Title: Impact of multimorbidity on mortality in HFrEF: Which comorbidities matter most? – An analysis of PARADIGM-HF and ATMOSPHERE

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ABSTRACT

Aims

Multimorbidity, the coexistence of two or more chronic conditions, is synonymous with heart failure(HF). How risk related to comorbidities compare at individual and population levels is unknown. The aim of this study is to examine the risk related to comorbidities, alone and in combination, both at individual and population levels.

Methods

Using two clinical trials in HF- the Prospective comparison of ARNI(Angiotensin Receptor Neprilysin Inhibitor) with ACEI(Angiotensin Converting Enzyme Inhibitor) to Determine Impact on Global Mortality and morbidity in HF trial(PARADIGM-HF) and the Aliskiren trial to Minimize OutcomeS in Patients with HF trial(ATMOSPHERE), we identified the ten most common comorbidities and examined 45 possible pairs. We calculated population attributable fractions(PAF) for all-cause death and relative excess risk due to interaction with Cox proportional hazard models.

Results

Of 15066 patients in the study, 14133(93.7%) had at least one and 11867(78.8%) had at least two of the ten most prevalent comorbidities. The greatest individual risk among pairs was associated with peripheral artery disease(PAD) in combinations with stroke(HR 1.73;95% CI 1.28-2.33) and anaemia(1.71;1.39-2.11). The combination of CKD and hypertension had the highest PAF(5.65%;95% CI 3.66 to 7.61). Two pairs demonstrated significant synergistic interaction(atrial fibrillation with CKD and coronary artery disease respectively) and one an antagonistic interaction(anaemia & obesity).

Conclusions

In HF, the impact of multimorbidity differed at the individual-patient and population level, depending on the prevalence of and the risk related to each comorbidity, and the interaction between individual comorbidities. Patients with co-existent PAD and stroke were at greatest individual risk whereas, from a population perspective, co-existent CKD and hypertension mattered most.

Keywords: Heart failure with reduced ejection fraction, multimorbidity.

ClinicalTrials.gov Identifiers:

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INTRODUCTION

Improving survival has led to an increase in the prevalence of older patients with heart failure (HF) who often suffer from multimorbidity, defined as the coexistence of two or more chronic conditions in an individual.[1] Multimorbidity more generally is recognised as a serious and growing challenge for healthcare systems worldwide.[2–8] As HF often arises as a consequence of other cardiovascular diseases (e.g. coronary heart disease, hypertension or both) and their associated comorbidities (e.g. diabetes) and itself leads to additional problems such as renal impairment and atrial fibrillation, multimorbidity is almost inevitable in patients with HF.[9–13] It is well-known that many individual comorbidities are associated with worse outcomes HF and therefore multimorbidity likely imparts even greater risk. The challenge, however, is how to quantify the incremental risk related to multiple morbidities. A variety of methods have been described, including simple counting, formulation of weighted indices and machine learning approaches.[11,12,14–16] However, none of these have provided an easily understood and clinically actionable description of which combinations of common comorbidities have the greatest impact in patients with HF.[4] Understanding this is key to targeting preventive and therapeutic interventions to maximize clinical benefit. Some studies conducted in the general population (but not in patients with HF) have shown that patients with certain combinations of chronic conditions may have a higher risk of a poorer outcome compared to other combinations.[16–18] In other words, these studies raise the possibility that the hazard related to multimorbidity does not reflect the simple addition of the risks related to individual conditions.[12] Moreover, the population impact of any combination of conditions must also account for the prevalence of each comorbidity.

Therefore, in the present investigation, we analysed the prevalence and consequences of multimorbidity in patients with HF and reduced ejection fraction (HFrEF), with a focus on identifying which combinations of conditions had the greatest impact on clinical outcomes. We studied 15066 patients with HFrEF enrolled in two global clinical trials, the Prospective comparison of ARNI (Angiotensin Receptor Neprilysin Inhibitor) with ACEI (Angiotensin Converting Enzyme Inhibitor) to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) and the Aliskiren trial to Minimize OutcomeS in Patients with Heart failure trial (ATMOSPHERE).[19,20]

METHODS

Trials and Participants

The design and main results of both PARADIGM-HF and ATMOSPHERE are published.[19–22] The inclusion and exclusion criteria of the two trials were almost identical. Briefly, patients ≥18 years of age were eligible if in New York Heart Association (NYHA) class II-IV, left ventricular ejection fraction (LVEF) ≤35% [changed from≤40% initially in PARADIGM-HF by amendment], had an elevated natriuretic peptide level, and took and angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), along with a beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist (MRA), if indicated. The natriuretic peptide eligibility criteria were a plasma B-type natriuretic peptide (BNP) ≥150 pg/mL or N terminal -pro-B-type natriuretic peptide (NT-proBNP) ≥600 pg/mL; patients with a lower natriuretic peptide concentration (BNP≥100 pg/mL or NT proBNP≥400 pg/mL) who had been hospitalised in the preceding 12 months were also eligible.

Exclusion criteria at screening included symptomatic hypotension or systolic blood pressure <95mmHg (<90mmHg in ATMOSPHERE), estimated glomerular filtration rate (eGFR) <30 (<35 in ATMOSPHERE) ml/min/1.73m^2 and potassium >5.4 (>5.2 in ATMOSPHERE) mmol/l. The trial was approved by ethics committees at all 1043 participating centres in 47 countries in PARADIGM-HF and 789 centres in 43 countries in ATMOSPHERE and all patients provided written informed consent.

On trial entry, ongoing therapy with an ACE inhibitor or ARB was stopped and patients entered a sequential run-in, first receiving enalapril followed by sacubitril/valsartan in PARADIGM-HF and enalapril followed by the combination of enalapril plus aliskiren in

ATMOSPHERE. Patients tolerating both run-in periods were randomly assigned to double blind therapy with sacubitril/valsartan or enalapril in a 1:1 ratio in PARADIGM-HF or enalapril, aliskiren or both drugs in a 1:1:1 ratio in ATMOSPHERE.

The investigation conforms with the principles outlined in the *Declaration of Helsinki.*

The median duration of follow up in the combined cohort was 29.8 months.

Definitions of comorbidities and multimorbidity

Multimorbidity was defined as the coexistence of two or more chronic conditions in an individual. However, there exists no standard approach for multimorbidity and selection of chronic conditions in different studies is based on the type of study and the data available.[23] In this analysis, we defined multimorbidity using the 10 most prevalent chronic conditions reported among the patients with HFrEF enrolled in the two trials: hypertension, coronary artery disease (CAD), chronic kidney disease (CKD), diabetes, obesity, atrial fibrillation, anaemia, chronic obstructive pulmonary disease (COPD), stroke and peripheral arterial disease (PAD).

Anaemia was defined as haemoglobin <12 gm/L in (non-pregnant) women and <13 gm/L in men according to World Health Organization (WHO) guidelines.[24] Obesity was also defined using WHO guidance (≥30kg/m^2).[25] Patients were categorized as having CKD if their eGFR was <60 mL/min/1.73m^2. Patients who had a previous MI, primary coronary intervention (PCI) or coronary artery bypass graft (CABG) are labelled as having CAD. PAD was defined in patients with a documented lower limb stenosis, prior lower limb revascularisation or known intermittent claudication. The rest were investigator reported. We excluded 320 patients who had missing haemoglobin or BMI at baseline from this study.

Clinical outcomes examined

The outcome of interest in this study was death from any cause (all-cause mortality).[14]

Statistical analysis

Cox proportional hazards model was used to examine the risk of all-cause death associated with each comorbidity, individually, and among the 45 possible pairs of the 10 most common comorbidities. Univariate models were adjusted for age at baseline, sex, race and randomized treatment. Multivariable models were additionally adjusted for all the other comorbidities not constituting each pair.

Population attributable fraction (PAF) was calculated for the univariate and multivariate models after deriving hazard ratios (HRs) from Cox models based on methods defined by Greenland and Drescher.[26,27] The PAF measures the population effect of a risk factor (in this study – comorbidity) by estimating the proportion of deaths that can hypothetically be prevented if the risk were to be removed. HRs and PAFs for cardiovascular (CV) and non-cardiovascular (non-CV) death for individual comorbidities were also examined.

Interactions are traditionally tested as multiplicative or additive. Biological interaction based on the additive approach is deemed to be more appropriate for assessing risk in population studies.[28] Excess risk for biological interaction was calculated using the relative excess risk due to interaction (RERI) as this allows the magnitude of the excess risk to be measured, with an interaction identified if RERI ≠ 0. A positive RERI indicates that the risk of death with both comorbidities is greater than the sum of the comorbidities individually, and a negative RERI the opposite. We only examined two-way interactions as

testing for three-way interactions would have been possible in only very small proportions of the population. Sensitivity analyses were conducted using the attributable proportion (AP) and synergy index (SI) which are shown in the supplementary material (interaction exists if AP ≠ 0 or SI ≠ 1).

Hazard ratios were derived for the combination of two comorbidities and each comorbidity, individually, in the absence of the other in the combination using Cox modelling. The hazard ratios so derived were used to calculate the RERI, AP and SI.[29] Models were adjusted for age at baseline, sex and race and the presence of all other comorbidities examined.

All analyses were done using Stata version 16 (Stata Corp. College Station, Texas, USA).

RESULTS

Baseline characteristics

Multimorbidity (i.e HF and at least one other comorbidity) was present in 14113 of the 15066 participants (93.7%) and in 11867 patients (78.8%) this included two or more of the 10 most prevalent comorbidities recorded (Table 1 & Supplementary table S1). Those with multimorbidity were older, and more likely to be male and white. These patients had more often been enrolled in North America or Europe. They were also more likely to have longer duration HF, worse NYHA functional classification, worse quality of life and higher NT-proBNP, than patients without additional comorbidities. Patients with multimorbidity were prescribed a greater number of drugs and had undergone more cardiovascular procedures than those without [Table 1].

Individual comorbidities

Prevalence of individual comorbidities

The most common comorbidity was a history of hypertension which was present in 66.6% of all individuals, followed by CAD (47.5%), CKD (31.8%) and diabetes (31.5%) [Table 2]. The least common comorbidities were COPD, stroke, and PAD with a prevalence of 12.1%, 7.9% and 5.5%, respectively.

All-cause mortality: hazard ratio and population attributable fraction (PAF)

As shown in Table 2, in the fully adjusted model, 7 of the 10 most common comorbidities were independently associated with a higher risk of death from any cause. The greatest risk (highest hazard ratio) was associated with PAD (HR 1.39; 95% CI 1.22–1.59), anaemia (1.36; 1.26–1.47) and CKD (1.31; 1.22–1.42). Diabetes and stroke we also associated with higher risk - hazard ratios 1.29 (1.19 – 1.39) and 1.26 (1.12 – 1.41), respectively. Conversely,

hypertension (0.95; 0.88–1.02) and CAD (0.96; 0.90–1.04) were not independent predictors of death in the fully adjusted model. Obesity (BMI ≥30 kg/m^2) was associated with a significantly lower risk of death (0.91; 0.84–0.99, P=0.023).

Considering both the individual risk of death and the prevalence of each comorbidity, CKD had the highest PAF (9.08; 95% CI 6.61-11.48%), followed by anaemia (7.33; 5.38 to 9.25%) and diabetes (6.65; 4.51-8.75%) – these analyses did not consider co-morbidity pairs which are described below.

CV and non-CV mortality: hazard ratio and population attributable fraction

Point estimates for the risk of CV death compared to non-CV death was higher in those with CKD (HR 1.33; 1.22 – 1.44 vs 1.24; 1.03 – 1.48) and atrial fibrillation (1.16; 1.06 – 1.27 vs 0.90; 0.73 – 1.10) [Supplementary tables S4 & S3]. Those with anaemia carried a higher risk of non-CV death compared to CV death (1.51; 1.25-1.83 vs 1.33; 1.22 – 1.45) and the same was true for COPD (1.44; 1.16 – 1.78 vs 1.07; 0.96 – 1.19).

CKD had the highest PAF for CV death (9.20; 6.91 – 11.44) and anaemia had the highest PAF for non-CV death (9.81;6.05 – 13.43) [Supplementary tables S4 & S5].

Pairwise comorbidities

Prevalence

11867 (78.8%) patients had at least two comorbidities. We examined the 45 possible pairs of the 10 most common comorbidities. The pair with the highest prevalence was concurrent CAD and hypertension (34.4%), followed by diabetes and hypertension (24.6%) and, third, hypertension and obesity (24.1%) [Table 3].

All-cause mortality: hazard ratio and population attributable fraction

The highest risk of death among the pairs was in patients with concomitant PAD and stroke (HR 1.73; 1.28–2.33), PAD and anaemia (1.71; 1.39–2.11) and PAD and CKD (1.67; 1.40–2.00) [Table 3,Graphical abstract & Supplementary figure 1]. Conversely, patients with coexistent hypertension and obesity had a 12% lower risk of death, compared with those who did not (HR 0.88; 0.81–0.96).

When both risk and prevalence were taken into consideration, the highest PAFs were for coexistent hypertension and CKD (5.65; 3.66–7.61%), anaemia and CKD (4.58; 3.38–5.76%) and hypertension and anaemia (4.41; 2.92–5.88%) [Table 3 & Figure 1].

Interactions between comorbidities

In the fully adjusted analysis, there were two significant synergistic interactions and one significant antagonistic interaction [Figure 2 & Supplementary table S2].

Patients with atrial fibrillation and CKD had a 22% excess risk of death i.e. the RERI was 0.22, 95% CI 0.02 to 0.43), derived from the actual HR of 1.53 (1.36, 1.73) compared with the expected HR of 1.34 (1.12, 1.55). Participants with atrial fibrillation and CAD had a 20% excess risk of death (RERI 0.20, 0.04 to 0.37).

Conversely, the risk of death was 26% lower than expected (RERI -0.26, -0.48 to -0.04) in patients who were obese and had anaemia [Figure 2 & Supplementary table S2].

DISCUSSION

Most studies of comorbidity in heart failure have reported the prevalence of specific conditions and the mortality risk related to each of these individually, usually as a hazard ratio or examined multimorbidity in HF using machine learning methods.[11,12,14,30,31] We, however know of none that examined the interactions between comorbidities in patients with HFrEF . Therefore, we studied how the interaction between comorbidities influences risk, both in individuals and in the whole study population i.e., taking into account the prevalence of comorbidities as well as the risk associated with them. As expected, the prevalence of specific comorbidities varied substantially, as did the hazard related to each. For example, hypertension was the most common comorbidity but also the one associated with the smallest individual risk. Conversely, PAD had the lowest prevalence but was associated with the highest hazard ratio. Because of the extreme difference between prevalence and hazard for each, neither of these comorbidities contributed the largest fraction of population attributable risk for mortality. This was accounted for by CKD, which was both relatively common and associated with high individual risk. Individually the pattern of the impact of individual comorbidities varied between CV and non-CV death. CKD had the greatest impact at a population level on CV death while this was found to be true for anaemia in the case of non-CV death.

In this study, >93% of patients were multimorbid (i.e HF and at least one other comorbidity) and 79% had at least 2 comorbidities in addition to HF. Because multimorbidity is so frequent in heart failure, assessment of risk requires consideration of combinations of comorbidities.[10–14,30,31] However, the contribution of these to individual risk and population risk is very different. Among the 45 possible pairs of the 10 most common comorbidities,

the three highest pairwise hazard ratios were for PAD with another condition (stroke, anaemia, and CKD), reflecting the powerful individual risk associated with PAD in the analysis of single comorbidities. However, the highest fraction of *population* risk was attributed to pairs involving hypertension, CKD, anaemia, and diabetes, reflecting both the relatively high prevalence and individual risk associated with each of these comorbidities.

These findings highlight why it is important to understand the nature of multimorbidity. Quite distinct approaches might be required, depending on whether therapeutic intervention is being considered at the individual patient or population level. The combination of PAD and stroke identified those at greatest individual risk (HR 1.73, 95%CI 1.28–2.33) but only afflicted 0.7% of patients and contributed a very small PAF (0.55, 0.19 to 0.91). Taking a population perspective, the pair of CKD and hypertension mattered most as this combination was found in 23.3% of participants, and the high prevalence along with the moderate elevation in individual risk (HR 1.26, 1.16–1.36) meant these two comorbidities contributed a substantial PAF (5.65, 3.66 to 7.61). Therapeutically, these findings might suggest that individually targeted antithrombotic treatment may be worthwhile in patients with poly-vascular disease but would not support such a strategy in patients with HFrEF more generally, as little population mortality benefit would likely accrue. Conversely, prevention or treatment of CKD (eg better control of hypertension and diabetes), potentially, could have a substantial benefit on population mortality in HFrEF. Of course, these hypotheses need to be tested prospectively in randomized trials as the associations described here do not necessarily imply causation.

The importance of specific comorbidity pairs can be refined further by testing for a formal interaction between the two comorbidities in question, something that has never, to

our knowledge, been done in HFrEF before. This new approach is relevant because a synergistic interaction could have important implications either at the individual or population level and might even in highlighting pathophysiological links. We found a significant synergistic interaction between two comorbidity pairs, both including atrial fibrillation (atrial fibrillation with CKD and atrial fibrillation with CAD). Although a study like this cannot explain why the interactions identified occurred, it is possible to speculate that the synergistic interactions identified for atrial fibrillation may relate to the underuse of anticoagulants in patients with kidney disease and concern about using anticoagulants in combination with antiplatelet therapy in patients with CAD.[32] Conversely, this interaction may simply reflect a close association between these two comorbidities and more advanced HFrEF (and therefore higher mortality).[33,34] Nevertheless, at the individual patient level, these interactions "flag up" patients deserving of special therapeutic attention.

One additional pair showed an *antagonistic* interaction, between anaemia and obesity, a combination that affected about 4% of patients. This might be "explained" by the well-known, albeit puzzling, association between obesity and lower risk of mortality in heart failure.[35]

Of these three interactions, the combination of atrial fibrillation with CKD, was important at the population as well as individual level, considering this pair of comorbidities contributed a PAF of 3.12 (2.25 to 3.97). New drug and procedural interventions for each of these comorbidities have been described and the interaction described here highlights the potential impact of these, should the comorbidities identified here be causally related to worse outcomes and modifiable.[32,36–44] The interaction between atrial fibrillation and CAD was also important at the population level, but to a lesser degree, with a PAF of 1.55 (0.46

to 2.63). The concern about the underuse of anticoagulation in these patients has been highlighted above.

Study limitations

As with all studies of this type, there are limitations. The main one is that the patients studied were all included in randomized trials and, as a result, were selected according to certain inclusion and exclusion criteria. The latter excluded patients with severe anaemia, COPD, liver disease and CKD. We only studied HFrEF and the picture may be different in patients with heart failure with preserved ejection fraction. We limited our analyses to pairs of comorbidities and did not evaluate more complex multiple interactions. We only examined all-cause mortality and the impact of multimorbidity on other outcomes might have been different. We did not analyse pairs and interactions between comorbidities according to CV and non-CV death due to fewer events when combinations were examined. Whether or not patients were on optimal treatment for their comorbidities could not be taken into account for this analysis but HF treatment had been optimized for all those enrolled in the two trials.

Conclusion

The impact of multimorbidity in heart failure differs at the individual patient and population level and depends on the prevalence of each specific comorbidity, the risk related to each comorbidity and the interaction between individual comorbidities. The combination of PAD and stroke identified those at greatest individual risk whereas, from a population perspective, the pair of CKD and hypertension mattered most. Two comorbidity pairs demonstrated synergistic augmentation of risk (atrial fibrillation with CKD and atrial fibrillation with CAD). These findings may help target therapeutic or improve interventions

in individual patients which could have a substantial impact on HFrEF mortality at a population level as well.

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Figure Legends

Figure 1 & Graphical abstract: Population attributable fraction and hazard ratio for all-cause death among pairs of comorbidities.

Figure 2: Relative excess risk due to interaction for pairs of comorbidities examined in HFrEF for all-cause death.

Table 1: Baseline characteristics

	Total N=15,066	No comorbidities N=953	With comorbidities N=14,113	p-value
Age - years	63.5 ± 11.6	53.7 ± 13.0	64.2 ± 11.2	<0.001
Sex				0.47
Men	11,777 (78.2)	736 (77.2)	11,041 (78.2)	
Women	3,289 (21.8)	217 (22.8)	3,072 (21.8)	
Region				<0.001
N America	758 (5.0)	8 (0.8)	750 (5.3)	
L America	2,508 (16.6)	204 (21.4)	2,304 (16.3)	
W Europe & Other	3,825 (25.4)	176 (18.5)	3,649 (25.9)	
E Europe	4,644 (30.8)	94 (9.9)	4,550 (32.2)	
Asia/Pacific	3,331 (22.1)	471 (49.4)	2,860 (20.3)	
Race				<0.001
White	9,864 (65.5)	349 (36.6)	9,515 (67.4)	
Black	526 (3.5)	44 (4.6)	482 (3.4)	
Asian	3,246 (21.5)	454 (47.6)	2,792 (19.8)	
Other/Unknown	1,430 (9.5)	106 (11.1)	1,324 (9.4)	
Systolic BP - mmHg	122.4 ± 16.7	115.5 ± 15.2	122.9 ± 16.7	<0.001
Heart rate - bpm	72.1 ± 12.3	71.4 ± 11.7	72.1 ± 12.3	0.061
BMI - kg/m2	27.1 (24.1 - 30.9)	24.1 (21.8 - 26.4)	27.4 (24.3 - 31.1)	<0.001
Current smoker	2,061 (13.7)	150 (15.7)	1,911 (13.5)	0.056
HF aetiology				<0.001
Ischaemic	8,743 (58.0)	162 (17.0)	8,581 (60.8)	
Non-ischaemic	6,323 (42.0)	791 (83.0)	5,532 (39.2)	
Duration of HF - years				<0.001
≤1	4,803 (31.9)	459 (48.2)	4,344 (30.8)	
1-5	5,699 (37.8)	315 (33.1)	5,384 (38.2)	

>5	4,560 (30.3)	178 (18.7)	4,382 (31.1)	
NYHA Class				<0.001
I/II	4,971 (71.5)	441 (81.4)	4,530 (70.7)	
III/IV	1,980 (28.5)	101 (18.6)	1,879 (29.3)	
KCCQ CSS	79.2 (62.5 - 91.7)	87.5 (72.4 - 95.8)	79.2 (62.0 - 91.3)	<0.001
NT-proBNP - pg/ml	1417 (769 - 2766)	1243 (665 - 2636)	1428 (776 - 2773)	<0.001
eGFR – ml/min/1.73m^2	70.6 ± 22.3	86.2 ± 24.5	69.5 ± 21.7	<0.001
LVEF - %	29.0 ± 6.0	26.4 ± 5.9	29.1 ± 6.0	<0.001
LV hypertrophy	2,687 (17.8)	171 (17.9)	2,516 (17.8)	0.93
QRS duration - msec	117.0 ± 35.5	119.0 ± 36.5	116.9 ± 35.4	0.076
Diuretics	12,054 (80.0)	699 (73.3)	11,355 (80.5)	<0.001
Digoxin	4,681 (31.1)	416 (43.7)	4,265 (30.2)	<0.001
Beta blockers	13,922 (92.4)	894 (93.8)	13,028 (92.3)	0.091
ACEI/ARB	15,037 (99.8)	948 (99.5)	14,089 (99.8)	0.016
MRAs	7,098 (47.1)	498 (52.3)	6,600 (46.8)	0.001
Statins	8,183 (54.3)	226 (23.7)	7,957 (56.4)	<0.001
Aspirin	7,754 (51.5)	313 (32.8)	7,441 (52.7)	<0.001
ICD	1,532 (10.2)	65 (6.8)	1,467 (10.4)	<0.001
CRT	938 (6.2)	52 (5.5)	886 (6.3)	0.31

All values presented as mean ± standard deviation, median (Q1, Q3) or no. (%).
BP – blood pressure; BMI – body mass index; HF – heart failure; NYHA – New York heart association; KCCQ – CSS – Kansas City Cardiomyopathy Questionnaire – Clinical summary score; NT-proBNP – N terminal – pro B-type natriuretic peptide; eGFR – estimated glomerular filtration rate; LVEF – left ventricular ejection fraction; LV – left ventricle; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; MRA – mineralocorticoid receptor antagonist; ICD – implantable cardioverter defibrillator; CRT – cardiac resynchronization therapy.

Table 2: Comorbidities in heart failure with reduced ejection fraction - All-cause mortality

	Number	Prevalence (%)	Event rate	Univariate HR	Univariate PAF (%)	Multivariable HR	Multivariablee PAF (%)
Hypertension	10031	66.6	8.7 (8.3 – 9.1)	0.98 (0.91 – 1.06) 0.648	-1.15 (-6.17 to 3.64)	0.95 (0.88 – 1.02) 0.173	-3.59 (-8.93 to 1.48)
Coronary artery disease	7163	47.5	9.0 (8.6 – 9.4)	1.02 (0.95 – 1.09) 0.609	0.89 (-2.55 to 4.21)	0.96 (0.90 – 1.04) 0.322	-1.84 (-5.61 to 1.79)
Chronic kidney disease	4793	31.8	10.9 (10.3 – 11.5)	1.37 (1.27 – 1.47) <0.001	10.20 (7.79 to 12.55)	1.31 (1.22 – 1.42) <0.001	9.08 (6.61 to 11.48)
Diabetes	4742	31.5	10.0 (9.4 – 10.7)	1.30 (1.20 – 1.40) <0.001	6.86 (4.77 to 8.90)	1.29 (1.19 – 1.39) <0.001	6.65 (4.51 to 8.75)
Obesity	4534	30.1	7.8 (7.3 – 8.3)	0.94 (0.86 – 1.01) 0.110	-1.80 (-4.01 to 0.37)	0.91 (0.84 – 0.99) 0.023	-2.67 (-4.99 to -0.41)
Atrial Fibrillation	3541	23.5	9.3 (8.7 – 9.9)	1.06 (0.98 – 1.15) 0.152	1.43 (-0.55 to 3.37)	1.11 (1.02 – 1.21) 0.013	2.52 (0.5 to 4.5)
Anaemia	3,303	21.9	11.6 (10.9 – 12.4)	1.42 (1.31 – 1.53) <0.001	8.16 (6.25 to 10.04)	1.36 (1.26 – 1.47) <0.001	7.33 (5.38 to 9.25)
Chronic obstructive pulmonary disease	1826	12.1	10.3 (9.4 – 11.3)	1.16 (1.05 – 1.28) 0.003	1.97 (0.63 to 3.28)	1.13 (1.03 – 1.25) 0.014	1.65 (0.30 to 2.98)
Stroke	1183	7.9	11.2 (10.1 – 12.5)	1.29 (1.15 – 1.45) <0.001	2.19 (1.15 to 3.22)	1.26 (1.12 – 1.41) <0.001	1.98 (0.93 to 3.03)
Peripheral arterial disease	833	5.5	13.0 (11.5 – 14.6)	1.49 (1.31 – 1.69) <0.001	2.58 (1.65 to 3.50)	1.39 (1.22 – 1.59) <0.001	2.21 (1.27 to 3.14)

All models adjusted for randomized treatment, age, sex and race at baseline.
HR – hazard ratio (95% confidence interval).
PAF – population attributable fraction expressed as %.

Table 3: Pairs of comorbidities with heart failure with reduced ejection fraction. – All-cause mortality

Comorbidity One	*Comorbidity Two*	Prevalence No. (%)	Event rate per 100 pt. years	Hazard ratio (95% CI)	PAF (95% CI)
Atrial Fibrillation	*Anaemia*	583 (3.9)	14.2 (12.4 - 16.4)	1.55 (1.34 - 1.79) <0.001	2.05 (1.50 to 2.60)
Atrial Fibrillation	*CKD*	1258 (8.4)	12.1 (10.9 - 13.4)	1.40 (1.25 - 1.57) <0.001	3.12 (2.25 to 3.97)
Atrial Fibrillation	*COPD*	480 (3.2)	10.8 (9.1 - 12.8)	1.18 (0.99 - 1.41) 0.067	0.59 (-0.08 to 1.25)
Atrial Fibrillation	*CAD*	1191 (7.9)	11.0 (9.9 - 12.3)	1.19 (1.06 - 1.34) 0.003	1.55 (0.46 to 2.63)
Atrial Fibrillation	*Diabetes*	1076 (7.1)	11.0 (9.7 - 12.4)	1.34 (1.17 - 1.53) <0.001	1.85 (0.93 to 2.77)
Atrial Fibrillation	*HTN*	2690 (17.9)	8.9 (8.3 - 9.7)	1.04 (0.95 - 1.14) 0.435	0.66 (-1.01 to 2.29)
Atrial Fibrillation	*Obesity*	1380 (9.2)	8.4 (7.5 - 9.4)	1.02 (0.90 - 1.15) 0.807	0.13 (-0.94 to 1.2)
Atrial Fibrillation	*PAD*	170 (1.1)	13.1 (10.0 - 17.1)	1.40 (1.07 - 1.85) 0.015	0.45 (0.15 to 0.76)
Atrial Fibrillation	*Stroke*	347 (2.3)	10.2 (8.3 - 12.5)	1.17 (0.95 - 1.45) 0.146	0.38 (-0.15 to 0.91)
Anaemia	*CKD*	1311 (8.7)	14.1 (12.8 - 15.5)	1.55 (1.40 - 1.72) <0.001	4.58 (3.38 to 5.76)
Anaemia	*COPD*	400 (2.7)	14.2 (12.0 - 16.8)	1.38 (1.16 - 1.64) <0.001	1.09 (0.45 to 1.73)

Anaemia	*CAD*	1654 (11.0)	12.1 (11.0 - 13.2)	1.25 (1.13 - 1.38) <0.001	2.83 (1.49 to 4.14)
Anaemia	*Diabetes*	1175 (7.8)	13.9 (12.4 - 15.5)	1.60 (1.42 - 1.80) <0.001	3.51 (2.49 to 4.53)
Anaemia	*HTN*	2044 (13.6)	12.3 (11.4 - 13.4)	1.33 (1.22 - 1.46) <0.001	4.41 (2.92 to 5.88)
Anaemia	*Obesity*	667 (4.4)	10.0 (8.5 - 11.7)	1.05 (0.89 - 1.23) 0.573	0.21 (-0.54 to 0.97)
Anaemia	*PAD*	225 (1.5)	17.7 (14.4 - 21.7)	1.71 (1.39 - 2.11) <0.001	1.12 (0.61 to 1.63)
Anaemia	*Stroke*	229 (1.5)	15.1 (12.1 - 18.8)	1.45 (1.16 - 1.82) 0.001	0.73 (0.24 to 1.23)
CKD	*COPD*	672 (4.5)	12.1 (10.5 - 13.9)	1.23 (1.06 - 1.42) 0.007	1.08 (0.27 to 1.88)
CKD	*CAD*	2634 (17.5)	10.9 (10.1 - 11.7)	1.17 (1.08 - 1.28) <0.001	3.07 (1.36 to 4.76)
CKD	*Diabetes*	1695 (11.3)	12.4 (11.3 - 13.7)	1.47 (1.32 - 1.63) <0.001	4.12 (2.87 to 5.35)
CKD	*HTN*	3509 (23.3)	11.0 (10.3 - 11.7)	1.26 (1.16 - 1.36) <0.001	5.65 (3.66 to 7.61)
CKD	*Obesity*	1479 (9.8)	10.0 (9.0 - 11.1)	1.16 (1.03 - 1.30) 0.011	1.43 (0.27 to 2.57)
CKD	*PAD*	352 (2.3)	16.6 (14.0 - 19.7)	1.67 (1.40 – 2.00) <0.001	1.59 (0.95 to 2.22)
CKD	*Stroke*	490 (3.3)	14.2 (12.1 - 16.5)	1.51 (1.28 - 1.77) <0.001	1.58 (0.88 to 2.28)
COPD	*CAD*	984 (6.5)	11.0 (9.8 - 12.4)	1.15 (1.01 - 1.31) 0.034	1.02 (0.04 to 1.99)
COPD	*Diabetes*	671 (4.5)	11.9 (10.2 - 13.9)	1.32 (1.12 - 1.55) 0.001	1.18 (0.43 to 1.92)

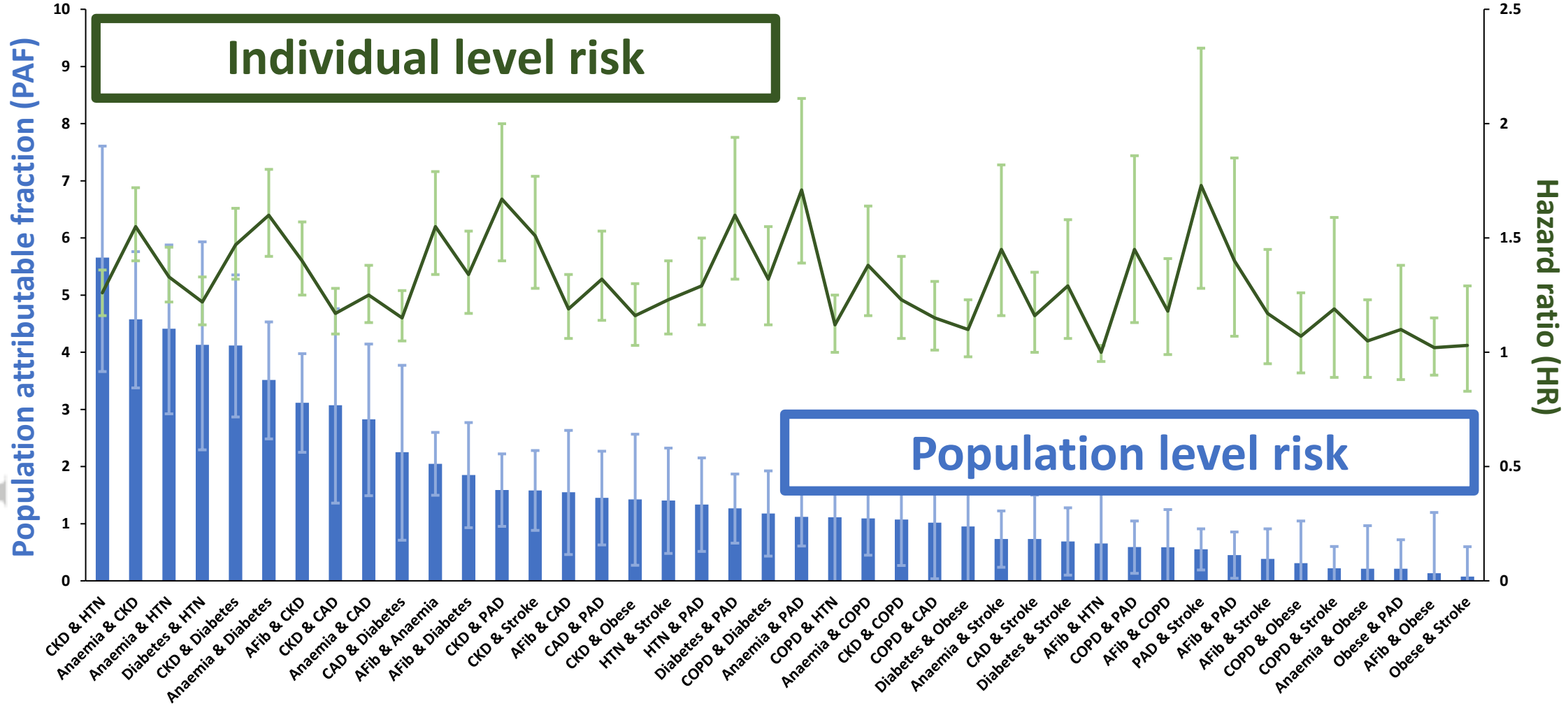
COPD	*HTN*	1398 (9.3)	10.4 (9.4 - 11.5)	1.12 (1.00 - 1.25) 0.052	1.11 (-0.04 to 2.25)
COPD	*Obesity*	648 (4.3)	9.6 (8.2 - 11.3)	1.07 (0.91 - 1.26) 0.398	0.31 (-0.43 to 1.05)
COPD	*PAD*	192 (1.3)	14.5 (11.3 - 18.5)	1.45 (1.13 - 1.86) 0.003	0.59 (0.13 to 1.05)
COPD	*Stroke*	160 (1.1)	11.9 (9.0 - 15.9)	1.19 (0.89 - 1.59) 0.246	0.22 (-0.16 to 0.6)
CAD	*Diabetes*	2693 (17.9)	10.0 (9.2 - 10.8)	1.15 (1.05 - 1.27) 0.003	2.25 (0.71 to 3.77)
CAD	*HTN*	5180 (34.4)	9.1 (8.6 - 9.6)	0.97 (0.90 - 1.04) 0.383	-1.2 (-3.95 to 1.48)
CAD	*Obesity*	2175 (14.4)	8.3 (7.6 - 9.1)	0.93 (0.84 - 1.03) 0.178	-1 (-2.42 to 0.41)
CAD	*PAD*	649 (4.3)	12.6 (11 - 14.5)	1.32 (1.14 - 1.53) <0.001	1.45 (0.63 to 2.27)
CAD	*Stroke*	662 (4.4)	10.9 (9.4 - 12.6)	1.16 (1.00 - 1.35) 0.056	0.73 (-0.04 to 1.5)
Diabetes	*HTN*	3704 (24.6)	9.9 (9.2 - 10.6)	1.22 (1.12 - 1.33) <0.001	4.13 (2.29 to 5.93)
Diabetes	*Obesity*	1886 (12.5)	8.9 (8.0 - 9.9)	1.10 (0.98 - 1.23) 0.107	0.95 (-0.24 to 2.13)
Diabetes	*PAD*	364 (2.4)	15.2 (12.6 - 18.2)	1.60 (1.32 - 1.94) <0.001	1.27 (0.66 to 1.87)
Diabetes	*Stroke*	422 (2.8)	11.8 (9.8 - 14.4)	1.29 (1.06 - 1.58) 0.011	0.69 (0.1 to 1.28)
HTN	*Obesity*	3628 (24.1)	7.7 (7.2 - 8.3)	0.88 (0.81 - 0.96) 0.004	-2.85 (-4.81to -0.92)

HTN	*PAD*	651 (4.3)	12.5 (10.9 - 14.4)	1.29 (1.12 - 1.50) 0.001	1.34 (0.52 to 2.15)
HTN	*Stroke*	929 (6.2)	11.3 (10 - 12.7)	1.23 (1.08 - 1.40) 0.002	1.41 (0.48 to 2.32)
Obesity	*PAD*	277 (1.8)	11.0 (8.8 - 13.7)	1.10 (0.88 - 1.38) 0.408	0.21 (-0.3 to 0.72)
Obesity	*Stroke*	362 (2.4)	9.1 (7.3 - 11.4)	1.03 (0.83 - 1.29) 0.772	0.08 (-0.44 to 0.6)
CAD	*Stroke*	112 (0.7)	16.9 (12.6 - 22.8)	1.73 (1.28 - 2.33) <0.001	0.55 (0.19 to 0.91)

CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; CAD – coronary artery disease; HTN – hypertension; PAD – peripheral artery disease

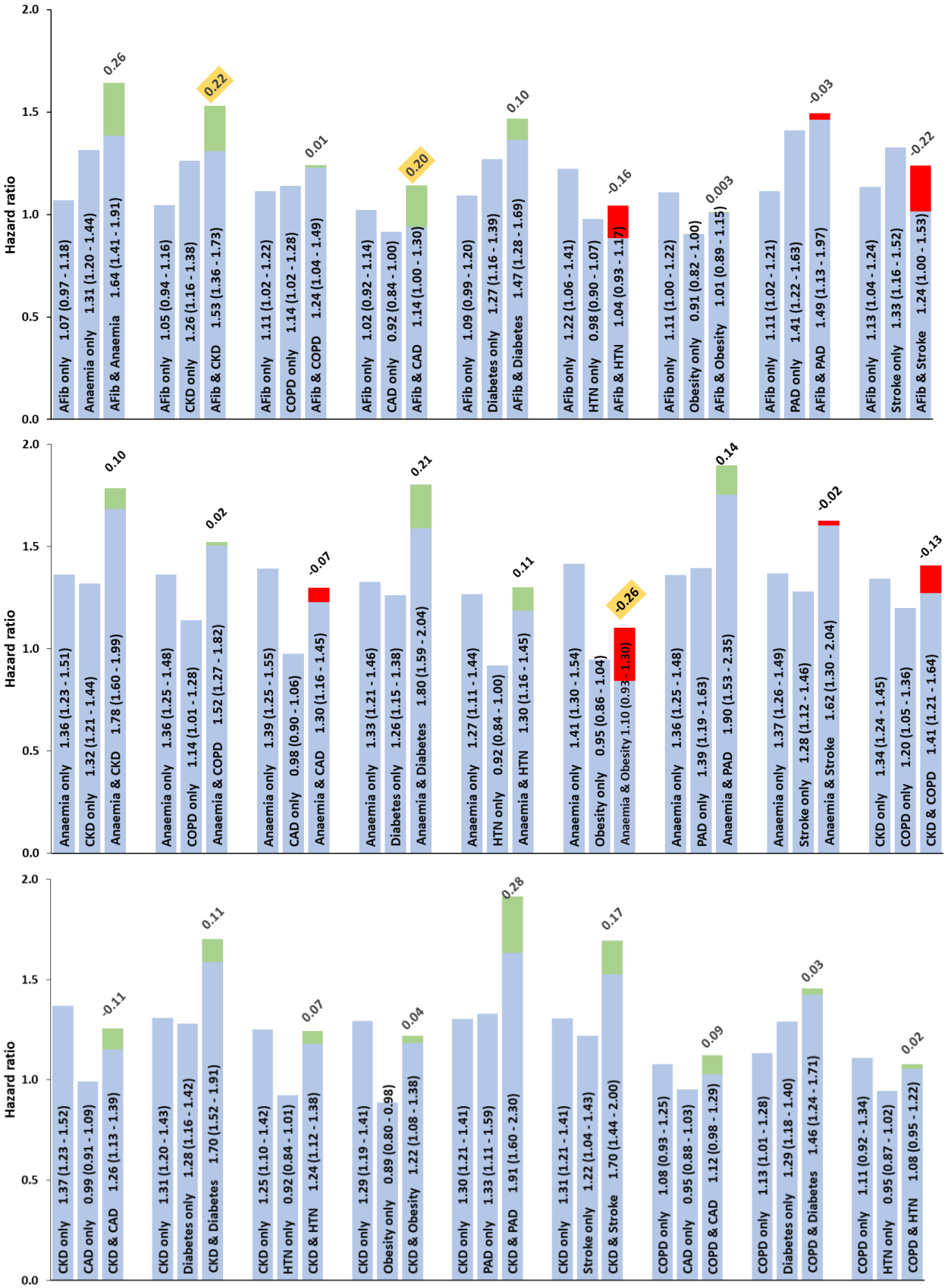
Hazard ratios with 95% CI adjusted for age, sex, race, randomised treatment and comorbidities. PAFR based on the same cox models.

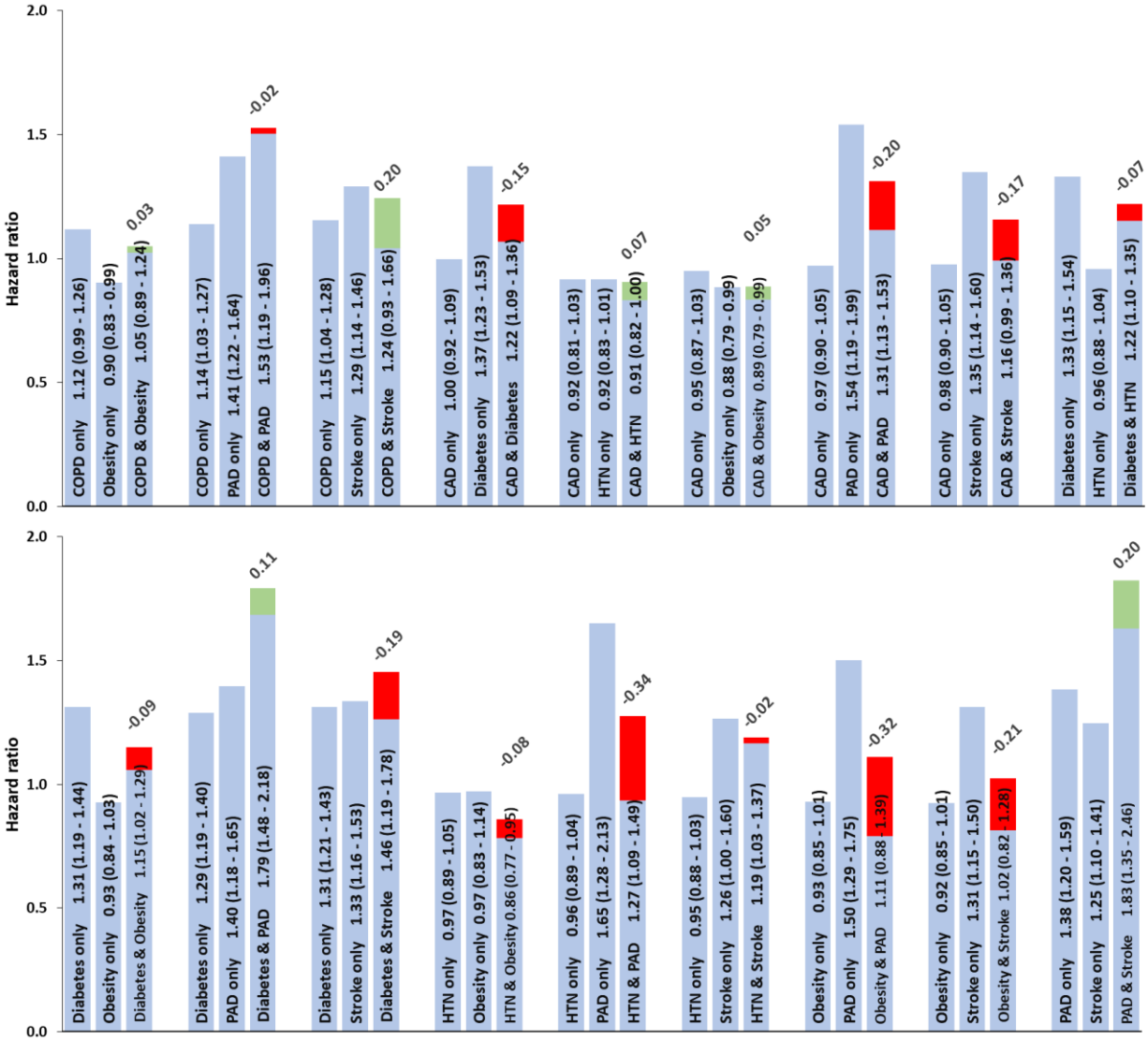
Impact of Multimorbidity on All-cause Mortality in Heart failure with reduced ejection fraction



All figures based on cox models adjusted for age, sex, randomised treatment and comorbidities.
3 of 45 pairs are not shown for better schematic representation (all were negative).
CKD – chronic kidney disease, HTN – hypertension, AFib – atrial fibrillation, CAD – coronary artery disease, PAD – peripheral artery disease, COPD – chronic obstructive kidney disease.

Figure 2: Relative excess risk due to interaction for pairs of comorbidities examined in HFrEF for all-cause death.





Hazard ratios with 95%CI shown in each bar each comorbidity pair examined.

Stacked bars in green represent synergistic interactions. Those in red represent antagonistic interactions.

All models adjusted for age, sex, race, randomised treatment and all other comorbidities examined in this analysis.

Significant interactions are highlighted in gold.

CKD – chronic kidney disease, HTN 0- hypertension, AFib – atrial fibrillation, CAD – coronary artery disease, PAD – peripheral artery disease, COPD – chronic obstructive pulmonary disease.