Effect of age and sex on efficacy and tolerability of blockers in patients with heart failure with reduced ejection fraction

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Brief Title: Age, gender and beta-blockers in heart failure

Authors: Dipak Kotecha (Clinician Scientist in Cardiovascular Medicine)\(^1,2,3\), Luis Manzano (Professor of Internal Medicine)\(^4\), Henry Krum (late; Professor of Medicine)\(^2\), Giuseppe Rosano (Professor of Cardiology)\(^5\), Jane Holmes (Statistician)\(^6\), Douglas G Altman (Professor of Statistics in Medicine)\(^6\), Peter D Collins (Professor of Cardiology)\(^3,7\), Milton Packer (Professor of Cardiovascular Science)\(^8\), John Wikstrand (Professor of Clinical Physiology)\(^9\), Andrew J S Coats (Professor & Academic Vice-President)\(^10\), John G F Cleland (Professor of Clinical Cardiology)\(^7\), Paulus Kirchhof (Professor of Cardiovascular Medicine)\(^1\), Thomas G von Lueder (Consultant Cardiologist)\(^11\), Alan S Rigby (Reader; Statistician)\(^12\), Bert Andersson (Professor of Cardiology)\(^9\), Gregory YH Lip (Professor of Cardiovascular Medicine)\(^1\), Dirk J van Veldhuisen(Professor of Cardiology)\(^13\), Marcelo C Shibata (Associate Clinical Professor of Medicine)\(^14\), Hans Wedel (Professor of Epidemiology and Biostatistics)\(^15\), Michael Böhm (Professor of Internal Medicine & Cardiology)\(^16\) and Marcus D Flather(Professor of Medicine and Clinical Trials)\(^17\), on behalf of the Beta-Blockers in Heart Failure Collaborative Group

From the (1) University of Birmingham Institute of Cardiovascular Sciences, Birmingham, UK; (2) Centre of Cardiovascular Research and Education in Therapeutics, Monash University, Melbourne, Australia; (3) Royal Brompton & Harefield NHS Trust, London, UK; (4) Internal Medicine Department, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid, Spain; (5) Department of Medical Sciences, IRCCS San Raffaele Pisana, Roma, Italy and Cardiovascular and Cell Science Institute, St George’s University of London, UK; (6) Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, UK; (7) National Heart & Lung Institute, Imperial College, London; (8) Department of Clinical Sciences, UT Southwestern Medical Center, Dallas,
USA; (9) Wallenberg Laboratory for Cardiovascular Research, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden; (10) Monash University, Melbourne, Australia and University of Warwick, Warwick, UK; (11) Department of Cardiology, Oslo University Hospital, Oslo, Norway; (12) Academic Cardiology, Castle Hill Hospital, Kingston upon Hull, UK; (13) Department of Cardiology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands; (14) Division of Cardiology, University of Alberta, Edmonton, Canada; (15) Nordic School of Public Health, Gothenburg, Sweden; (16) Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; and (17) Norwich Medical School, University of East Anglia, Norwich, UK.

Address for correspondence:
Dr Dipak Kotecha
University of Birmingham Institute of Cardiovascular Sciences,
The Medical School, Vincent Drive, Edgbaston, Birmingham, B15 2TT, United Kingdom.
Email: d.kotecha@bham.ac.uk
Tel: +44 7974 115676 Fax: +44 121 554 4083

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Beta-Blockers in Heart Failure Collaborative Group
Abstract

**Background:** Beta-blockers are recommended in heart failure patients with reduced ejection fraction (HFrEF) and sinus rhythm, but prescription rates are consistently lower in older patients and women.

**Objectives:** We sought to determine the efficacy and tolerability of beta-blockers in a broad age-range of adult women and men with HFrEF by pooling individual patient data (IPD) from placebo-controlled randomized trials.

**Methods:** The study was a prospectively designed IPD meta-analysis of patients aged 40-85 years in sinus rhythm at baseline, with left-ventricular ejection fraction <0.45. The primary outcome was all-cause mortality and major secondary outcome heart failure hospitalization. Analysis was by intention to treat using an adjusted one-stage Cox proportional hazards model. Registration: PROSPERO CRD42014010012; Clinicaltrials.gov NCT00832442.

**Results:** 13,833 patients were included from 11 trials, with median age 64 years and 24% women. Beta-blockers were effective in reducing mortality versus placebo across all ages: Quartile 1 (median age 50) hazard ratio (HR) 0.66 (95% CI 0.53 to 0.83); Quartile 2 (median 60) HR 0.71 (0.58 to 0.87); Quartile 3 (median 68) HR 0.65 (0.53 to 0.78); Quartile 4 (median 75) HR 0.77 (0.64 to 0.92). There was no significant interaction when age was modelled continuously (p=0.10) and the absolute mortality reduction was 4.3% over a median follow-up of 1.3 years (number needed to treat=23). Heart failure hospitalization was significantly reduced by beta-blockers, although this effect was attenuated at older age (interaction p=0.05). There was no evidence of an interaction between treatment effect and gender in any age group. Drug discontinuation was similar regardless of treatment allocation, age or gender (14.4% beta-blockers, 15.6% placebo).

**Conclusion:** Irrespective of age or gender, patients with HFrEF in sinus rhythm should receive beta-blockers to reduce the risk of death and hospitalization.
Introduction

Beta blockers reduce morbidity and mortality in patients with heart failure (HF) and reduced left-ventricular ejection fraction (LVEF), and are a cornerstone of modern evidence-based treatment. Current HF guidelines do not differentiate treatment on the basis of age or gender, although initiation and maintenance of therapy is suboptimal both in older people and women.(1-3) With increasing age, the likelihood of being a woman and having a less marked reduction in LVEF are both greater. This interaction, along with relatively low numbers of older patients in randomized controlled trials (RCTs), 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 dosage required or the tolerability of therapy.(4, 5) Although sub-group 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 beta-blockers is retained in older patients(6-8), low uptake and poor maintenance of therapy continue to be a clinical reality.

The Beta-blockers in Heart Failure Collaborative Group was set up to combine individual patient data (IPD) from the major RCTs in HF and provide clear direction on clinically-relevant patient subsets where there is uncertainty about the balance of safety and efficacy of beta-blockers.(9, 10) IPD meta-analysis allows more robust examination of treatment effects in sub-groups and enables time-to-event analyses adjusted for baseline covariates, making it the “gold standard” for the appropriate pooling of original data.(11) We recently demonstrated that morbidity and mortality are not improved by beta-blockers in patients with HFrEF and concomitant atrial fibrillation, in contrast to those in sinus rhythm who had substantial reductions in hospitalization and all-cause mortality.(12) In this analysis, we explore the interactions of beta-blocker efficacy and tolerability with age and gender, utilizing the largest and most robust dataset of pooled
randomized trial data. 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 RCTs investigating the use of beta-blockers in HF. 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 (AstraZeneca, 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) guidelines(13) and prospectively registered with Clinicaltrials.gov (NCT0083244) and the PROSPERO database of systematic reviews (CRD42014010012).(10) Detailed rationale and methods have previously been published.(9, 12)

**Eligibility, search strategy and data collection**

Published or unpublished RCTs were identified through computer aided searches (e.g. Medline and Current Contents), scrutiny of reference lists of trials, trials registries, meeting abstracts, review articles as well as discussion with group members and pharmaceutical manufacturers. RCTs were included that reported mortality as a primary or part of a composite outcome comparing beta-blockers versus placebo. Only unconfounded head-to-head trials were eligible, with recruitment of >300 patients and planned follow-up of >6 months to make the project technically feasible and clinically-relevant. The search results, individual study demographics and a standardized data request form to obtain IPD from each trial have been published.(9)

Eleven studies were included that account for 95.7% of eligible participants recruited in RCTs
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 Randomized 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(8) and the U.S. Carvedilol Heart Failure Study (US-HF).(24) All included studies had low risk of bias, as determined using the Cochrane Collaborations 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 eleven trials.

Data were extracted from original source files and additional follow-up mortality outcomes were available in seven studies. The primary outcome of this analysis 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 CV deaths, HF and CV hospitalization, fatal and non-fatal myocardial infarction (MI), fatal and non-fatal stroke, and composites of mortality and hospitalization. One smaller study (1.4% of patients) did not provide data on hospitalization or other adverse clinical events(21), however all studies contributed to the primary outcome (Figure 1). Safety outcomes focused on discontinuation of study drug therapy due to adverse events (hypotension, bradycardia, HF-exacerbation, renal impairment and respiratory dysfunction). We defined tolerability as the dose achieved as a percentage of maximum target dose, according to the particular beta-blocker and specific trial design.
Population

Individual patient data were available on a total of 18,637 patients. For this analysis, restriction to patients with HFrEF was pre-specified with an LVEF 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 LVEF. Only those in sinus rhythm at baseline were evaluated in light of our prior findings regarding the lack of prognostic benefit of beta-blockers in patients with atrial fibrillation.(12) 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 years). 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 pre-specified division into quartiles. Gender was explored as a secondary interaction variable across the age quartiles.

Statistical analysis

Data are presented as percentages, or median and interquartile range (IQR; displayed as 25th to 75th centiles). Estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula, normalized to a body surface area of 1.73 m². All analyses followed the principle of intention to treat. Outcomes were analysed using a stratified Cox proportional hazards regression model.(26) 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 (HR) and 95% confidence intervals (CI) are presented, along with corresponding p-values. We pre-specified adjustment in Cox models for age, gender, prior MI and baseline NYHA class (I/II vs. III/IV), LVEF, heart rate, systolic blood pressure, diuretic therapy and angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB). Age was explored using numerous non-linear methods, including fractional polynomial
models, but the best fit was obtained with a linear relation. The amount of missing data for baseline characteristics was minimal (see legend for Table 1) and hence imputation was not required. The final population size for the fully-adjusted Cox model for the primary outcome was 13,670 (Figure 1). Kaplan Meier plots are used to graph the data (pooling data from all trials). As the follow-up periods in individual studies varied, data were censored at 1200 days (3.3 years) from randomization. Heterogeneity for the primary outcome was assessed using the chi-squared test and $I^2$ statistic, with the estimate of heterogeneity taken from the inverse-variance fixed-effects two-stage model.(27) A range of predefined sensitivity analyses were performed, including alternative censor points, analysis of the entire age-range, different LVEF cut-offs, exclusion of specific studies, additional baseline adjustment and random effects modelling.(28) Exploratory analyses included a per-protocol assessment of patients who remained on study therapy throughout the trial. All models demonstrated valid proportional hazards as determined by Schoenfeld residuals.(29) Interactions were assessed in all models according to best practice.(30, 31) A two-tailed p-value of 0.05 was considered statistically significant. Analyses were performed on Stata Version 13.1 (StataCorp LP, Texas) and R Version 3.0.2 (R Core Team, Vienna).

Results

Age, gender and baseline characteristics

A total of 13,833 HFrEF patients in sinus rhythm were included in the analysis. The median age was 64 years (IQR 55-71). Women accounted for 24% of patients overall (n=3,283) and were older than men (66 years [IQR 58-73] versus 63 [IQR 55-71]) (Supplementary Figure A). The median duration of HF before enrolment was 3 years (IQR 1-6) and median LVEF 0.27 (IQR 0.20-0.33). Baseline demographics according to age quartile are presented in Table 1 and by
Primary outcome

Overall 16% of patients died over a median follow-up period of 1.3 years (IQR 0.8-1.9). As expected, all-cause mortality was higher in older patients, with relatively higher rates of death due to HF and non-CV causes than younger patients (Supplementary Table B). Compared to men, women had lower absolute rates of all-cause mortality (14% versus 16%), but causes of death were similar (Supplementary Table C).

Beta-blockers significantly reduced all-cause mortality compared to placebo (968 deaths/7,060 [13.7%] versus 1,222/6,773 [18.0%]). The relative risk reduction with beta-blockers was 24%, with an absolute risk reduction of 4.3% (number needed to treat, NNT=23). The adjusted HR was 0.70, 95% CI 0.64 to 0.77, p<0.0001. Figure 2 displays the primary age analysis, assessing the hazard of death for beta-blockers compared to placebo across the range of age, modelled as a continuous variable. No statistical interaction with age was identified (interaction p-value=0.10). Table 2 displays the hazard ratio and Figure 3 the Kaplan-Meier plots for each age quartile, confirming efficacy for the primary outcome in all quartiles, including the oldest patients. Similar absolute risk reductions with beta-blockers were noted in all age quartiles (Supplementary Table D). Beta-blockers were effective in both women and men, in the whole group and within specific age quartiles (Table 2 and Figure 4). All sensitivity analysis for the primary outcome identified similar results to the main statistical model (Supplementary Table E).

Secondary outcomes

There was attenuation of the benefits of beta blockers on CV death by age (interaction p-value of 0.04) but there remained a statistically significant reduction in events even in the oldest age group.
Similar findings were seen with HF hospitalization (Figure 3 and Supplementary Table D), CV hospitalization and composite clinical outcomes. Fatal and non-fatal MI or stroke were not reduced with beta-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 Figure 4).

All-cause, CV and HF-related hospitalization data are detailed in Table 3, divided by age quartiles and gender. Hospitalization rates increased with age and were similar in both genders. In the oldest quartile, patients had more than one hospitalization per year, with half of these admissions due to HF, and a median length of stay of 7 days in hospital.

Tolerability of therapy

There were similar rates of discontinuation due to adverse events in the placebo and beta-blocker arms across age quartiles and gender, although these increased slightly with age (Table 4). Overall, a numerically lower number of patients discontinued beta-blockers (14.4% versus 15.6% in placebo). Specific causes of beta-blocker discontinuation according to age and gender are displayed in Supplementary Table F. Small numbers of patients discontinued therapy due to hypotension (0.7-1.6%), bradycardia (0-3.5%), HF exacerbation (2.0-4.9%), renal impairment (0-1.2%) and respiratory compromise (0.5-1.2%). Discontinuation was similar across age and gender, apart from a small excess in HF exacerbation in the youngest quartile for women compared to men (5.4% versus 2.2%) and in bradycardia in the oldest men (3.5% versus 0.7% in the oldest women). Beta-blocker dose did not differ across age and gender, with patients attaining 73% of the target dose at the interim study point (Supplementary Table G), compared to 84% achieving the corresponding dose of placebo.
Discussion

Principal findings

Using the near-totality of available data from RCTs of beta-blockers in patients with HFrEF and sinus rhythm, our analysis shows that there is no evidence of a clinically significant interaction with age or gender with respect to all-cause mortality. We observed a significant benefit from beta-blockers in each age quartile, with absolute mortality reductions of about 4% in the youngest and oldest patients. Similar results were observed for HF-related hospital admission, with significant reductions in each age quartile, albeit with minor attenuation of treatment effect in older patients. Discontinuation of therapy was similar in patients randomized to beta-blockers or placebo, even in older patients, suggesting that beta-blocker ‘intolerance’ in clinical practice may reflect false attribution to intercurrent events or pre-conceptions about side-effects.

Clinical context: Age

Heart failure guidelines recommend beta-blockers for patients with HFrEF, but have not previously been able to exclude an interaction with age.(32, 33) As a result, prescription of therapy and long-term continuation have been lower in older patients(34-36), 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 years was 30%, which does not reflect the “real world” population of HFrEF. In the three largest US HF registries (ADHERE, OPTIMIZE-HF and Get With The Guidelines), the average age of HFrEF patients was 70 years (SD 14, 14 and IQR 58-80 respectively; total of 101,066 patients).(37) Similarly, in the Swedish Heart Failure Registry of 21,864 HFrEF patients, the mean age was 72 years (SD 12).(38) This confirms that older patients are under-represented in HF RCTs, necessitating the pooling of data to provide information on treatment efficacy. In this context, IPD provides the only robust method to adequately combine sub-group data.(39)
There are important demographic changes noted with advancing age. Compared to the youngest quartile, older patients were more often women (31% to 18%), had more ischemic aetiology (81% to 54%), higher LVEF (0.29 to 0.25), higher systolic BP (130 to 120 mmHg), lower heart rate (77 to 82 beats per minute), reduced kidney function (55 to 73 mL/min) and received digoxin less frequently (44% to 62%). These factors are known to affect prognosis in HF in different ways. Age is the most powerful predictor of prognosis but is not itself a predictor of response to treatment. The higher systolic BP, higher LVEF and lower heart rate observed in older patients are predictors of better prognosis, whilst chronic renal impairment is associated with poor prognosis. The median length of pre-trial HF was 2 years in the lowest age quartile and 3 years in the other age quartiles 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; Fifty percent of deaths in the youngest quartile are classified as “sudden” compared to 34% in the oldest quartile, whereas HF deaths accounted for 16% compared to 31% respectively. Thus the heterogeneity in age in the trials also reflects heterogeneity in HF aetiology and comorbidity patterns. The results of this IPD meta-analysis, showing the clear benefit of beta-blockers across all age groups in spite of this heterogeneity, is an important finding that cannot be predicted by analysing 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 beta-blocker therapy, a novel and important finding that informs clinical practice and underpins the applicability of current clinical guidelines.(32, 33)

In general, the effect of beta-blockers was consistent on the major secondary outcomes analysed. We did identify attenuated prevention of hospital admission by beta-blockers with age (p=0.05 for first HF related and p=0.04 for first CV hospitalization). However, adjusted hazard ratios remained significant across age quartiles and for all outcomes, apart from two secondary outcomes (first CV hospitalization and the composite of CV death or HF hospitalization).
Reassuringly, we did not identify differences in HF-related hospital admissions according to age or gender, and the length of hospital stay was similar in all patients, regardless of age or gender.

**Clinical context: Gender**

Baseline demographics show that women with HF entered into RCTs are older than men and differences such as higher systolic BP, higher LVEF and lower eGFR may simply reflect this age difference. Women have a lower incidence of ischemic aetiology and prior MI, although similar HF prevalence compared to men. Prognosis has been shown to be better in women, however mortality rates are still 25% over 3 years. Previous sub-group data from RCTs have provided conflicting results about the efficacy of beta-blockers in women, including equal benefit (for example the MERIT-HF and CIBIS trials), enhanced mortality reduction compared to men (US Heart Failure trial) and also no effectiveness in women (BEST trial). Our results confirm that there is no difference in beta-blocker efficacy in HFrEF according to gender. Cause of death in women and men showed identical proportions and patterns for sudden, HF and non-CV deaths, which further support the concordance for recommendation of beta-blockers. Thus, beta-blocker therapy should not be withheld from women with HFrEF, a practice that has been reported alongside fewer cardiology assessments and cardiac procedures. Women were under-represented in the clinical trials we analysed, and this continues to be the case; for example in the recent large RCT 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 in order to provide realistic expectations of their risk and benefit from treatment.

**Side effects and tolerability**

Importantly for all ages and both genders, we identified low rates of beta-blocker discontinuation due to adverse events and similar withdrawal rates to placebo. Although beta-blockers are often associated with side effects, data from randomised trials consistently show no true difference
compared to placebo in dizziness, diarrhoea, elevated blood sugar or depression, and little or no increase in lethargy with modern generation beta-blockers.(47-49) This information should reassure clinicians about the tolerability of beta-blockers in view of the prognostic benefit we have identified in women and the elderly of both genders. Elderly patients were able to reach similar maximal dosage compared to younger HFrEF patients.

**Strengths and limitations of study**

It is plausible that the benefits of beta blockers are attenuated in the very elderly (e.g. >80 years) although the amount of information on these patients in existing RCTs is scarce. Extrapolation from Figure 2 indicates that any attenuation of prognostic benefit with age is actually quite mild and the effect of beta-blockers in patients >80 years 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 IPD from all large datasets, there are limitations to inference of treatment effects in subgroups. Examining treatment interactions by age shows significant treatment benefits in each quartile, but assessing interactions of age and gender 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 may not provide full information on treatment effects in very elderly women due to 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 age or gender interaction, direct extrapolation to patients with LVEF>0.45 cannot be made. Similarly, we have previously reported on outcomes for beta-blockers in patients with concomitant HF and atrial fibrillation(12), and although these patients have poor prognosis(50), they are distinctly different to patients with HF in sinus rhythm and require specific management.(51)
There have been changes in risk factor profiles and treatment patterns since the component studies were completed (for example the use of cardiac resynchronization therapy), however, beta-blockers are still a vital component of optimal care in these patients(52), and may have a synergistic effect (for example with mineralocorticoid receptor antagonists).(53) 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 IPD from high quality RCTs, with near-totality of available data and methodical data extraction from original datasets(9), resulting in improved quality of outcome data across trials.

Conclusions and policy implications

This analysis confirms that beta-blockers reduce mortality and HF-related hospitalization in HFrEF patients with sinus rhythm, irrespective of age or gender. Absolute effect sizes for all-cause mortality were similar across age quartiles with no significant interaction using an adjusted continuous hazard model. In addition, the tolerability of beta-blockers was similar to placebo, reinforcing the use of beta-blockers in all HFrEF patients in sinus rhythm, and discouraging the practice of withholding such therapy in women or elderly patients.
Summary Box

What is already known on this topic

- Beta-blockers can reduce mortality and hospital admission in heart failure patients with reduced ejection fraction and sinus rhythm
- Older patients and women frequently receive less evidence-based treatment, and often at lower dosage than demonstrated as effective in clinical trials

What this study adds

- Our study used individual patient data from all major randomised controlled trials comparing beta-blockers versus placebo in heart failure patients with reduced ejection fraction and sinus rhythm
- In these patients, we found that beta-blockers reduce all-cause mortality and heart failure hospitalisation, regardless of age or gender, and that tolerability of therapy was the same with beta-blockers and placebo
Print Abstract

Study question:
Is the effectiveness and tolerability of beta-blockers in heart failure patients with reduced ejection fraction and sinus rhythm the same in older patients and women?

Methods:
This study is a prospectively designed, individual patient data meta-analysis of randomised controlled trials comparing beta-blockers with placebo. We included heart failure patients with left-ventricular ejection fraction <0.45, aged 40-85 years in sinus rhythm (n=13,833). The primary outcome was all-cause mortality, analysed using an intention to treat, adjusted, one-stage Cox proportional hazards model.

Study answer and limitations:
Beta-blockers reduced all-cause mortality compared to placebo in all age-groups and both genders, with an adjusted hazard ratio of 0.70 (95% CI 0.64 to 0.77), absolute risk reduction of 4.3%, and number needed to treat of 23 to prevent one death. There was no interaction of treatment effect with age (p=0.10), and women received the same benefit even in the oldest age quartile (interaction p=0.54). Drug discontinuation was similar, irrespective of age or gender (overall 14.4% for beta-blockers and 15.6% for placebo). We are limited to the patients originally recruited, but were able to obtain a near-totality of available data from high quality randomised controlled trials.

What this study adds:
Our study shows that heart failure patients with reduced ejection fraction and sinus rhythm should not be deprived of beta-blocker therapy, regardless of age or gender, and that all patients tolerate
therapy well with similar withdrawal rates compared to placebo.

**Funding and competing interests:**

This project was investigator initiated. Menarini Farmaceutica provided an unrestricted research grant for administrative costs and GlaxoSmithKline provided data extraction support. None of the pharmaceutical groups had any role in data analysis or manuscript preparation. A number of authors have received research grants and honoraria from pharmaceutical companies.

**Study registration:**

Clinicaltrials.gov (NCT0083244) and the PROSPERO database of systematic reviews (CRD42014010012).

**RECOMMEND FIGURE 2 FOR INCLUSION IN PRINT:**

**All-cause mortality:**
**Beta-blockers versus placebo according to age**

![Graph showing all-cause mortality for beta-blockers versus placebo according to age. The graph includes a line for hazard ratio, a dashed line for 95% CI, markers for hazard ratio by age quartile, and a line for 95% CI for age quartile.](image-url)
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Author contributions:

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 performed the primary statistical analyses. All named authors read, revised and approved the final manuscript.

Competing interests:

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**Ethics Statement:**

All original trials operated under supervision of an appropriate Human Ethics Committee. The current analysis involves anonymized data only, hence ethics committee approval was deemed unnecessary by the National Research Ethics Service London – Chelsea (letter of confirmation available on request).

**Data Sharing:**

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

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**Licence:**

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References


32. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC
Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-847.


Table 1: Baseline characteristics by age quartile

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile 1 (youngest) n=3,458</th>
<th>Quartile 2 n=3,590</th>
<th>Quartile 3 n=3,327</th>
<th>Quartile 4 (oldest) n=3,458</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (IQR)</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, n (%)</td>
<td>639 (18%)</td>
<td>764 (21%)</td>
<td>794 (24%)</td>
<td>1,086 (31%)</td>
</tr>
<tr>
<td>Ischaemic HF aetiology, n (%)</td>
<td>1,856 (54%)</td>
<td>2,478 (69%)</td>
<td>2,544 (76%)</td>
<td>2,798 (81%)</td>
</tr>
<tr>
<td>Prior myocardial infarction, n (%)</td>
<td>1,648 (48%)</td>
<td>2,158 (60%)</td>
<td>2,190 (66%)</td>
<td>2,287 (66%)</td>
</tr>
<tr>
<td>Prior coronary revascularization, n (%)</td>
<td>592 (18%)</td>
<td>785 (24%)</td>
<td>769 (25%)</td>
<td>753 (23%)</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>681 (21%)</td>
<td>892 (27%)</td>
<td>833 (27%)</td>
<td>897 (26%)</td>
</tr>
<tr>
<td>Years with HF diagnosis, median (IQR)</td>
<td>2 (1-5)</td>
<td>3 (1-6)</td>
<td>3 (1-7)</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td>LVEF, median (IQR)</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>NYHA class III/IV, n (%)</td>
<td>2,359 (68%)</td>
<td>2,440 (68%)</td>
<td>2,285 (69%)</td>
<td>2,081 (61%)</td>
</tr>
<tr>
<td>Systolic BP, median mmHg (IQR)</td>
<td>120 (110-130)</td>
<td>120 (110-136)</td>
<td>126 (113-140)</td>
<td>130 (115-142)</td>
</tr>
<tr>
<td>Diastolic BP, median mmHg (IQR)</td>
<td>78 (70-84)</td>
<td>78 (70-83)</td>
<td>77 (70-80)</td>
<td>75 (69-80)</td>
</tr>
<tr>
<td>Heart rate, median bpm (IQR)</td>
<td>82 (74-91)</td>
<td>80 (72-88)</td>
<td>78 (72-86)</td>
<td>77 (70-85)</td>
</tr>
<tr>
<td>Body mass index, median kg/m² (IQR)</td>
<td>28 (25-33)</td>
<td>27 (25-31)</td>
<td>27 (24-30)</td>
<td>26 (24-29)</td>
</tr>
<tr>
<td>Estimated GFR, median mL/min (IQR)</td>
<td>73 (61-86)</td>
<td>66 (54-79)</td>
<td>59 (48-71)</td>
<td>55 (44-67)</td>
</tr>
<tr>
<td>Any diuretic therapy, n (%)</td>
<td>2,896 (84%)</td>
<td>3,055 (85%)</td>
<td>2,859 (86%)</td>
<td>3,000 (87%)</td>
</tr>
<tr>
<td>ACEi or ARB, n (%)</td>
<td>3,332 (96%)</td>
<td>3,410 (95%)</td>
<td>3,154 (95%)</td>
<td>3,207 (93%)</td>
</tr>
<tr>
<td>Aldosterone antagonists, n (%)</td>
<td>255 (8%)</td>
<td>188 (6%)</td>
<td>256 (8%)</td>
<td>369 (11%)</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>2,090 (62%)</td>
<td>1,956 (56%)</td>
<td>1,652 (51%)</td>
<td>1,504 (44%)</td>
</tr>
</tbody>
</table>

ACEi, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; GFR, glomerular filtration rate; HF, heart failure; IQR, interquartile range; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association functional class.

Missing data (total across all quartiles): Prior myocardial infarction n=30; Prior coronary revascularization n=900; Diabetes Mellitus n=809; Years with HF diagnosis n=2817; Systolic BP n=59; Diastolic BP n=65; Heart rate n=8; Body mass index n=128; GFR n=662; NYHA n=73; Diuretics n=1; Aldosterone antagonists n=890; Digoxin n=348.
Table 2: Hazard ratios for primary and secondary outcomes according to age quartile

<table>
<thead>
<tr>
<th>Beta-blockers versus placebo / Outcome</th>
<th>Age (continuous) interaction p-value</th>
<th>Quartile 1 (youngest)</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4 (oldest)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HR, 95% CI</td>
<td>Gender interaction p-value</td>
<td>HR, 95% CI</td>
<td>Gender interaction p-value</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>
</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>
</tr>
<tr>
<td>CV 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>
</tr>
<tr>
<td>First HF-related hospitalization</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>
</tr>
<tr>
<td>First CV hospitalization</td>
<td>0.04</td>
<td>0.65, 0.55 to 0.77</td>
<td>0.38</td>
<td>0.78, 0.68 to 0.91</td>
<td>0.70</td>
</tr>
<tr>
<td>Death or CV hospitalization</td>
<td>0.03</td>
<td>0.66, 0.57 to 0.77</td>
<td>0.64</td>
<td>0.78, 0.68 to 0.89</td>
<td>0.46</td>
</tr>
<tr>
<td>CV death or HF hospitalization</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>
</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>
</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>
</tr>
</tbody>
</table>

Analysed using the one-stage Cox regression model, with studies as strata (censor 1200 days); adjusted for age, gender, MI, NYHA class (I/II vs. III/IV), LVEF, heart rate, systolic blood pressure and baseline ACEi/ARB and diuretic therapy. Gender interaction p-values are given for treatment allocation and gender within each age quartile. Note the MDC trial only contributes to mortality outcomes. CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.
<table>
<thead>
<tr>
<th>Hospitalization type</th>
<th>Quartile 1 (youngest)</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 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 hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage with 1 or more admission</td>
<td>39%</td>
<td>31%</td>
<td>35%</td>
<td>36%</td>
<td>39%</td>
</tr>
<tr>
<td>Average number of admissions per patient</td>
<td>0.94 (range 0-18)</td>
<td>0.67 (range 0-18)</td>
<td>0.78 (range 0-14)</td>
<td>0.76 (range 0-22)</td>
<td>0.79 (range 0-11)</td>
</tr>
<tr>
<td>Annualized hospitalization rate per patient</td>
<td>0.67 /year</td>
<td>0.69 /year</td>
<td>0.85 /year</td>
<td>0.81 /year</td>
<td>0.87 /year</td>
</tr>
<tr>
<td><strong>CV-hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage with 1 or more admission</td>
<td>25%</td>
<td>20%</td>
<td>23%</td>
<td>25%</td>
<td>27%</td>
</tr>
<tr>
<td>Average number of admissions per patient</td>
<td>0.48 (range 0-13)</td>
<td>0.38 (range 0-14)</td>
<td>0.44 (range 0-13)</td>
<td>0.46 (range 0-16)</td>
<td>0.47 (range 0-10)</td>
</tr>
<tr>
<td>Annualized hospitalization rate per patient</td>
<td>0.36 /year</td>
<td>0.38 /year</td>
<td>0.47 /year</td>
<td>0.45 /year</td>
<td>0.56 /year</td>
</tr>
<tr>
<td>Average length of stay a</td>
<td>6 days (IQR 3-9)</td>
<td>6 days (IQR 3-10)</td>
<td>6 days (IQR 3-9)</td>
<td>6 days (IQR 3-12)</td>
<td>7 days (IQR 3-11)</td>
</tr>
<tr>
<td><strong>HF-related hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percentage with 1 or more admission</td>
<td>19%</td>
<td>13%</td>
<td>16%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Average number of admissions per patient</td>
<td>0.36 (range 0-7)</td>
<td>0.25 (range 0-12)</td>
<td>0.32 (range 0-13)</td>
<td>0.31 (range 0-16)</td>
<td>0.29 (range 0-10)</td>
</tr>
<tr>
<td>Annualized hospitalization rate per patient</td>
<td>0.24 /year</td>
<td>0.27 /year</td>
<td>0.32 /year</td>
<td>0.30 /year</td>
<td>0.33 /year</td>
</tr>
<tr>
<td>Average length of stay a</td>
<td>6 days (IQR 3-10)</td>
<td>6 days (IQR 4-11)</td>
<td>7 days (IQR 4-10)</td>
<td>7 days (IQR 4-13)</td>
<td>7 days (IQR 4-12)</td>
</tr>
</tbody>
</table>

a Based on the first five hospital admissions for a cardiovascular (CV)/heart failure (HF) cause. Note the MDC trial does not contribute to hospitalization outcomes.
### Table 4: Discontinuation of study therapy

<table>
<thead>
<tr>
<th>Discontinuation due to any adverse event</th>
<th>Placebo</th>
<th>Beta-blockers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quartile 1</strong> (youngest)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women: 51/300 (17.0%)</td>
<td>Women: 47/335 (14.0%)</td>
<td></td>
</tr>
<tr>
<td>Men: 192/1375 (14.0%)</td>
<td>Men: 167/1435 (11.6%)</td>
<td></td>
</tr>
<tr>
<td>All: 243/1,675 (14.5%)</td>
<td>All: 214/1,770 (12.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Quartile 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women: 53/366 (14.5%)</td>
<td>Women: 51/394 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>Men: 201/1371 (14.7%)</td>
<td>Men: 183/1449 (12.6%)</td>
<td></td>
</tr>
<tr>
<td>All: 254/1,737 (14.6%)</td>
<td>All: 234/1,843 (12.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Quartile 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women: 59/383 (15.4%)</td>
<td>Women: 59/411 (14.4%)</td>
<td></td>
</tr>
<tr>
<td>Men: 205/1259 (16.3%)</td>
<td>Men: 186/1271 (14.6%)</td>
<td></td>
</tr>
<tr>
<td>All: 264/1,642 (16.1%)</td>
<td>All: 245/1,682 (14.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Quartile 4</strong> (oldest)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women: 90/537 (16.8%)</td>
<td>Women: 86/549 (15.7%)</td>
<td></td>
</tr>
<tr>
<td>Men: 200/1165 (17.2%)</td>
<td>Men: 233/1207 (19.3%)</td>
<td></td>
</tr>
<tr>
<td>All: 290/1,702 (17.0%)</td>
<td>All: 319/1,756 (18.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>All ages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women: 253/1586 (16.0%)</td>
<td>Women: 243/1689 (14.4%)</td>
<td></td>
</tr>
<tr>
<td>Men: 798/5170 (15.4%)</td>
<td>Men: 769/5362 (14.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>All:</strong> 1,051/6,756 (15.6%)</td>
<td>All: 1,012/7,051 (14.4%)</td>
<td></td>
</tr>
</tbody>
</table>
Figure Legends

Figure 1: Study flowchart
Flow diagram for included and excluded participants. *The MDC trial only contributes to mortality outcomes.

Figure 2: Beta-blockers versus placebo hazard model for all-cause mortality and age
Hazard ratio for beta-blockers compared to placebo in HFrEF patients with sinus rhythm.
Age modelled as a continuous variable, with quartile results superimposed.

Figure 3: Kaplan-Meier event curves according to age quartile
All-cause mortality (primary outcome; top panel) and HF hospitalization (major secondary outcome; lower panel) for beta-blockers versus placebo by age quartile. ARR, absolute risk reduction; NNT, number needed to treat.

Figure 4: Kaplan-Meier event curves according to gender
All-cause mortality (primary outcome; left panel) and HF hospitalization (major secondary outcome; right panel) for beta-blockers versus placebo by gender. ARR, absolute risk reduction; NNT, number needed to treat.