Full title: Effect of digoxin in patients with heart failure and mid-range (borderline) left ventricular ejection fraction.

Brief title: Digoxin in HFmrEF

Authors:

Azmil H. Abdul-Rahim MD MSc[1]

Li Shen MBChB[2]

Christopher J. Rush MBChB[2]

Pardeep S. Jhund MBChB PhD[2]

Kennedy R. Lees MD[2]

John J.V. McMurray MD[2*]

*On behalf of the VICCTA-Heart Failure Collaborators**

1. Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, UK

2. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

*** Correspondence:** Professor John J.V. McMurray.

British Heart Foundation Cardiovascular Research Centre

University of Glasgow, 126 University Place

Glasgow, G12 8TA

United Kingdom.

Tel: +44-141-330-3479 Fax:+44-141-330-6955

Email: john.mcmurray@glasgow.ac.uk

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ABSTRACT

Aims: To evaluate the effects of digoxin in patients with the newly described phenotype of heart failure (HF) and mid-range ejection fraction (HFmrEF), attributed to mild left ventricular systolic dysfunction.

Methods and Results: We carried out a retrospective analysis of the Digitalis Investigators Group trial (DIG) which had 7788 patients available for analysis with a left ventricular ejection fraction (LVEF) ranging between 3% and 85%. We compared the effect of digoxin to placebo in three mutually exclusive groups of patients defined by LVEF category: <40% (HF with reduced LVEF, HFrEF, n=5874), 40-49% (HFmrEF, n=1195) and ≥50% (HF with preserved LVEF, HFpEF, n=719). The primary outcome was the composite of cardiovascular death or HF hospitalization. Patients with HFmrEF resembled patients with HFrEF, more than those with HFpEF, with respect to age, sex and aetiology but were more like HFpEF patients with respect to blood pressure and the prevalence of hypertension. Event rates in patients with HFmrEF were similar to those in HFpEF and much lower than in HFrEF. Digoxin reduced the primary endpoint in patients with HFrEF, mainly due to reduced HF hospitalisation: the digoxin/placebo hazard ratio for HF hospitalisation was 0.71 (0.65-0.77). The digoxin/placebo hazard ratio for heart failure hospitalisation in patients with HFmrEF was 0.80 (0.63-1.03) and 0.85 (0.62-1.17) in those with HFpEF. The digoxin/placebo hazard ratio for the composite of HF death or HF hospitalisation was 0.74 (0.68, 0.81) in HFrEF, 0.83 (0.66, 1.05) in HFmrEF and 0.88 (0.65, 1.19) in HFpEF.

Conclusions: In this study, event-rates in patients with HFmrEF were closer to those in HFpEF than HFrEF. Digoxin had most effect on HF hospitalization in patients with HFrEF, an intermediate effect in HFmrEF and the smallest effect in HFpEF.

Keywords: heart failure with mid-range ejection fraction; digoxin; outcome

INTRODUCTION

In 2016, the European Society of Cardiology (ESC) guidelines on heart failure introduced the term heart failure with mid-range ejection fraction (HFmrEF) to describe patients with a left ventricular ejection fraction (LVEF) in the range 40-49%.[1] These are patients who neither have a clearly reduced LVEF (i.e. do not have heart failure with reduced ejection fraction, HFrEF, the phenotype of patients enrolled in the majority of previous clinical trials) nor a near normal or normal ("preserved") LVEF i.e. ≥50% (here after referred to as HFpEF). Patients with a LVEF 40-49% were either the minority of those enrolled in prior trials, or were excluded from previous trials, and represent a "grey area" with respect to pathophysiological understanding and treatment choices.[2-4]

The ESC guidelines suggested that patients with HFmrEF may represent an intermediate phenotype, likely characterised by the presence of mild left ventricular systolic dysfunction..[1] One way to test the hypothesis is to examine the effect of treatments that are known to be beneficial in HFrEF in patients with HFmrEF. Perhaps the prototypical agent of this type is digoxin. As an inotrope, digoxin might be expected to be of benefit in systolic dysfunction but not in diastolic dysfunction. The Digitalis Investigators Group trial (DIG) which enrolled patients with a LVEF ranging between 3% and 85% offered the opportunity to compare the effect of digoxin in HFrEF, HFmrEF and HFpEF.[5, 6] We have carried out a retrospective analysis of the effect of digoxin in patients with HFmrEF in DIG.

METHODS

DIG inclusion and exclusion criteria

The rationale, design and results of DIG have been published.[5, 6] Patients were randomised at 302 clinical centres in the United States and Canada. The study was approved by the ethics committee at each participating centre and all patients gave written informed consent. Patients were eligible for the main trial if they had heart failure and a LVEF fraction of 45% or less and were in normal sinus rhythm (6800 patients).[5] Patients with heart failure and a LVEF of more than 45% were enrolled in an ancillary trial conducted in parallel to the main trial (988 patients).[6] The diagnosis of heart failure was based on current or previous symptoms (limitation of activity, fatigue, and dyspnoea or orthopnea), signs (oedema, elevated jugular venous pressure, rales, or a third heart sound/gallop rhythm), or radiologic evidence of pulmonary congestion. Exclusion criteria included a serum potassium concentration less than 3.2 mmol/l or above 5.5 mmol/l and significant renal insufficiency (creatinine greater than 3.0 mg/dl) or severe liver disease. Investigators were strongly encouraged to give study patients an angiotensin-converting–enzyme inhibitor.[5, 6]

Study drug randomisation and dosing and trial outcomes

Patients were randomly assigned to receive digoxin or placebo and follow-up visits took place at 4 weeks and 16 weeks after randomisation and every 4 months thereafter.[5, 6]

The primary outcome in DIG was death from any cause. The trial secondary outcomes included death from cardiovascular causes, death from worsening heart failure, and hospitalization for worsening heart failure.[5, 6] For the purposes of the present study, we used the composite of cardiovascular death or heart failure hospitalization as the primary outcome, reflecting the most commonly used endpoint in contemporary heart failure trials.

LVEF categories (definition of HFrEF, HFmrEF and HFpEF)

For the purposes of comparing the clinical characteristics of and outcomes in HFrEF, HFmrEF and HFpEF, patients were divided into three mutually exclusive LVEF categories: less than 40% (HFrEF), 40-49% (HFmrEF), and greater than or equal to 50% (HFpEF).[1]

Statistical analysis

We had full access to anonymised individual-patient data via the Virtual international Cardiovascular and Cognitive Trials Archive (VICCTA).[7, 8] Descriptive statistics were used to compare patients across the three LVEF categories. Data are presented as means (standard deviation [SD]) or medians (inter-quartile range [IQR]) for continuous variables and frequency (percent) for categorical variables. We examined the effect of randomised treatment on the following major clinical outcomes: the composite of cardiovascular (CV) death or heart failure (HF) hospitalisation (primary endpoint for the present study); the composite of HF death or HF hospitalisation (a pre-specified composite outcome in the DIG and considered to be the outcome most sensitive to the effect of digoxin); the components of these composites; and all-cause death (the pre-specified primary endpoint in DIG). Comparison of clinical outcomes among treatment groups was performed using Kaplan-Meier estimates, with log-rank test, and a supportive Cox proportional-hazards regression model to calculate hazard ratios and 95% confidence intervals. The reported hazard ratios were adjusted for age and sex. The interaction between LVEF category and the effect of treatment was also examined for each clinical outcome. The analyses were undertaken using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

The interaction between LVEF as a continuous variable and the effect of treatment on the composite outcome was also examined and graphically displayed using fractional polynomial function.[9] The rates of the composite outcome across LVEF was examined using the

restricted cubic spline method. The fractional polynomial and restricted cubic spline analyses were undertaken using the *mfpi* and *incspline* commands respectively in STATA version 14 (College Station, TX, USA).

RESULTS

There were 7788 patients with a LVEF available for analysis in the public use version of the DIG database. The median LVEF was 30% (IQR 23 to 39%). Of the 7788 patients analysed, 5874 (75%) had HFrEF, 1195 (15%) HFmrEF and 719 had HFpEF (9%).

Baseline characteristics

The baseline characteristics of the patients in each LVEF category are shown in Table 1. The characteristics of patients with HFmrEF were intermediate between the other two groups. In terms of age (HFmrEF 64.5 versus HFrEF 63.4 versus HFpEF 67.3 years), sex (female 28.9 versus 21.1 versus 47.4%, respectively), and history of myocardial infarction (63.1 versus 65.3 versus 44.7%, respectively), HFmrEF patients were more similar to patients with HFrEF than those with HFpEF. Conversely, with respect to history of hypertension (HFmrEF 53.6 versus HFrEF 44.0 versus HFpEF 62.5%, respectively), blood pressure (systolic pressure 133.4 versus 124.6 versus 138.9 mmHg, respectively), heart rate (76.1 versus 79.1 versus 76.2 bpm, respectively) and renal function (creatinine 110.5 versus 113.9 versus 111.2 μmol/l, respectively), HFmrEF patients resembled those with HFpEF more than individuals with HFrEF.

Symptoms and signs of heart failure

With two exceptions, the prevalence of all symptoms and signs was lowest in patients with HFmrEF, compared to the other two LVEF categories (Table 2). The exceptions were dyspnoea at rest or on exertion which had the same prevalence in HFmrEF and HFrEF (95.2%), compared with HFpEF (96.9%) and the frequency of a third heart sound gallop rhythm which was considerably less common in both patients with HFmrEF (37.9%) and

HFpEF (33.0%) than in those with HFrEF (51.9%). Cardiothoracic ratio was also lower in patients with HFmrEF (0.51) and HFpEF (0.52) than in individuals with HFrEF (0.53).

Clinical outcomes

Comparison of the primary composite outcome in the placebo group across LVEF categories showed a significantly higher rate in the HFrEF patients compared with the other two groups (Table 3, Figures 1 and 2). The rate of this endpoint was similar in HFmrEF and HFpEF groups (Table 3, Figure 1). The same was true for each component of the composite i.e. cardiovascular death and heart failure hospitalisation separately and the pre-specified DIG composite of heart failure death or heart failure hospitalisation (and its components).

A similar pattern was observed for all-cause death (Table 3). Overall, 86.0% of deaths in patients with HFrEF were due to a cardiovascular cause; this proportion was 74.4% in patients with HFmrEF and 78.4% in patients with HFpEF.

The restricted cubic spline analysis suggested a LVEF inflection point of around 35%, below which the rate of the primary composite outcome increased linearly (Figure 2).

Effect of digoxin

Digoxin reduced the risk of the primary composite outcome in patients with HFrEF, an effect mainly due to significant reduction in heart failure hospitalisation: the digoxin/placebo hazard ratio for HF hospitalisation in patients with HFrEF was 0.71 (0.65-0.77) (Table 3). The digoxin/placebo hazard ratio for heart failure hospitalisation in patients with HFmrEF was 0.80 (0.63-1.03) and 0.85 (0.62-1.17) in those with HFpEF (Table 3). The digoxin/placebo hazard ratio for the composite of HF death or HF hospitalisation was 0.74 (0.68, 0.81) in patients with HFrEF, 0.83 (0.66, 1.05) in those with HFmrEF and 0.88 (0.65, 1.19) in participants with HFpEF.

The fractional polynomial analysis showed a clear benefit of digoxin on the primary composite endpoint up to a LVEF of around 35%, with a smaller, if any, effect above that value although the interaction p-value examining effect of digoxin according to LVEF was 0.604 (Figure 3).

DISCUSSION

Prior studies of ambulatory cohorts have shown that approximately 10-20% of patients with heart failure have a LVEF in the range 40-49% i.e. have the newly designated category of HFmrEF. We found that 15% of patients in DIG fell within this category, consistent with the 17% of 7598 patients in the Candesartan in Heart Failure: Assessment of Mortality and morbidity (CHARM), 15% of 9134 patients the ESC Heart Failure Long-Term Registry and 13% of a Spanish cohort of 3446 patients.[10-13] However, the largest study (n=41,446) of ambulatory patients from Sweden found that 21.5% had HFmrEF.[14] It is not clear why the Swedish cohort had a higher prevalence than the other studies, especially the ESC registry, although our patients all were in sinus rhythm whereas the Swedish Registry included many patients with atrial fibrillation (65%, 60%, and 53% in HFpEF, HFmrEF and HFrEF, respectively).

We found that patients with HFmrEF resembled patients with HFrEF, more than those with HFpEF, with respect to age, sex and aetiology (particularly ischaemic aetiology). On the other hand, blood pressure and the prevalence of hypertension were higher in patients with HFmrEF than in patients with HFrEF, although not as high as in HFpEF. This pattern is consistent with the prior studies alluded to earlier.

Despite the similarities to HFrEF mentioned above, the rates of non-fatal and fatal heart failure events were considerably lower in patients with HFmrEF and much more like those in HFpEF (at around half the rate of these events in patients with HFrEF). Again, this finding was very similar to what was seen in CHARM, the ESC Long-Term Registry in the Spanish cohort and in a recent analysis of beta-blocker trials (see below).[10-13, 15]

The unique aspect of the present study was the evaluation of the effect of digoxin according to LVEF category. Overall, in DIG, the predominant effect of digoxin was on hospital admission for heart failure and the composite of death from heart failure or hospitalization for heart failure.[5] The size of the effect of digoxin treatment on this heart failure hospitalisation (and composites of this with either heart failure death or cardiovascular death) was larger in patients with HFrEF than in those with either HFmrEF or HFpEF. The effect of digoxin, if any, was similar (and small) in patients with HFmrEF and HFpEF.

It is of interest to compare these findings with similar analyses from CHARM and the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT). [12, 13] Notably, none of the CHARM-Preserved, DIG or TOPCAT trials were positive for their primary endpoint but, interestingly, all three showed an overall significant reduction in HF hospitalization (arguably the endpoint most "sensitive" to the effect of a drug in heart failure). If we look at the effect of treatment on this endpoint in patients with HFmrEF in each of these 3 trials we see: CHARM (n= 1322 patients with HFmrEF) candesartan/placebo hazard ratio [HR] 0.72 (0.55-0.95); TOPCAT (n=520) spironolactone/placebo HR 0.76 (0.46, 1.27); and DIG (n=1195) digoxin/placebo HR 0.80 (0.63-1.03), all of which overlap. Only CHARM showed a nominally statistically significant effect of study drug. Where the three trials differ is in relation to cardiovascular (CV) death: here the HRs were CHARM 0.81 (0.60-1.11), TOPCAT 0.69 (0.43, 1.12) and DIG 1.24 (0.94-1.64) and hence the composite of CV death or HF hospitalization: CHARM 0.76 (0.61-0.96), TOPCAT 0.72 (0.50, 1.05) [the TOPCAT primary also included a few cases of resuscitated cardiac arrest] and DIG 0.96 (0.79-1.17). In another recent report, 575 patients with HFmrEF were included in a meta-analysis of beta-blocker trials. Unfortunately, HF hospitalization was not reported as an endpoint but there was the suggestion that fatal outcomes might be reduced by beta-blockers in patients in this subgroup in sinus rhythm but

the numbers were small and the estimate of treatment effect uncertain/unreliable. This benefit was not as apparent for the non-fatal outcome examined which was CV hospitalization (or the composite of CV death or CV hospitalization).

The discrepancy between the studies may reflect the play of chance, given that all analyses were retrospective and had only moderate power or it may represent true differences in responsiveness to distinct pharmacological interventions among the three heart failure phenotypes identified. Beta-blockers and angiotensin converting enzyme (ACE) inhibitors (and probably ARBs) are beneficial in patients with coronary artery disease (and hypertension and diabetes), even in the absence of a reduced LVEF. No such suggestion has been made for digoxin in patients in sinus rhythm. Hence, beta-blockers and candesartan may truly have had a beneficial effect on cardiovascular mortality in patients with HFmrEF whereas such a benefit might not have been anticipated with digoxin. Interpretation of the effect of spironolactone is more difficult. This drug does not seem to reduce mortality in patients with a normal or near-normal LVEF and whether there is a mortality benefit in patients with HFmrEF is uncertain because of the small size of this subgroup in TOPCAT and the resultant wide confidence intervals around the estimate of treatment-effect in these patients.

It is important to expression a word of caution about all three of these studies. The retrospective nature and low power of each has been alluded to above. The beta-blocker analyses did not report tests of whether there was an interaction between treatment effect and LVEF (using LVEF as either a categorical or as a continuous variable) and in both CHARM and DIG, where such tests were done, they were not significant for the primary composite outcome, cardiovascular death or HF hospitalization. Although such tests have low power, they suggest that we cannot definitively conclude that the effect of the treatments reviewed differ according to LVEF, even if the overall impression is that they do. This is a significant

limitation of all 3 analyses discussed. The TOPCAT investigators could not do a similar analysis because the trial did not include patients with a LVEF <45%.

That all patients in DIG were in sinus rhythm is both a weakness and a strength of this analysis – clearly many patients with HF do have atrial fibrillation but inclusion of those only in sinus rhythm removed the confounding influence of this arrhythmia when interpreting outcomes and effect of therapy. DIG is also an old dataset, collected at a time when neither beta-blockers or mineralocorticoid receptor antagonists were routinely used to treat patients with HF. Again, this is both a weakness and strength. While the effects of digoxin might be less in patients treated with contemporary therapy, lack of two of these therapies makes it easier to identify the effect of digoxin. Lack of these treatments also makes it less likely that the HFmrEF patients in DIG included many patients with "recovered LVEF" i.e. the HFmrEF patients in DIG were likely a more homogenous group than in more current cohorts.[2, 16]

In summary, while patients with HFmrEF exhibited some similarities to those with HFrEF in terms of baseline characteristics, their rates of fatal and non-fatal heart failure events were substantially lower than in individuals with HFrEF. This and a smaller effect of digoxin on HF hospitalization in patients with HFmrEF do not support the view that left ventricular systolic dysfunction is as important in this type of heart failure as in HFrEF.

Appendix: *VICCTA-Heart Failure Steering Committee members: K.R Lees, J.J.V McMurray and A.H Abdul-Rahim.

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FIGURE LEGENDS

Figure 1. Kaplan-Meier cumulative risk of composite outcome of CV death or HF hospitalisation according to LVEF stratum.

Figure 2. Incidence rate of composite outcome of CV death or HF hospitalisation according to LVEF (spline analysis)

Point estimates (the black solid line) and 95% confidence intervals (area between the dotted lines) for the rates of the composite outcome of cardiovascular death or heart failure hospitalisation according to LVEF. Rates are shown as per 100 patient-years.

Figure 3. Effect of digoxin on the composite outcome of CV death or HF hospitalisation according to LVEF (fractional polynomial analysis).

Digoxin to placebo hazard ratio (the black solid line) and 95% confidence interval (area between the dotted lines) for the composite outcome of cardiovascular death or heart failure hospitalisation according to LVEF. A hazard ratio of 1.0 is indicated by the solid horizontal line. A hazard ratio of <1.0 favours digoxin.

TABLES

Table 1. Baseline characteristics according to the ejection fraction stratum.

	HFrEF (n=5874)	**HFmrEF** (n=1195)	**HFpEF** (n=719)	**p-value**
***Demographics,* n (%)**				
Age, year	63.4 ±10.9	64.5 ±10.6	67.3 ±10.4	<0.001
Caucasians	5010 (85.3)	1034 (86.5)	616 (85.7)	0.538
Female sex	1240 (21.1)	345 (28.9)	341 (47.4)	<0.001
NYHA class				<0.001
I	757 (12.9)	197 (16.5)	149 (20.7)	
II	3095 (52.7)	745 (62.3)	397 (55.2)	
III	1886 (32.1)	240 (20.1)	161 (22.4)	
IV	131 (2.2)	12 (1.0)	11 (1.5)	
Duration of heart failure, year	2.5 ±3.1	2.4 ±2.9	2.2 ±2.8	0.041
LV Ejection Fraction, %	26.4 ±7.5	43.3 ±2.8	58.5 ±7.6	<0.001
Cardiothoracic ratio	0.53 ±0.1	0.51 ±0.1	0.52 ±0.1	<0.001
No. of signs or symptoms of CHF[†]				<0.001
0	67 (1.1)	9 (0.8)	4 (0.6)	
1	125 (2.1)	33 (2.8)	7 (1.0)	
2	379 (6.5)	131 (11.0)	39 (5.4)	
3	499 (8.5)	145 (12.1)	60 (8.3)	
≥4	4802 (81.8)	877 (73.3)	609 (84.7)	
Baseline vital signs				
BP, mmHg				
Systolic	124.6 ±19.6	133.4 ±19.9	138.9 ±21.9	<0.001
Diastolic	74.6 ±11.3	77.1 ±10.7	76.5 ±11.7	<0.001
Heart rate, beats/min	79.1 ±12.7	76.1 ±12.1	76.2 ±11.8	<0.001
BMI, kg/m^2	27.0 ±5.2	27.7 ±5.2	29.0 ±6.7	<0.001
Serum creatinine, μmol/L	113.9 ±32.4	110.5 ±32.9	111.2 ±35.8	0.001
***Medical history,* n (%)**				
Myocardial Infarction	3833 (65.3)	754 (63.1)	321 (44.7)	<0.001
Angina	1553 (26.4)	350 (29.3)	212 (29.5)	0.043
Hypertension	2585 (44.0)	640 (53.6)	449 (62.5)	<0.001
Diabetes	1647 (28.0)	362 (30.3)	209 (29.1)	0.264
Previous digoxin use	2655 (45.2)	446 (37.3)	264 (36.7)	<0.001
***Medication,* n (%)**				
Potassium-sparing diuretic	452 (7.7)	91 (7.6)	53 (7.4)	0.907
Other diuretics	4669 (79.5)	841 (70.4)	566 (78.7)	<0.001
ACE inhibitor	5576 (94.9)	1081 (90.5)	617 (85.8)	0.097
Nitrate	2508 (42.7)	497 (41.6)	282 (39.2)	<0.001
Hydralazine	114 (1.9)	31 (2.6)	13 (1.8)	<0.001
Randomised to digoxin	2932 (49.9)	607 (50.8)	350 (48.7)	0.668

All continous values are given in mean ± standard deviation unless stated otherwise. n(%): number of observations (percentage of observations within the group). HFrEF: heart failure with redcued ejection fraction. HFmrEF: heart failure with mid-range ejection fraction. HFpEF: heart failure with preserved ejection fraction. LV: left ventricle. CHF: chronic heart failure. NYHA: New York Heart Association. BMI: body mass index. ACE: angiotensin converting enzyme.

† The clinical signs or symptoms studied included rales, elevated jugular venous pressure, peripheral oedema, dyspnoea at rest or on exertion, orthopnoea, limitation of activity, S_3 gallop and radiological evidence of pulmonary congestion.

Table 2. Clinical signs or symptoms as baseline according to the ejection fraction stratum.

	HFrEF (n=5874)	**HFmrEF** (n=1195)	**HFpEF** (n=719)	**p-value**
Presence of clinical signs or symptoms				
Limitation of activity	5464 (93.0)	1082 (90.5)	672 (93.5)	0.008
Dyspnoea at rest or on exertion	5593 (95.2)	1138 (95.2)	697 (96.9)	0.128
Orthopnoea	4186 (71.3)	759 (63.5)	521 (72.5)	<0.001
Peripheral oedema	3054 (52.0)	610 (51.1)	449 (62.5)	<0.001
Elevated jugular venous pressure	3142 (53.5)	527 (44.1)	356 (49.5)	<0.001
Rales	4233 (72.1)	788 (65.9)	544 (75.7)	<0.001
Radiological pulmonary congestion	4026 (68.5)	706 (59.1)	461 (64.1)	<0.001
S_3 gallop	3049 (51.9)	453 (37.9)	237 (33.0)	<0.001

Table 3. Clinical outcomes accoridng to ejection fraction stratum and randomised treatment assignment.

Outcome, n (rate)	HFrEF (<40%)			HFmrEF (40-49%)			HFpEF (≥50%)			p-value for interaction
	Placebo (n= 2942)	Digoxin (n= 2932)	HR (95% CI)	Placebo (n= 588)	Digoxin (n= 607)	HR (95% CI)	Placebo (n= 369)	Digoxin (n= 350)	HR (95% CI)	
CV death or HF hospitalisation	1498 (22.2)	1344 (18.3)	0.83 (0.77-0.89)	194 (11.9)	198 (11.5)	0.96 (0.79-1.17)	119 (12.1)	107 (10.8)	0.92 (0.71-1.20)	0.327
- CV death	929 (11.0)	926 (10.9)	0.99 (0.91-1.09)	90 (4.8)	113 (6.0)	1.24 (0.94-1.64)	71 (6.3)	67 (6.2)	1.03 (0.74-1.44)	0.326
- HF hospitalisation	1067 (15.8)	812 (11.0)	0.71 (0.65-0.77)	139 (8.5)	118 (6.9)	0.80 (0.63-1.03)	82 (8.3)	69 (6.9)	0.85 (0.62-1.17)	0.395
HF death or HF hospitalisation	1168 (17.3)	932 (12.7)	0.74 (0.68-0.81)	152 (9.3)	134 (7.8)	0.83 (0.66-1.05)	90 (9.1)	77 (7.7)	0.88 (0.65-1.19)	0.448
- HF death	422 (5.0)	371 (4.4)	0.87 (0.76-1.01)	31 (1.7)	29 (1.5)	0.93 (0.56-1.55)	30 (2.7)	24 (2.2)	0.89 (0.52-1.52)	0.959
All-cause death	1091 (12.9)	1066 (12.6)	0.97 (0.89-1.06)	130 (7.0)	143 (7.6)	1.08 (0.85-1.37)	89 (7.9)	87 (8.0)	1.06 (0.79-1.42)	0.693

Rate per 100 patient years. CV=cardiovascular. HF=heart failure. P-value for interaction between treatment groups with ejection fraction categories.

All reported hazard ratios were adjusted for age and sex.