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ORIGINAL RESEARCH ARTICLE

# Effect of disease-modifying agents and their association with mortality in multi-morbid patients with heart failure with reduced ejection fraction

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## Abstract

**Aims** An increasing proportion of patients with heart failure with reduced ejection fraction (HFrEF) have co-morbidities. The effect of these co-morbidities on modes of death and the effect of disease-modifying agents in multi-morbid patients is unknown.

**Methods and results** We performed a prospective cohort study of ambulatory patients with HFrEF to assess predictors of outcomes. We identified four key co-morbidities—ischaemic aetiology of heart failure, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD)—that were highly prevalent and associated with an increased risk of all-cause mortality. We used these data to explore modes of death and the utilization of disease-modifying agents in patients with and without these co-morbidities. The cohort included 1789 consecutively recruited patients who had an average age of 69.6 ± 12.5 years, and 1307 (73%) were male. Ischaemic aetiology of heart failure was the most common co-morbidity, occurring in 1061 (59%) patients; 503 (28%) patients had diabetes mellitus, 283 (16%) had COPD, and 140 (8%) had CKD stage IV/V. During mean follow-up of 3.8 ± 1.6 years, 737 (41.5%) patients died, classified as progressive heart failure ($n$ = 227, 32%), sudden ($n$ = 112, 16%), and non-cardiovascular deaths ($n$ = 314, 44%). Multi-morbid patients were older ($P < 0.001$), more likely to be male ($P < 0.001$), and had higher New York Heart Association class ($P < 0.001$), despite having higher left ventricular (LV) ejection fraction ($P = 0.001$) and lower LV end-diastolic diameter ($P = 0.001$). Multi-morbid patients were prescribed lower doses of disease-modifying agents, especially patients with COPD who received lower doses of beta-adrenoceptor antagonists (2.7 ± 3.0 vs. 4.1 ± 3.4 mg, $P < 0.001$) and were less likely to be implanted with internal cardioverter defibrillators (7% vs. 13%, $P < 0.001$). In multivariate analysis, COPD and diabetes mellitus conferred a >2.5-fold and 1.5-fold increased risk of sudden death, whilst higher doses of beta-adrenoceptor antagonists were protective (hazard ratio per milligram 0.92, 95% confidence interval 0.86–0.98, $P = 0.009$). Each milligram of bisoprolol-equivalent beta-adrenoceptor antagonist was associated with 9% ($P = 0.001$) and 11% ($P = 0.023$) reduction of sudden deaths in patients with <2 and ≥2 co-morbidities, respectively.

**Conclusions** Higher doses of beta-adrenoceptor antagonist are associated with greater protection from sudden death, most evident in multi-morbid patients. Patients with COPD who appear to be at the highest risk of sudden death are prescribed the lowest doses and less likely to be implanted with implantable cardioverter defibrillators, which might represent a missed opportunity to optimize safe and proven therapies for these patients.

**Keywords** Heart failure; Sudden cardiac death; Co-morbidities

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# Introduction

## Background

The prevalence of chronic heart failure continues to rise, at least in part owing to the widespread implementation of disease-modifying pharmacological therapies.[1–3] Use of these therapies has been accompanied by changes in the distribution of modes of death, particularly the relative contribution of sudden death.[4,5] Nevertheless, sudden death remains an important contributor to potentially preventable mortality in patients with heart failure with reduced ejection fraction (HFrEF),[6] with those with previous myocardial infarction, severe left ventricular (LV) systolic dysfunction, prior ventricular tachyarrhythmia, and co-existent diabetes mellitus being at the greatest risk.[7–9]

Additional contemporary epidemiologic changes include an increasingly older population of patients with HFrEF and proportion with co-morbidities.[10] Not only do co-morbidities contribute to disability, impairment of quality of life, and poor outcomes,[10] but they also complicate management strategies and result in more frequent and increased duration of hospitalizations.[11–13] It is not known whether multi-morbid patients achieve doses of disease-modifying agents, including angiotensin-converting enzyme-inhibitors (ACEi) and beta-adrenoceptor antagonists achieved in clinical trials. Furthermore, the effect of these medications in terms of reducing cardiovascular deaths in multi-morbid patients is not known.

The aims of this analysis were therefore, firstly, to report the real-world provision of disease-modifying agents in a cohort of patients with HFrEF attending specialist heart failure clinics in the UK and secondly, to explore the impact of multi-morbidity on modes of death in HFrEF, specifically whether co-morbidities alter the relative risk of sudden death. Finally, we aimed to determine whether multi-morbidity altered the effects of disease-modifying agents in preventing sudden death.

# Methods

## Study design

As described previously,[14–16] this was a prospective cohort study in unselected, ambulatory patients with HFrEF attending specialist cardiology clinics, with the *a priori* aim of describing contributors to outcome.

## Participants

Between June 2006 and December 2014, consecutive patients attending specialist cardiology clinics in four UK hospitals were approached to participate. Inclusion required patients to have stable signs and symptoms of chronic heart failure for at least 3 months, age $\geq$ 18 years, and LV ejection fraction (LVEF) $\leq$ 45% on transthoracic echocardiogram, based upon guidelines for diagnostic and therapeutic criteria in place at the time.[17,18]

## Variables and data sources

At the time of study recruitment, patient demographics, aetiology of LV impairment, past medical history, and functional capacity according to the New York Heart Association (NYHA) classification were collected. A venous blood sample was taken at enrolment and tested for serum haemoglobin, estimated glomerular filtration rate to stage chronic kidney disease (CKD) and serum albumin. We performed two-dimensional echocardiography and measured LV end-diastolic diameter (LVEDd), LVEF by Simpson's biplane method, pulmonary artery systolic pressure, and the presence of regional wall motion abnormality determined by qualitative method according to the American Society of Echocardiography recommendations at the time.[19] Prescription of ACEi, beta-adrenoceptor antagonist, loop diuretic, and mineralocorticoid receptor antagonist (MRA) were recorded. For the purpose of analysis, doses of ACEi, beta-adrenoceptor antagonist, and loop diuretic are expressed as equivalent doses, relative to the maximum licensed dosages of ramipril, bisoprolol, and furosemide as previously described.[20] Receipt of implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) was assessed during the 6 month period after study recruitment.

## Assessment of outcomes

All patients were registered with the UK Office of Population Censuses and Surveys, which provided details of the time of death, with final censorship occurring in November 2018. The primary outcomes of the current analysis were modes of death in patients with and without major co-morbidities. Secondly, we examined the association between doses of medication, provision of device therapy, and all-cause mortality and mode of death.

## Definitions

We identified four key co-morbidities: ischaemic aetiology of heart failure, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and CKD stage IV/V, which were highly prevalent in the population and associated with an increased risk of all-cause mortality (*Figure* S1). We then used these data to modes of death, which were classified as

cardiovascular (including stroke) or non-cardiovascular. Cardiovascular deaths were further divided into progressive heart failure or sudden deaths. Death due to progressive heart failure was a death occurring during decompensation or in patients with refractory symptoms. Sudden deaths were any death, witnessed or unwitnessed, occurring within 1 h of change in symptoms, or occurring during sleep or whilst the patient was unobserved.[21] Aetiology of LV impairment was classified as either due to ischaemic heart disease when there was previous myocardial infarction, coronary artery bypass grafting, coronary stenting at index presentation, evidence of inducible ischaemia on non-invasive imaging or scar suggesting infarction on cardiac magnetic resonance imaging, or non-ischaemic cardiomyopathy.

### Statistics

All statistical analyses were performed using IBM SPSS Statistics version 26 (IBM Corporation, Armonk, NY). After normality of distribution was demonstrated, continuous variables are expressed as mean ± standard deviation. Discrete variables are presented as number and percentages in parentheses. Groups were compared using $\chi^2$ for categorical variables and by Student's *t*-test or by one-way analysis of variance for continuous variables, as appropriate. Kaplan–Meier curves were used to plot survival and compared with log-rank test. Age–sex-adjusted and multivariate analyses used Cox proportional hazards regression. In all analyses, statistical significance was defined as $P < 0.05$.

### Ethical considerations

Ethical approval was given by the Leeds West Research Ethics Committee (07/Q1205/17) and conducted in accordance with the principles outlined in the Declaration of Helsinki. All patients gave informed written consent for inclusion and long-term electronic follow-up.

## Results

### Patients

During the study period, a total of 1802 patients with HFrEF were recruited. Of these, five had missing medication doses and eight were missing data on major co-morbidities. The final dataset for this analysis consisted on 1789 patients with an average age of 69.6 ± 12.5 years, of whom 1307 (73%) were male. A total of 472 (26%), 763 (43%), 446 (25%), and 108 (6%) had 0, 1, 2, or ≥3 major co-morbidities, respectively. Ischaemic aetiology of heart failure was the most common co-morbidity, occurring in 1061 (59%) patients; 503 (28%) patients had diabetes mellitus, 283 (16%) had COPD, and 140 (8%) had CKD stage IV/V (*Table 1*).

Descriptive data divided by the number of major co-morbidities are displayed in *Table 1*. Multi-morbid patients tended to be older and were more likely to be male. They were more symptomatic, as evidenced by a higher proportion with NYHA class III/IV symptoms despite higher LVEF and lower LVEDd. Serum haemoglobin and albumin were also lower in multi-morbid patients.

### Utilization of disease-modifying agents

Overall, patients with multi-morbidity were prescribed lower equivalent doses of beta-adrenoceptor antagonists and ACEi and were less likely to be prescribed the maximum licensed doses (*Table 1*). This was particularly evident in patients with COPD who were prescribed lower doses of beta-adrenoceptor antagonist, and those with CKD IV/V who received lower doses of ACEi (*Table 2*). The presence of any co-morbidity was associated with a higher furosemide equivalent dose of loop diuretic. In contrast, patients with ischaemic aetiology of heart failure received similar doses of beta-adrenoceptor antagonist and ACEi as those with non-ischaemic cardiomyopathy, and patients with diabetes mellitus were on average prescribed higher doses of both classes of medications. There was no clear relationship between the number of co-morbidities and the prescription of MRA, although those with ischaemic aetiology of heart failure and diabetes mellitus were more likely to be prescribed these. The provision of CRT was similar in patients divided by number of major co-morbidities (*Table 1*). Patients with an ischaemic aetiology were more likely to be implanted with CRT or ICD, whilst patients with COPD were less likely to receive an ICD than were those without COPD (*Table 2*).

### Mortality and modes of death

During an average follow-up of 3.8 ± 1.6 years, a total of 737 (41.5%) patients died. Modes of death were available for 713 (97%), and 24 were unclassifiable owing to lack of information. Of the classifiable deaths, progressive heart failure caused 227 (32%) deaths, whereas 112 (16%) were sudden. Non-cardiovascular death occurred in 314 (44%) patients.

### Mode of death and effect of multi-morbidity

We observed a stepwise increase in the rate of all modes of death in parallel with the number of major co-morbidities (*Figure 1*). When adjusted for age and sex, all major co-morbidities were associated with an increased risk of all-cause mortality (*Figure 2*). COPD was not associated with an increased risk of death from progressive heart failure,

**Table 1** Baseline characteristics of patients with 0, 1, 2, or ≥3 major co-morbidities

| | All patients (*n* = 1789) | 0 (*n* = 472) | 1 (*n* = 763) | 2 (*n* = 446) | ≥3 (*n* = 108) | *P*-value |
|---|---|---|---|---|---|---|
| Demographics | | | | | | |
| Age (years) | 69.6 ± 12.5 | 64.4 ± 14.9 | 70.6 ± 12.0 | 72.9 ± 9.4 | 72.7 ± 8.3 | **<0.001** |
| Male sex [*n* (%)] | 1307 (73) | 310 (66) | 578 (76) | 342 (77) | 77 (71) | **<0.001** |
| Major co-morbidities | | | | | | |
| Ischaemic aetiology [*n* (%)] | 1061 (59) | 0 (0) | 537 (70) | 417 (94) | 107 (99) | **<0.001** |
| Diabetes mellitus [*n* (%)] | 503 (28) | 0 (0) | 121 (16) | 283 (63) | 99 (92) | **<0.001** |
| COPD [*n* (%)] | 283 (16) | 0 (0) | 77 (10) | 135 (30) | 71 (66) | **<0.001** |
| Observations | | | | | | |
| NYHA class III/IV [*n* (%)] | 550 (31) | 92 (20) | 238 (31) | 166 (37) | 54 (50) | **<0.001** |
| SBP (mmHg) | 122.4 ± 21.6 | 122.4 ± 22.2 | 122.1 ± 20.9 | 121.4 ± 21.6 | 129.2 ± 23.1 | **0.02** |
| DBP (mmHg) | 71.5 ± 11.4 | 73.2 ± 11.9 | 71.3 ± 10.8 | 70.2 ± 11.5 | 70.1 ± 12.1 | **0.002** |
| Heart rate (b.p.m.) | 75.3 ± 17.9 | 79.2 ± 18.8 | 73.8 ± 18.0 | 74.1 ± 16.6 | 73.3 ± 15.0 | **<0.001** |
| Echocardiogram | | | | | | |
| LVEDd (mm) | 57.2 ± 8.9 | 58.5 ± 9.1 | 57.0 ± 8.8 | 56.4 ± 8.8 | 55.8 ± 8.6 | **0.001** |
| LVEF (%) | 32.0 ± 9.5 | 30.6 ± 10.0 | 32.3 ± 9.3 | 32.6 ± 9.1 | 33.7 ± 9.0 | **0.001** |
| PASP (mmHg) | 37.0 ± 13.6 | 34.6 ± 12.7 | 37.4 ± 13.1 | 37.0 ± 13.0 | 44.4 ± 19.6 | **0.002** |
| RWMA [*n* (%)] | 689 (39) | 92 (34) | 324 (72) | 220 (86) | 53 (83) | **<0.001** |
| Blood tests | | | | | | |
| Hb (g/L) | 13.5 ± 1.8 | 14.1 ± 1.6 | 13.4 ± 1.7 | 13.1 ± 1.8 | 12.4 ± 1.8 | **<0.001** |
| eGFR (mL/min/1.73 $m^2$) | 57.7 ± 19.7 | 65.4 ± 16.1 | 58.6 ± 18.3 | 52.3 ± 20.5 | 40.9 ± 22.8 | **<0.001** |
| Albumin (g/L) | 42.9 ± 3.6 | 43.4 ± 3.4 | 43.0 ± 3.7 | 42.5 ± 3.4 | 42.4 ± 3.6 | **<0.001** |
| Device therapy | | | | | | |
| ICD/CRT-D [*n* (%)] | 209 (12) | 23 (5) | 117 (15) | 62 (14) | 7 (7) | **<0.001** |
| CRT-P [*n* (%)] | 452 (25) | 103 (22) | 206 (27) | 118 (27) | 25 (23) | 0.19 |
| Medications | | | | | | |
| Bisoprolol dose (mg) | 3.9 ± 3.4 | 4.0 ± 3.3 | 3.9 ± 3.4 | 3.9 ± 3.4 | 3.3 ± 3.0 | 0.26 |
| Maximum bisoprolol dose [*n* (%)] | 271 (15) | 71 (15) | 122 (16) | 66 (15) | 12 (11) | 0.61 |
| Ramipril dose (mg) | 4.9 ± 3.5 | 4.8 ± 3.4 | 5.1 ± 3.6 | 5.0 ± 3.6 | 3.9 ± 3.4 | **0.009** |
| Maximum ramipril dose [*n* (%)] | 492 (28) | 114 (24) | 229 (30) | 130 (29) | 19 (18) | **0.012** |
| Furosemide dose (mg) | 51.3 ± 49.6 | 41.6 ± 46.1 | 45.1 ± 43.1 | 64.7 ± 54.3 | 82.6 ± 62.3 | **<0.001** |
| MRA [*n* (%)] | 684 (38) | 161 (34) | 287 (38) | 196 (44) | 40 (37) | **0.021** |

Continuous variables are expressed as mean ± standard deviation; discrete variables are presented as number and percentages in parentheses. Comparisons across groups by ANOVA or $\chi^2$ for continuous and discrete variables, respectively.
CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; ICD, implantable cardioverter defibrillator; LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RWMA, regional wall motion; SBP, systolic blood pressure.
Bold emphasis is for *P* values which are statistically significant (<0.05).

although it was associated with a 2.5-fold increased risk of sudden death. CKD stage IV/V was associated with all-cause mortality and death from progressive heart failure, but the association with sudden death was non-significant. Diabetes mellitus and ischaemic aetiology of heart failure increased the risk of all modes of death.

In the multivariate analysis, major co-morbidities were associated with all-cause mortality, with the exception of ischaemic aetiology of heart failure (*Table 3*). However, compared with all-cause mortality and progressive heart failure deaths (*Table 4*), sudden deaths were not associated with age, NYHA class III/IV symptoms, or LVEDd but were associated with lower LVEF (as a continuous variable) (*Table 5*).

## Mode of death and disease-modifying agents

In unadjusted survival analysis, higher doses of beta-adrenoceptor antagonist were associated with lower rates of all-cause, progressive heart failure, and sudden deaths (*Figure 3*), whereas reductions in all-cause mortality with higher doses of ACEi were primarily driven by a reduction in progressive heart failure deaths and not sudden deaths (*Figure 4*). Prescription of MRA was not associated with lower rates of all-cause mortality or sudden deaths; however, there was a lower rate of progressive heart failure deaths.

There were similar rates in the rates of sudden deaths stratified by the dose of beta-adrenoceptor antagonist in those with and without specific co-morbidities, which were most evident in patients with ≥2 co-morbidities (*Figure 5*). When adjusted for age and sex, there was a relative reduction in sudden death of 9% per milligram bisoprolol equivalent dose of beta-adrenoceptor antagonist (*P* = 0.001), which was 11% (*P* = 0.023) in patients with ≥2 co-morbidities and 8% (*P* = 0.071) in patients with <2 co-morbidities, with the exception of diabetes mellitus, which was associated with a relative reduction in sudden death of 14% per milligram (*P* = 0.005) compared with 7% (*P* = 0.084) in those without diabetes. In the multivariate analysis, dosing of either class of medication was not associated with all-cause mortality or non-cardiovascular deaths

**Table 2** Baseline characteristics of patients with specific co-morbidities

| | Ischaemic heart failure ($n$ = 1061) | Non-ischaemic cardiomyopathy ($n$ = 728) | Diabetes mellitus ($n$ = 503) | No diabetes mellitus ($n$ = 1286) | COPD ($n$ = 283) | No COPD ($n$ = 1506) | CKD IV/V ($n$ = 140) | No CKD ($n$ = 1649) |
|---|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | | |
| Age (years) | 72.2 ± 10.3** | 65.9 ± 14.4 | 70.2 ± 10.7 | 69.4 ± 13.2 | 73.2 ± 8.5** | 69.0 ± 13.0 | 74.1 ± 11.8** | 69.3 ± 12/5 |
| Male sex [$n$ (%)] | 832 (78)** | 475 (65) | 383 (76) | 924 (72) | 195 (69) | 1112 (74) | 85 (61)** | 1222 (74) |
| Observations | | | | | | | | |
| NYHA class III/IV [$n$ (%)] | | | | | | | | |
| SBP (mmHg) | 121.9 ± 21.6 | 123.2 ± 21.7 | 125.0 ± 21.0** | 121.5 ± 21.8 | 122.9 ± 22.5 | 122.4 ± 21.5 | 124.1 ± 23.4 | 122.3 ± 21.5 |
| DBP (mmHg) | 70.5 ± 11.1** | 72.9 ± 11.7 | 71.0 ± 11.2 | 71.7 ± 11.5 | 71.3 ± 12.0 | 71.5 ± 11.3 | 68.9 ± 11.8* | 71.7 ± 11.4 |
| Heart rate (b.p.m.) | 71.9 ± 16.2** | 80.3 ± 19.1 | 75.3 ± 17.2 | 75.3 ± 18.1 | 79.2 ± 17.4** | 74.6 ± 17.9 | 73.0 ± 18.0 | 75.5 ± 17.9 |
| Echocardiogram | | | | | | | | |
| LVEDd (mm) | 56.9 ± 8.8 | 57.6 ± 9.1 | 56.3 ± 8.8* | 57.5 ± 9.0 | 55.9 ± 8.7* | 57.4 ± 8.9 | 55.3 ± 9.0* | 57.3 ± 8.9 |
| LVEF (%) | 32.5 ± 9.1* | 31.2 ± 10.0 | 33.1 ± 9.1** | 31.5 ± 9.6 | 32.1 ± 9.6 | 31.9 ± 9.5 | 33.1 ± 9.2 | 31.9 ± 9.5 |
| PASP (mmHg) | 37.0 ± 14.0 | 36.9 ± 13.1 | 40.8 ± 15.1** | 35.8 ± 12.9 | 38.0 ± 13.8 | 36.8 ± 13.6 | 43.4 ± 16.8** | 36.4 ± 13.1 |
| RWMA [$n$ (%)] | 564 (86)** | 125 (33) | 193 (72)* | 496 (64) | 112 (70) | 577 (66) | 57 (74) | 632 (66) |
| Blood tests | | | | | | | | |
| Hb (g/L) | 13.3 ± 1.7** | 13.7 ± 1.8 | 13.0 ± 1.8** | 13.6 ± 1.7 | 13.4 ± 1.8 | 13.5 ± 1.8 | 11.8 ± 1.7** | 13.6 ± 1.7 |
| eGFR (mL/min/1.73 $m^2$) | 54.6 ± 19.3** | 62.4 ± 19.3 | 54.4 ± 20.7** | 59.1 ± 19.1 | 58.1 ± 20.1 | 57.7 ± 19.6 | 22.3 ± 6.7** | 60.8 ± 17.3 |
| Albumin (g/L) | 42.8 ± 3.5 | 43.0 ± 3.7 | 42.8 ± 3.4 | 43.0 ± 3.6 | 42.4 ± 3.5** | 43.0 ± 3.6 | 40.9 ± 4.1** | 43.1 ± 3.5 |
| Device therapy | | | | | | | | |
| ICD/CRT-D [$n$ (%)] | 175 (17)** | 34 (5) | 58 (12) | 151 (12) | 19 (7)** | 190 (13) | 10 (7) | 199 (12) |
| CRT-P [$n$ (%)] | 295 (28)* | 157 (22) | 125 (25) | 327 (25) | 62 (22) | 390 (26) | 36 (26) | 416 (25) |
| Medications | | | | | | | | |
| Bisoprolol equivalent dose (mg) | 3.9 ± 3.4 | 3.8 ± 3.4 | 4.2 ± 3.5* | 3.7 ± 3.3 | 2.7 ± 3.0** | 4.1 ± 3.4 | 3.6 ± 3.0 | 3.9 ± 3.4 |
| Maximum bisoprolol dose [$n$ (%)] | 161 (15) | 110 (15) | 92 (18)* | 179 (14) | 20 (7)** | 251 (17) | 17 (12) | 254 (15) |
| Ramipril equivalent dose (mg) | 5.0 ± 3.6 | 4.9 ± 3.5 | 5.3 ± 3.7** | 4.8 ± 3.5 | 4.5 ± 3.3* | 5.0 ± 3.6 | 3.1 ± 3.2** | 5.1 ± 3.5 |
| Maximum ramipril dose [$n$ (%)] | 301 (28) | 191 (26) | 168 (33)** | 324 (25) | 60 (21)* | 432 (29) | 18 (13)** | 474 (29) |
| Furosemide equivalent dose (mg) | 53.8 ± 50.5* | 47.7 ± 48.1 | 68.3 ± 55.9** | 44.7 ± 45.3 | 58.2 ± 50.0* | 50.0 ± 49.5 | 83.0 ± 62.1** | 48.6 ± 47.5 |
| MRA [$n$ (%)] | 436 (41)** | 248 (34) | 216 (43)* | 468 (36) | 101 (36) | 583 (39) | 48 (34) | 636 (39) |

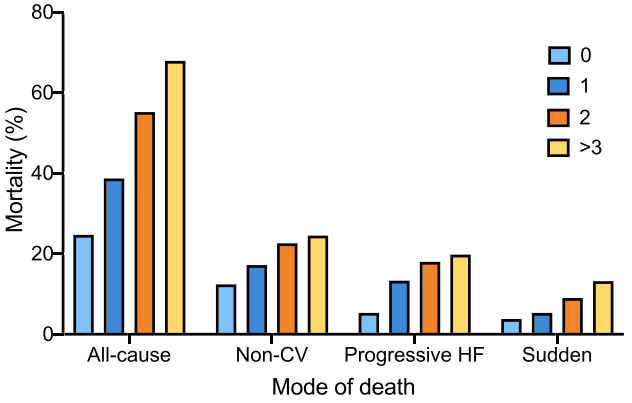
Continuous variables are presented as mean ± standard deviation; discrete variables as number (percentage).
CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; HF, heart failure; ICD, implantable cardioverter defibrillator.
*$P < 0.05$.
**$P < 0.005$.

(*Table 3*); however, the association between dose of ACEi and progressive heart failure death (*Table 4*) and of beta-adrenoceptor antagonist and sudden death was statistically significant (*Table 5*).

## Discussion

In this analysis, we have reported the real-world provision of disease-modifying agents in patients with HFrEF attending specialist heart failure clinics in the UK. The novel findings are that multi-morbidity confers an additional risk of all-cause mortality, particularly due to sudden death, despite the competing risk of non-cardiovascular death for these patients. A diagnosis of COPD or diabetes mellitus was associated with >2.5-fold and 1.5-fold increased risk, even when corrected for age, ischaemic aetiology of heart failure, and degree of LV impairment. Patients with multi-morbidity, especially COPD, were on average prescribed lower doses of beta-adrenoceptor antagonist and less likely to be implanted

**Figure 1** Bar chart to show the modes of death in patients with 0, 1, 2, and ≥3 major co-morbidities. Patients with multi-morbidity are at increased risk of all-cause, non-cardiovascular, progressive heart failure and sudden death.




with ICDs. Higher doses of beta-adrenoceptor antagonists were associated with lower rates of sudden death, especially evident in multi-morbid patients, and there was a modest reduction in sudden death associated with ICD implantation. Cumulatively, these data suggest that there might be a missed opportunity to optimize disease-modifying agents to reduce the risk of sudden death in patients with HFrEF and that patients with co-morbidity might have the most to gain from targeted dose optimization and device implantation.

## Multi-morbidity and the risk of sudden death in heart failure with reduced ejection fraction

To date, few studies have reported the association between multi-morbidity and modes of death in HFrEF. In one retrospective analysis of an historic cohort including 824 patients, multi-morbidity was found to reduce the risk of sudden death, attributed to the competing risk of non-sudden death.[22] However, this study was limited by a low rate of sudden deaths ($n$ = 30), and patients were enrolled between 1998 and 2004, predating the increased penetration of contemporaneous medical therapy in HFrEF. This study also defined multi-morbidity using the Charlson co-morbidity index, which is heavily weighted towards advanced age. In our analysis, we have shown that age is not associated with an increased risk of sudden death in HFrEF but is a major driver of all-cause mortality. Our dataset included 112 sudden death events allowing the description of a stepwise increase in the relative risk of sudden death in those with multiple major co-morbidities. Our data do not describe the effects of other co-morbidities, such as hypertension and atrial fibrillation on modes of death; however, in our patients, there were no significant differences in all-cause mortality in patients with and without these.[23]

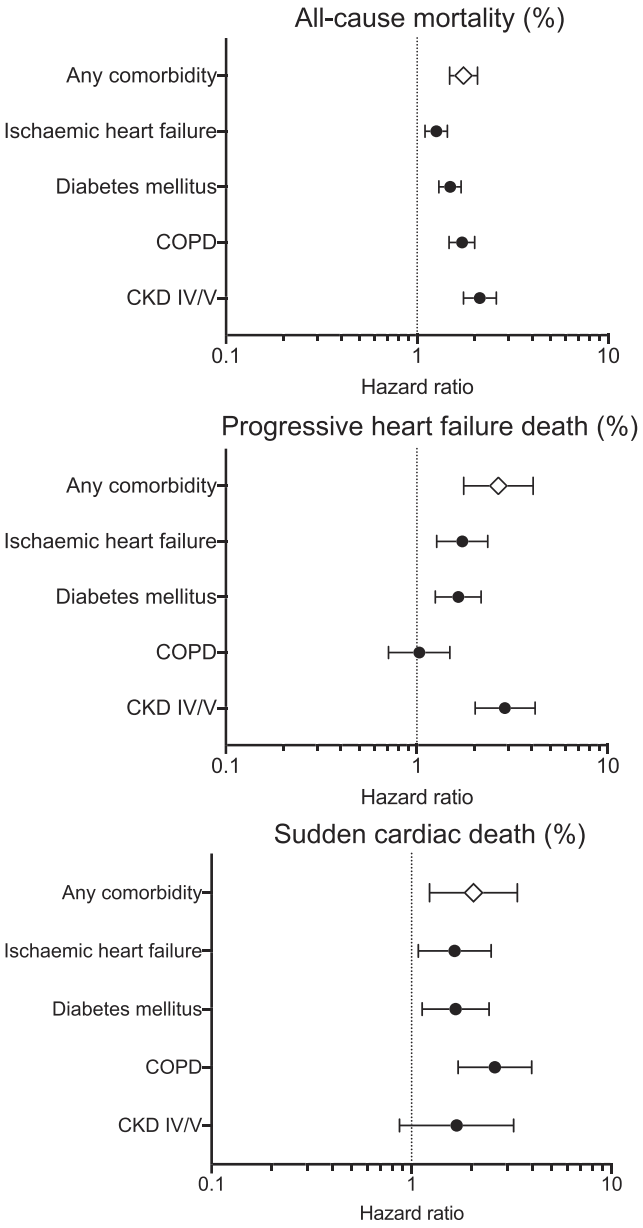
Sudden deaths in patients with HFrEF are often caused by ventricular tachyarrhythmias, one driver of which could be acute coronary syndromes.[24] Our findings might therefore be partially explained by a greater burden of coronary artery disease in patients with diabetes mellitus, COPD, and CKD. However, we found that diabetes mellitus and COPD were independent risk factors for sudden death even after correction for ischaemic aetiology of heart failure. Furthermore, clinical trials of statins,[25,26] aspirin, and anticoagulants,[27,28] which reduce the incidence of acute coronary syndromes, do not reduce sudden death in HFrEF. Alternative contributors could include myocardial fibrosis, which is more common in people with diabetes mellitus, is found in patients with and without ischaemic heart disease,[29] and is a substrate for ventricular tachyarrhythmias. Diabetes mellitus increased the risk of sudden death, despite higher doses of beta-adrenoceptor antagonists and ACEi in this cohort and a similar ICD implantation rate as non-diabetic patients. COPD is associated with sudden death and an increased risk of ventricular tachyarrhythmias[30] in patients with and without HFrEF, related to the duration of disease and the frequency of exacerbations[31] possibly due to autonomic dysregulation,[32] higher resting heart rates,[33] hypoxia, and chronic systemic inflammation.[31]

## The role of medical and device therapy in preventing sudden death

Contemporary medical and device therapies have resulted in dramatic reductions in sudden deaths in patients with HFrEF between therapeutic eras.[4] Medical therapy including ACEi,[34,35] beta-adrenoceptor antagonists,[2,3] and MRA[36,37] synergistically reduce all-cause mortality in HFrEF; and in our patients, we observed a clear stepwise reduction in the risk of all-cause mortality in patients receiving the highest doses of ACEi and beta-adrenoceptor antagonists. The association between higher doses of ACEi and all-cause mortality was primarily due to lower rates of progressive heart failure, whereas beta-adrenoceptor antagonists were associated with lower rates of both progressive heart failure and sudden deaths. The prescription of MRA was associated with lower rates of progressive heart failure deaths but not all-cause mortality or sudden deaths.

Multi-morbid patients were on average prescribed lower doses of disease-modifying pharmacotherapies than were patients without co-morbidities; in particular, we observed lower dosing of ACEi in those with CKD and of beta-adrenoceptor antagonists in those with COPD. Although key co-morbidities were associated with lower dosage of pharmacological therapy, we lack qualitative data on the reasons for failure to up-titrate for patients in whom blood pressure and heart rate allowed. The prescription of beta-adrenoceptor antagonists for patients with COPD is typically well tolerated with minimal changes in lung function

**Figure 2** Forrest plot showing the hazard of all-cause, progressive heart failure, and sudden death in patients with major co-morbidities. Any co-morbidities, but particularly COPD and diabetes mellitus, increase the risk of sudden death.




and improvements in survival even in those with the most severe disease.[38] However, the use of non-selective agents has been shown to reduce persistence time and to increase discontinuation rates and the risk of heart failure hospitalization, and so therapies should be tailored for individual patients.[39] In our patients, those with diabetes mellitus were prescribed, on average, higher doses of beta-adrenoceptor antagonists. Historically, there have been concerns about prescribing these medications to those receiving insulin or sulfonylureas owing to perceived risks of masking symptoms of hypoglycaemia or prolonging these episodes.[40] However, in clinical trials, rates of hypoglycaemia are not different, and the theoretical risks are far outweighed by the established benefits.[3]

In our patients, more severely impaired LV function was strongly associated with an increased risk of sudden death. Treatments such as CRT[41,42] and angiotensin-receptor neprilysin inhibitor (ARNI) reduce the risk of sudden death, primarily by their ability to promote reverse ventricular remodelling, and beta-adrenoceptor antagonists might also reduce the risk of sudden mechanical failure by facilitating dose-related improvement in LV function and are associated


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**Table 3** Multivariate regression analysis of all-cause mortality in all patients

| | Hazard ratio | 95% CI | *P*-value |
|---|---|---|---|
| Age (per year) | 1.04 | 1.03–1.05 | **<0.001** |
| Male sex | 1.75 | 1.49–2.06 | **<0.001** |
| Ischaemic heart failure | 1.09 | 0.94–1.26 | 0.27 |
| Diabetes mellitus | 1.32 | 1.14–1.53 | **<0.001** |
| COPD | 1.65 | 1.40–1.94 | **<0.001** |
| NYHA class III/IV | 1.26 | 1.10–1.45 | **0.001** |
| LVEDd (per mm) | 1.00 | 0.99–1.01 | 0.73 |
| LVEF (per %) | 0.99 | 0.98–0.99 | **<0.001** |
| Hb (per g/dL) | 0.88 | 0.84–0.92 | **<0.001** |
| eGFR (per mL/min/1.73 $m^2$) | 0.99 | 0.99–1.00 | **0.001** |
| Albumin (per g/L) | 0.96 | 0.94–0.97 | **<0.001** |
| Bisoprolol equivalent dose (per mg) | 1.00 | 0.98–1.02 | 0.73 |
| Ramipril equivalent dose (per mg) | 0.98 | 0.96–1.00 | 0.066 |
| Furosemide equivalent dose (per mg) | 1.00 | 1.00–1.00 | **<0.001** |

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; Hb, haemoglobin; LVEDd, left ventricular diameter in diastole; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure.
Bold emphasis is for *P* values which are statistically significant (<0.05).

with similar improvements in survival whether target dose or heart rate is achieved.[43,44] However, beta-adrenoceptor antagonists are also protective against ventricular tachyarrhythmias and surges in the autonomic nervous system, which can precipitate electrical and mechanical instability and in part reduce the risk of sudden death, improving survival in those prescribed the highest doses.

Patients with COPD are around twice as likely to receive appropriate therapies when implanted with ICDs than are those without,[45] yet patients with COPD in our cohort were less likely to be implanted, the implications being that implantation should not be avoided in multi-morbid patients who are at the highest risk of sudden death. Whilst ICDs have an established role in the prevention of sudden cardiac death in both ischaemic heart failure and non-ischaemic cardiomyopathies,[46–48] in clinical trials, ~50–70% of sudden deaths are not prevented by implantation.[6] This is confirmed in the present study where ICDs were only modestly protective against sudden death contrasting with the strong associations with beta-adrenoceptor antagonists. Hence, other mechanisms of sudden death must be at play in HFrEF, which could include rapidly deteriorating pump function.

**Table 4** Multivariate regression analysis of progressive heart failure deaths in all patients

| | Hazard ratio | 95% CI | *P*-value |
|---|---|---|---|
| Age (per year) | 1.05 | 1.03–1.06 | **<0.001** |
| Male sex | 1.78 | 1.25–2.54 | **0.001** |
| Ischaemic heart failure | 1.45 | 1.04–2.01 | **0.028** |
| Diabetes mellitus | 1.32 | 0.98–1.79 | 0.072 |
| NYHA class III/IV | 1.41 | 1.06–1.87 | **0.019** |
| LVEDd (per mm) | 1.03 | 1.01–1.05 | **0.004** |
| LVEF (per %) | 0.98 | 0.96–0.99 | **0.007** |
| Hb (per g/dL) | 0.88 | 0.80–0.96 | **0.005** |
| eGFR (per mL/min/1.73 $m^2$) | 0.99 | 0.98–1.00 | **0.002** |
| Albumin (per g/L) | 0.96 | 0.93–1.00 | **0.045** |
| Bisoprolol equivalent dose (per mg) | 0.96 | 0.92–1.01 | 0.11 |
| Ramipril equivalent dose (per mg) | 0.93 | 0.89–0.97 | **0.001** |
| Furosemide equivalent dose (per mg) | 1.01 | 1.00–1.01 | **<0.001** |

CI, confidence interval; COPD, chronic obstructive pulmonary disease; DCM, dilated cardiomyopathy; Hb, haemoglobin; LVEDd, left ventricular diameter in diastole; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure.
Bold emphasis is for *P* values which are statistically significant (<0.05).

**Table 5** Multivariate regression analysis of sudden death in all patients

| | Hazard ratio | 95% CI | *P*-value |
|---|---|---|---|
| Age (per year) | 0.99 | 0.97–1.01 | 0.33 |
| Male sex | 1.83 | 1.11–3.00 | **0.017** |
| Ischaemic heart failure | 1.48 | 0.95–2.29 | 0.08 |
| Diabetes mellitus | 1.59 | 1.06–2.38 | **0.024** |
| COPD | 2.53 | 1.64–3.90 | **<0.001** |
| LVEF (per %) | 0.97 | 0.95–0.99 | **0.005** |
| eGFR (per mL/min/1.73 $m^2$) | 0.99 | 0.98–1.00 | **0.013** |
| Bisoprolol equivalent dose (per mg) | 0.92 | 0.86–0.98 | **0.009** |

CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.
Bold emphasis is for *P* values which are statistically significant (<0.05).

## Strengths and limitations

This is an analysis of data from a carefully characterized cohort of patients with HFrEF, with long-term follow-up. Our study reports the provision of medical and device therapy in a real-world population, with doses achieved similar to other observational studies with similar proportions with major co-morbidities, albeit a lower proportion with COPD.[49,50] The exclusion of patients with LVEF > 45% means that our findings are not generalizable to patients with heart failure with preserved ejection fraction but are applicable to many patients with heart failure and mid-range ejection fraction. The study was a retrospective analysis of modes of death, and misclassification is a possibility, although this is unlikely to be biased to a particular mode. We did not analyse the effect of other co-morbidities on modes of death or the effects of non-cardiovascular medications; however, we present an analysis of the four most prevalent major co-morbidities in the patient population studied.[10] The study predated the availability of ARNI, which are associated with additional reductions in progressive heart failure and sudden deaths.

**Figure 3** Kaplan–Meier plots of all-cause, progressive heart failure, and sudden death stratified by bisoprolol equivalent dose of beta-adrenoceptor antagonist. Escalating doses of beta-adrenoceptor antagonists are protective against all-cause, progressive heart failure, and sudden death.

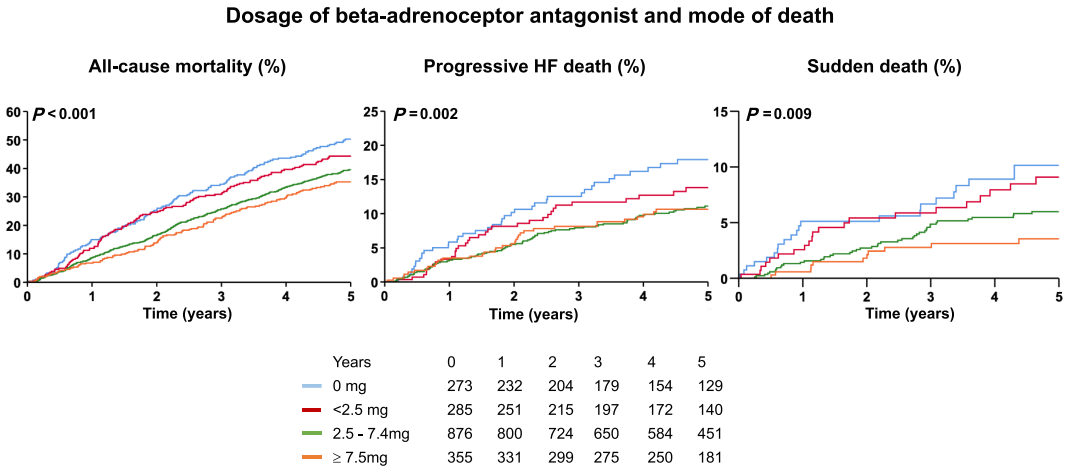


**Figure 4** Kaplan–Meier plots of all-cause, progressive heart failure, and sudden death stratified by ramipril equivalent dose of angiotensin-converting enzyme-inhibitors (ACEi). Escalating dose of ACEi is protective against all-cause and progressive heart failure death, but not sudden death.

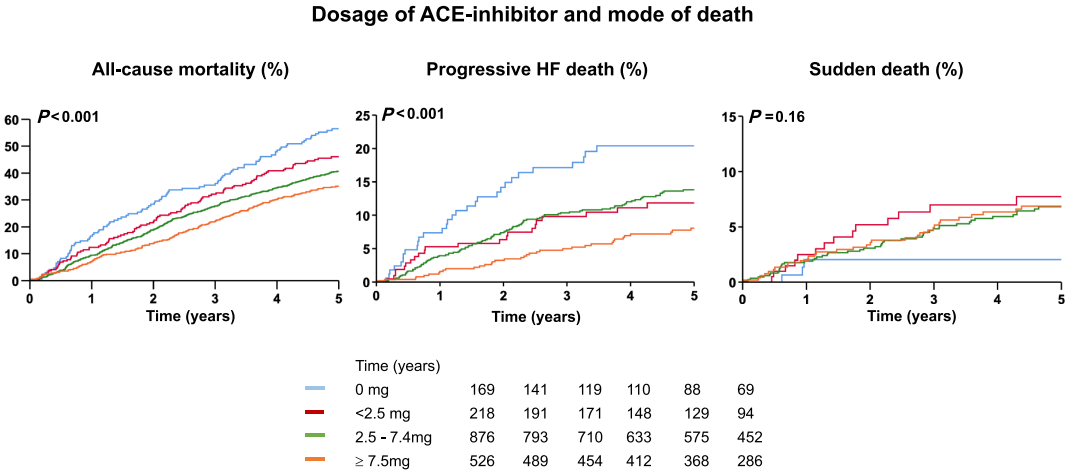



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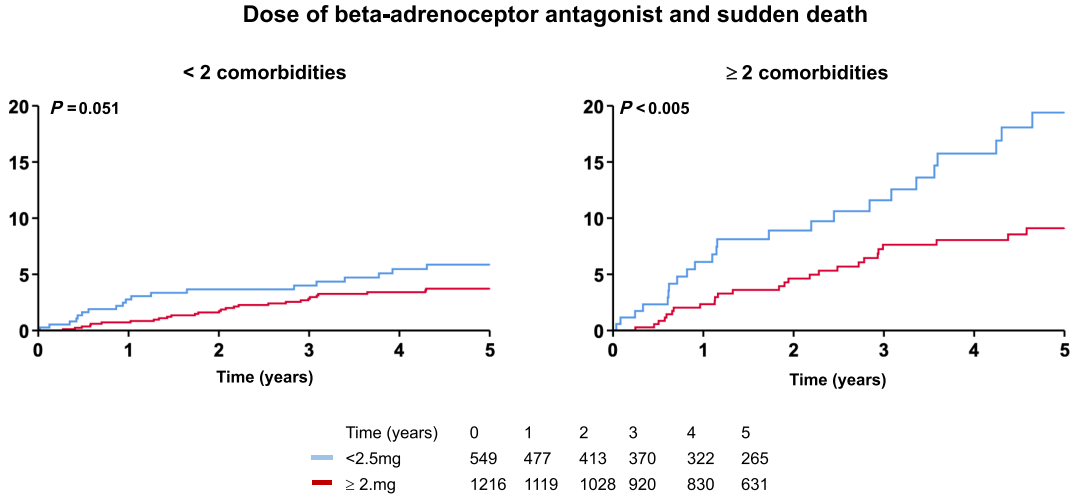
**Figure 5** Kaplan–Meier plots of sudden death stratified by bisoprolol equivalent dose of beta-adrenoceptor antagonist in patients with <2 and ≥2 major co-morbidities. Difference in survival between patients stratified by dose of beta-adrenoceptor antagonist is the greatest in those with ≥2 major co-morbidities.




## Conclusions

This study is the first to report real-world provision of disease-modifying agents and demonstrate an increased risk of sudden death in multi-morbid patients with HFrEF. Higher doses of beta-adrenoceptor antagonist are associated with greater protection from sudden death, most evident in multi-morbid patients. Patients with COPD who appear to be at the highest risk of sudden death are prescribed the lowest doses of beta-adrenoceptor antagonists and less likely to be implanted with ICDs. This might represent a missed opportunity to optimize safe and proven therapies, and additional efforts are needed where co-morbidities exist.

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## Conflict of interest

K.K.W. has received speakers' fees and honoraria from Medtronic, Cardiac Dimensions, Novartis, Abbott, BMS, Pfizer, and Bayer and has received an unconditional research grant from Medtronic to fund a collaborative PhD fellowship program, which supports A.O.K. and J.E.L None of the other authors have conflicts of interest to declare.

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## Author Contributions

S.S., K.K.W., and M.T.K. researched the topic and devised the study. R.C. and M.T.K. collected and maintained a prospective patient registry of HFrEF patients. S.S. and R.C. undertook primary statistical analysis. S.S. and K.K.W. produced the first draft of the manuscript. All other co-authors contributed equally to manuscript preparation.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** All-cause mortality in patients with and without major co-morbidities.

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