</td>
<td>794 (24%)</td>
<td>1086 (31%)</td>
</tr>
<tr>
<td>Ischaemic heart failure aetiology</td>
<td>1856 (54%)</td>
<td>2478 (69%)</td>
<td>2544 (76%)</td>
<td>2798 (81%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>1648 (48%)</td>
<td>2158 (60%)</td>
<td>2190 (66%)</td>
<td>2287 (66%)</td>
</tr>
<tr>
<td>Previous coronary revascularization</td>
<td>592 (18%)</td>
<td>892 (27%)</td>
<td>833 (27%)</td>
<td>897 (26%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>681 (21%)</td>
<td>892 (27%)</td>
<td>833 (27%)</td>
<td>897 (26%)</td>
</tr>
<tr>
<td>Median (IQR) years with heart failure diagnosis</td>
<td>2 (1-5)</td>
<td>3 (1-6)</td>
<td>3 (1-7)</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td>Median (IQR) LVEF</td>
<td>0.25 (0.20-0.32)</td>
<td>0.26 (0.20-0.32)</td>
<td>0.27 (0.21-0.32)</td>
<td>0.29 (0.22-0.34)</td>
</tr>
<tr>
<td>Median (IQR) systolic BP (mm Hg)</td>
<td>120 (110-130)</td>
<td>120 (110-136)</td>
<td>126 (113-140)</td>
<td>130 (115-142)</td>
</tr>
<tr>
<td>Median (IQR) diastolic BP (mm Hg)</td>
<td>78 (70-84)</td>
<td>78 (70-83)</td>
<td>77 (70-80)</td>
<td>75 (69-80)</td>
</tr>
<tr>
<td>Median (IQR) heart rate (bpm)</td>
<td>82 (74-91)</td>
<td>80 (72-88)</td>
<td>78 (72-86)</td>
<td>77 (70-85)</td>
</tr>
<tr>
<td>Median (IQR) BMI</td>
<td>2359 (68%)</td>
<td>2440 (68%)</td>
<td>2285 (69%)</td>
<td>2081 (61%)</td>
</tr>
<tr>
<td>Median (IQR) LVEF</td>
<td>0.25 (0.20-0.32)</td>
<td>0.26 (0.20-0.32)</td>
<td>0.27 (0.21-0.32)</td>
<td>0.29 (0.22-0.34)</td>
</tr>
<tr>
<td>ACEi or ARB</td>
<td>3332 (96%)</td>
<td>3410 (95%)</td>
<td>3154 (95%)</td>
<td>3207 (93%)</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>255 (8%)</td>
<td>209 (6%)</td>
<td>256 (8%)</td>
<td>369 (11%)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>2090 (62%)</td>
<td>1956 (56%)</td>
<td>1652 (51%)</td>
<td>1504 (44%)</td>
</tr>
</tbody>
</table>

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BP=blood pressure; BMI=body mass index; GFR=glomerular filtration rate; IQR=interquartile range; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association functional class.

*Missing data (total across all quarters): previous myocardial infarction n=348.

Fig 2 | β blockers versus placebo hazard model for all cause mortality and age. Hazard ratio for β blockers compared with placebo in HFrEF patients with sinus rhythm. Age modelled as continuous variable, with results for each quarter superimposed

Table 3 provides date on hospital admissions related to cardiovascular, events, all causes, and heart failure, divided by quarters of the age distribution and sex. Admission rates increased with age and were similar in both sexes. In the oldest quarter of age, patients had more than one admission per year, with half of these admissions because of heart failure, and a median length of stay of seven days in hospital.

Tolerability of therapy

There were similar rates of discontinuation because of adverse events in the placebo and β blocker arms across quarters of the age distribution and sex, although these increased slightly with age (table 4). Overall, a numerically lower number of patients discontinued β blockers (14.4% v 15.6% in placebo). Table F in the appendix shows specific causes of β blocker discontinuation according to age and sex. Small numbers of patients discontinued treatment because of hypotension (0.7-1.6%), bradycardia (0-3.5%), exacerbation of heart failure (2.0-4.9%), renal impairment (0-1.2%), and respiratory compromise (0.5-1.2%). Discontinuation was similar across age and sex, apart from a small excess in exacerbation of heart failure in the youngest age quarter for women compared with men (5.4% v 2.2%) and in bradycardia in the oldest men (3.5% v 0.7% in the oldest women). Dose of β blocker did not differ across age and sex, with patients attaining 73% of the target dose at the interim study point (table G in appendix) compared with 84% achieving the corresponding dose of placebo.

Discussion

Principal findings

Using the near totality of available data from randomised controlled trials of β blockers in patients with heart failure with reduced ejection fraction (HFrEF) and sinus rhythm, our analysis shows that there is no evidence of a clinically significant interaction with age or sex with respect to all cause mortality. We observed a significant benefit from β blockers in each quarter of the age distribution, with absolute reductions in mortality of about 4% in the youngest and oldest patients. Results for hospital admission related to heart failure were similar, with significant reductions in each age quarter, albeit with minor attenuation of treatment effect in older patients. Discontinuation of treatment was similar in patients randomised to β blockers or placebo, even in older patients, suggesting that “intolerance” of β blockers in clinical practice could reflect false attribution to intercurrent events or preconceptions about side effects.
### Hazard ratios for primary and secondary outcomes in patients with heart failure with reduced ejection fraction and sinus rhythm by quarter of age distribution*

<table>
<thead>
<tr>
<th>Quarter</th>
<th>HR (95% CI)</th>
<th>P value for age (continuous)</th>
<th>Quarter 1 interaction P value‡</th>
<th>Quarter 2 P value‡</th>
<th>Quarter 3 P value‡</th>
<th>Quarter 4 (oldest) P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>β blockers placebo/outcome†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause mortality (primary outcome)</td>
<td>0.10</td>
<td>0.66 (0.53 to 0.83)</td>
<td>0.70</td>
<td>0.71 (0.58 to 0.87)</td>
<td>0.66</td>
<td>0.65 (0.53 to 0.78)</td>
</tr>
<tr>
<td>All cause mortality (during study period only)</td>
<td>0.08</td>
<td>0.62 (0.48 to 0.78)</td>
<td>0.74</td>
<td>0.72 (0.58 to 0.88)</td>
<td>0.80</td>
<td>0.64 (0.52 to 0.78)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>0.04</td>
<td>0.66 (0.52 to 0.84)</td>
<td>0.46</td>
<td>0.70 (0.56 to 0.87)</td>
<td>0.57</td>
<td>0.59 (0.47 to 0.73)</td>
</tr>
<tr>
<td>First admission related to heart failure</td>
<td>0.05</td>
<td>0.59 (0.4 to 0.74)</td>
<td>0.64</td>
<td>0.65 (0.54 to 0.78)</td>
<td>0.54</td>
<td>0.68 (0.56) to 0.83)</td>
</tr>
<tr>
<td>First admission related to CV event</td>
<td>0.04</td>
<td>0.65 (0.55 to 0.77)</td>
<td>0.38</td>
<td>0.78 (0.68 to 0.89)</td>
<td>0.46</td>
<td>0.77 (0.64 to 0.92)</td>
</tr>
<tr>
<td>Cardiovascular death or admission for heart failure</td>
<td>0.03</td>
<td>0.66 (0.56 to 0.77)</td>
<td>0.79</td>
<td>0.78 (0.68 to 0.89)</td>
<td>0.52</td>
<td>0.72 (0.62) to 0.83)</td>
</tr>
<tr>
<td>Fatal and non-fatal MI</td>
<td>0.10</td>
<td>0.66 (0.39 to 1.09)</td>
<td>0.16</td>
<td>0.64 (0.43 to 0.98)</td>
<td>0.46</td>
<td>0.73 (0.46 to 1.14)</td>
</tr>
<tr>
<td>Fatal and non-fatal stroke</td>
<td>0.55</td>
<td>0.73 (0.34 to 1.56)</td>
<td>0.66</td>
<td>1.21 (0.65 to 2.25)</td>
<td>0.62</td>
<td>1.00 (0.55 to 1.84)</td>
</tr>
</tbody>
</table>

**Clinical context: age**

Heart failure guidelines recommend β blockers for patients with HFrEF but have not previously been able to exclude an interaction with age. As a result, prescription of treatment and long term continuation have been lower in older patients, presumably as clinicians trade off a perceived lower efficacy with other considerations such as potential adverse events and polypharmacy. The proportion of patients in our analysis aged >70 was 30%, which does not reflect the “real world” population of HFrEF. In the three largest US heart failure registries (ADHERE, OPTIMIZE-HF, and Get With The Guidelines), the average age of patients with HFrEF was 70 (SD 14 and 14 and IQR 58-80, respectively; total 101 066 patients). Similarly, in the Swedish Heart Failure Registry of 21 864 patients with HFrEF, the mean age was 72 (SD 12). This confirms that older patients are under-represented in randomised controlled trials in heart failure, necessitating the pooling of data to provide information on treatment efficacy. In this context, individual patient data provide the only robust method to adequately combine subgroup data.

There are important demographic changes noted with advancing age. Compared with the youngest quarter, older patients were more often women (31% v 18%) and had more ischaemic aetiology (81% v 54%), higher left ventricular ejection fraction (0.29 v 0.25), higher systolic blood pressure (130 mm Hg v 20 mm Hg), lower heart rate (77 v 82 beats/min), and reduced kidney function (55 v 73 mL/min) and fewer received digoxin (44% v 62%). These factors are known to affect prognosis in heart failure in different ways. Age is the most powerful predictor of prognosis but is not itself a predictor of response to treatment. The higher systolic blood pressure, higher left ventricular ejection fraction, and lower heart rate observed in older patients are predictors of better prognosis, while chronic renal impairment is associated with poor prognosis. The median length of heart failure before the trial was two years in the lowest age quarter and three years in the other age quarters, suggesting that patients were entered into the trials at a similar time after initial diagnosis, irrespective of age. Type of death also differed between age groups. Half of deaths in the youngest quarter are classified as “sudden” compared with 34% in the oldest quarter, whereas deaths from heart failure accounted for 16% compared with 31%, respectively. Thus the heterogeneity in age in the trials also reflects heterogeneity in aetiology of heart failure and comorbidity patterns. The results of this individual patient data meta-analysis, showing the clear benefit of β blockers across all age groups despite this heterogeneity, is an important finding that cannot be predicted by analysis of patient characteristics and outcomes in observational datasets or mechanistic studies. Our assessment confirms that irrespective of different patient factors associated with age, patients in sinus rhythm benefit from treatment with a β blocker, a novel and important finding that informs clinical practice and underpins the applicability of current clinical guidelines.

In general, the effect of β blockers was consistent on the major secondary outcomes analysed. We did identify...
Fig 3 | Kaplan-Meier event curves according to quarter of age distribution for primary outcome (all cause mortality) and major secondary outcome (admission for heart failure) for β blockers v placebo by age. ARR=absolute risk reduction; NNT=number needed to treat.
Table 3 | Admission to hospital in patients with heart failure with reduced ejection fraction and sinus rhythm by quarter of age distribution

<table>
<thead>
<tr>
<th>Admission type</th>
<th>Quarter 1 (youngest)</th>
<th>Quarter 2</th>
<th>Quarter 3</th>
<th>Quarter 4 (oldest)</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td><strong>All cause</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with ≥1 admission</td>
<td>39%</td>
<td>31%</td>
<td>35%</td>
<td>36%</td>
<td>39%</td>
</tr>
<tr>
<td>Average No (range) of admissions</td>
<td>0.94 (0-18)</td>
<td>0.67 (0-18)</td>
<td>0.78 (0-14)</td>
<td>0.76 (0-22)</td>
<td>0.79 (0-11)</td>
</tr>
<tr>
<td>Annualised rate/patient</td>
<td>0.67</td>
<td>0.69</td>
<td>0.85</td>
<td>0.81</td>
<td>0.87</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with ≥1 admission</td>
<td>25%</td>
<td>20%</td>
<td>23%</td>
<td>25%</td>
<td>27%</td>
</tr>
<tr>
<td>Average No (range) of admissions</td>
<td>0.48 (0-13)</td>
<td>0.38 (0-14)</td>
<td>0.44 (0-13)</td>
<td>0.46 (0-22)</td>
<td>0.47 (0-10)</td>
</tr>
<tr>
<td>Annualised rate/patient</td>
<td>0.36</td>
<td>0.38</td>
<td>0.47</td>
<td>0.45</td>
<td>0.50</td>
</tr>
<tr>
<td>Average (IQR) length of stay (days)*</td>
<td>6 (3-9)</td>
<td>6 (3-10)</td>
<td>6 (3-9)</td>
<td>6 (3-12)</td>
<td>7 (3-11)</td>
</tr>
<tr>
<td><strong>Related to heart failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with ≥1 admission</td>
<td>19%</td>
<td>13%</td>
<td>16%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Average No (range) of admissions</td>
<td>0.16 (0-7)</td>
<td>0.25 (0-12)</td>
<td>0.32 (0-13)</td>
<td>0.31 (0-14)</td>
<td>0.29 (0-10)</td>
</tr>
<tr>
<td>Annualised rate/patient</td>
<td>0.24</td>
<td>0.27</td>
<td>0.32</td>
<td>0.30</td>
<td>0.33</td>
</tr>
<tr>
<td>Average (IQR) length of stay (days)*</td>
<td>6 (3-10)</td>
<td>6 (4-11)</td>
<td>7 (4-10)</td>
<td>7 (4-13)</td>
<td>7 (4-12)</td>
</tr>
</tbody>
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*Based on first five hospital admissions for cardiovascular/heart failure cause. MDC trial does not contribute to admission outcomes.
example, in the recent large randomised controlled trial of angiotensin-neprilysin inhibition versus enalapril in HFrEF, women accounted for only 22% of the patients recruited. There is a clear need to improve the enrolment of women to provide realistic expectations of their risk and benefit from treatment.

Side effects and tolerability

Importantly for all ages and both sexes, we identified low rates of discontinuation of β blockers because of adverse events and similar withdrawal rates to placebo. Although β blockers are often associated with side effects, data from randomised trials consistently show no true difference compared with placebo in dizziness, diarrhoea, increased blood sugar concentration, or depression and little or no increase in lethargy with modern generation β blockers. This information should reassure clinicians about the tolerability of β blockers in view of the prognostic benefit we have identified in women and elderly people of both sexes. Elderly patients were able to reach similar maximal dose compared with younger patients with HFrEF.

Strengths and limitations of study

It is plausible that the benefits of β blockers are attenuated in very old people (aged >80), although the amount of information on these patients from existing randomised controlled trials is scarce. Extrapolation from figure 2 indicates that any attenuation of prognostic benefit with age is actually quite mild and the effect of β blockers in patients aged >80 will still be associated with hazard ratios of around 0.8 (giving a worthwhile 20% proportional reduction in the average risk of death). In the extreme elderly, it is worth noting that there are competing mortality risks. Even with pooling of individual patient data from all large datasets, there are limitations to inference of treatment effects in subgroups. Examination of treatment interactions by age shows significant treatment benefits in each age group, but assessment of interactions of age and sex will be limited by the size of the groups, number of events, and inclusion criteria for the component studies. For example, a lack of interaction might not provide full information on treatment effects in very elderly women because of the atypical elderly cohort included in the original trials. We specifically included only patients with HFrEF in sinus rhythm at baseline. Although sensitivity analyses including all patients showed a similar lack of interaction with age or sex, direct extrapolation to patients with left ventricular ejection fraction >0.45 cannot be made. Similarly, we have previously reported on outcomes for β blockers in patients with concomitant heart failure and atrial fibrillation, and, although these patients have poor prognosis, they are distinctly different to patients with heart failure in sinus rhythm and require specific management.

There have been changes in risk factor profiles and treatment patterns since the component studies were completed (for example, the use of cardiac resynchronisation treatment), however, β blockers are still a vital component of optimal care in these patients and might have a synergistic effect (for example, with mineralocorticoid receptor antagonists). Finally, as with all meta-analytical techniques, we are limited by the data provided from the individual studies, with the inherent heterogeneity of patient populations. The strength of our analysis was the use of individual patient data from high quality randomised controlled trials, with near totality of available data and methodical data extraction from original datasets, resulting in improved quality of outcome data across trials.

Conclusions and policy implications

This analysis confirms that treatment with β blockers reduces mortality and hospital admissions related to heart failure in patients with HFrEF with sinus rhythm, irrespective of age or sex. Absolute effect sizes for all cause mortality were similar across age quarters with no significant interaction when we used an adjusted continuous hazard model. In addition, the tolerability of β blockers was similar to placebo, reinforcing the use of β blockers in all patients with HFrEF in sinus rhythm and discouraging the practice of withholding such treatment in women or elderly patients.
Australia support (for full list, please see design paper), the steering We are indebted to the other members of the Beta-blockers in Heart 15Division of Cardiology, University of Alberta, Edmonton, Canada 14Department of Cardiology, University Medical Centre Groningen, 13Academic Cardiology, Castle Hill Hospital, Kingston upon Hull, UK 10Monash Warwick Alliance, Monash University, Melbourne, 8Baylor University Medical Center, Dallas, USA 7National Heart and Lung Institute, Imperial College, London, UK 6Centre for Statistics in Medicine, Nuffield Department of 5Division of Cardiology, University of Alberta, Edmonton, Canada 4Nordic School of Public Health, Gothenburg, Sweden 3Universitätsklinikum des Saarlandes, Homburg/Saar, Germany 2Norwich Medical School, University of East Anglia, Norwich, UK We are indebted to the other members of the Beta-blockers in Heart Failure Collaborative Group for database access and extraction support (for full list, please see design paper), the steering committees of the included trials (in particular representatives of the MERIT-HF trial), as well as the late Philip Poole-Wilson (National Heart and Lung Institute, Imperial College, London, UK). This project was possible only with the support of the pharmaceutical companies that have marketed β blockers in heart failure, and the group thanks AstraZeneca, GlaxoSmithKline, Menarini Farmaceutica, and Merck Serono for full access to trial data. We gratefully acknowledge incorporation of data from the BEST trial through the National Heart Lung and Blood Institute BioLINC programme. This work is dedicated to the memory of Henry Krum (1958–2015).

**Contributors.** DK participated in the design of the study, manages the collaborative group and performed data management, statistical analysis, and manuscript preparation. LM, HK, and MDF participated in the design and coordination of the study and manuscript preparation. JH and DGA independently performed the primary statistical analyses. All named authors read, revised and approved the final manuscript. DK is guarantor.

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**Competing Interests.** All authors have completed the ICJME uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: DK received grants from Menarini during the conduct of the study, and non-financial support from Daiichi Sankyo, outside the submitted work. PDC has received lecture fees from Menarini, outside the submitted work. MP has received personal fees from AstraZeneca, Amgen, BioControl, Boston Scientific, Cardiokinetics, Cardiorentis, Cardio3, Novartis, Pfizer, and Takeda, all outside the submitted work. JW has received grants and personal fees from AstraZeneca during the conduct of the MERIT-HF study. ASJC reports personal fees from Menarini during the conduct of the study but outside the submitted work. PK has received grants from British Heart Foundation, German Ministry of Education and Research, DZHK, Leducq Foundation, several industry partners and personal fees from several industry companies, outside the submitted work. TGN has received personal fees from Novartis and Vifor, outside the submitted work. BA has received grants and personal fees from AstraZeneca, during the conduct of the study, grants and personal fees from Servier, outside the submitted work. GWL has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Biotronik, Portola, and Boehringer Ingelheim and has been on the speakers’ bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi-Aventis, all outside the submitted work. HW has received personal fees from AstraZeneca during the conduct of the study. MB has received personal fees from Servier, Boehringer Ingelheim, Medtronic, Bayer, during the conduct of the study but outside the submitted work.

**Ethical approval** All original trials operated under supervision of an appropriate human ethics committee. The current analysis involves anonymised data only, hence ethics committee approval was deemed unnecessary by the National Research Ethics Service London.

**Data sharing** No additional data are available, though details on statistical analysis are available from the corresponding author on request.

**Transparency** The lead author (the manuscript’s guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

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Appendix: Supplementary tables A-G and fig A