Age-related differences in Heart Failure with Preserved Ejection Fraction: data from TOPCAT, I-Preserve and CHARM-Preserved.

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ABSTRACT
Background. Although, heart failure with preserved ejection fraction (HFpEF) is considered a disease of the elderly, younger patients are not spared from this syndrome.
Objectives: We therefore investigated the associations between age, clinical characteristics and outcomes in patients with HFpEF.
Methods. Using data on patients with LVEF≥45% from three large HFpEF trials (TOPCAT, I-Preserve and CHARM-Preserved), we categorized patients according to age: ≤55 years (n=522), 56-64 years (n=1678), 65-74 (n=3402), 75-84 (n=2461) and ≥85 years (n=398). We compared clinical and echocardiographic characteristics, as well as mortality and hospitalization rates, mode of death and quality-of-life across age categories.
Results. Younger patients (≤55 years) with HFpEF were more often obese, non-white men, while older patients with HFpEF were more often white women with a higher prevalence of atrial fibrillation, hypertension and CKD (eGFR<60 ml/min/1.73m^2). Despite fewer comorbidities, younger patients had worse quality of life compared to older patients (≥85 years). Compared to patients ≤55 years, patients ≥85 years had higher mortality (hazard ratio: 6.9; 95%CI 4.2-11.4). However, among patients who died, sudden death (SD) was, proportionally, the most common mode of death (P <0.001) in patients ≤55 years. In contrast, older patients (≥85) died more often of non-cardiovascular causes (34% versus 20% in patients ≤55 years; P<0.001).
Conclusion. Compared to the elderly, younger patients with HFpEF were less likely to be white, more frequently obese men who die more often of CV causes, particularly SD. In contrast, elderly patients with HFpEF have more comorbidities and die more often of non-CV causes.

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CONDENSED ABSTRACT: Limited data is available on age related differences in heart failure with preserved ejection fraction(HFpEF) Using data on patients with LVEF{greater than or equal to>45% from three large HFpEF trials(TOPCAT, I-Preserve and CHARM-Preserved), we compared clinical and echocardiographic characteristics, as well as mortality and hospitalization rates, mode of death and quality-of-life across age categories. Younger patients with HFpEF were more likely to be obese non-white men with fewer comorbidities. Nevertheless, younger patients had worse quality of life and among patients who died, younger patients more often died of cardiovascular causes compared to the elderly, particularly sudden death.

Keywords: HFpEF, young, heart failure, race

ABBREVIATIONS
ANOVA: one-way analysis of variance
ASE: American Society of Echocardiography
CV: Cardiovascular
BMI: body mass index
CHARM: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity
HFpEF: heart failure with preserved ejection fraction
I-Preserve: Irbesartan in Heart Failure with Preserved Ejection Fraction trial
KCCQ: Kansas City Cardiomyopathy Questionnaire

LA: left atrial
LVEF: left ventricular ejection fraction
LVH: left ventricular hypertrophy
MLWHFQ: Minnesota Living with Heart Failure questionnaire
RWT: relative wall thickness
TOPCAT: Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial

Introduction

Heart failure with preserved ejection fraction (HFpEF) is generally considered a disease of the elderly, with the majority of patients >65 years (1, 2). Yet, several studies have reported that many patients with HFpEF are younger than this: a study among 2398 patients hospitalized with confirmed HFpEF from central Massachusetts, showed that 14.9% of patients were below 65 years(3). Furthermore, results from the MAGGIC meta-analyses group suggested that 14% of all patients with HF below 40 years have HFpEF (4).

Several studies have investigated differences between age strata for patients with HF(5–10). Data from the MAGGIC meta-analysis and Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program, showed that elderly patients with HF have higher mortality rates compared to the young(4, 6). However, younger patients with HF had worse signs and symptoms and a longer hospital stay. An important limitation of these previous studies is that they either included only patients with HFrEF or did not differentiate between patients with HFrEF and HFpEF due to unavailability of data on left ventricular ejection fraction (LVEF)(6, 9, 10). Two previous studies investigated age related differences in HFpEF, however these studies were either restricted to hospitalized patients from a single US state with a limited age range and no data on cause-specific outcomes(3), or limited to patients from Asia with scant data on clinical outcomes (11). Since age is an important determining factor of HFpEF, more data is needed. Therefore, in this study we analyzed differences in clinical and echocardiographic characteristics, as well as in clinical outcomes, including mode of death in patients with HFpEF across age categories using individual patient data form the three largest HFpEF trials conducted to date i.e. CHARM-Preserved, Irbesartan in Heart Failure with Preserved Ejection Fraction trial

(I-Preserve) and the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial (TOPCAT).

Methods

Patient population

This study utilized data from CHARM-preserved, I-Preserve and TOPCAT(12–14). Briefly, patients enrolled in CHARM-Preserved were ≥18 years, had been in NYHA functional class II-IV for at least 4 weeks, and had a prior hospital admission for a cardiac reason and a LVEF >40%(14). I-Preserve included patients ≥60 years in NYHA functional class II-IV, a LVEF of ≥45% and echocardiographic, electrocardiographic or radiologic evidence supporting a diagnosis of heart failure; patients in NYHA functional class II were also required to have had a hospitalization for HF within the previous 6 months(13). TOPCAT included patients ≥50 years with at least one symptom and one sign of heart failure, a LVEF of ≥45%, and either a hospitalization for HF within the previous 12 months or an elevated natriuretic peptide level within 60 days before randomization (B-type natriuretic peptide [BNP] ≥100 pg per milliliter or an N-terminal pro-BNP [NT-proBNP] level ≥360 pg per milliliter). We excluded patients with an LVEF <45% from CHARM-preserved and patients from Russia and Georgia in TOPCAT (n=1678), due to doubts about the reliability of diagnosis of HFpEF(15, 16).

Echocardiographic sub-study

Echocardiography was performed in 735 patients in I-Preserve and 654 patients in TOPCAT(17, 18). In both studies, LV mass was calculated by the American Society of Echocardiography (ASE) recommended formula for estimation of LV mass from LV linear dimensions and indexed to body surface area in both studies. The presence of left ventricular hypertrophy (LVH) was determined using partition values of LV mass indexed to body surface

area ≥115 g/m^2 for men and ≥95 g/m^2 for women. Concentric remodeling was defined as relative wall thickness (RWT) >0.42. LV geometry was determined as normal when RWT ≤0.42 and there was no LVH, concentric remodeling: RWT >0.42 and no LVH, eccentric hypertrophy RWT ≤0.42 and LVH and concentric hypertrophy RWT>0.42 and LVH. Left atrial (LA) size was categorized as mildly enlarged if LA area was 20 to 30 cm^2 and moderately-to-severely enlarged if LA area was >31 cm^2 (17, 18).

Outcomes

The primary outcome in the present analysis was all-cause mortality censored at 5 years. Secondary outcomes include cause-specific mortality (cardiovascular [CV] vs. non-CV) at 5 years and hospitalization for HF within 5 years as well as a composite outcome of CV death or HF hospitalization within 5 years. Mode/cause of death examined included death due to pump-failure, sudden death (SD), myocardial infarction, stroke and "other" CV death. All deaths and hospitalizations were adjudicated by an independent end-point committee in each trial (the same committee in CHARM-Preserved and TOPCAT). Patient self-reported quality of life (QoL) was measured using the Minnesota Living with Heart Failure questionnaire (MLWHFQ) in CHARM-Preserved and I-Preserve and with the Kansas City Cardiomyopathy Questionnaire (KCCQ) in TOPCAT; a higher MLWHFQ score indicates worse QoL whereas a lower score represents worse QoL using the KCCQ.

Statistical analysis

Patients were categorized according to clinical meaningful cutoffs of age, as follows: ≤55 years, 56-64 years, 65-74 years, 75-84 years and ≥85 years. Differences in baseline characteristics between age groups were compared using the chi^2 test, a one-way analysis of variance (ANOVA) test or the Kruskal-Wallis test where appropriate. Multivariable adjustment

included sex, body mass index (BMI) NYHA class, race, history of myocardial infarction, diabetes, hypertension, serum creatinine, LVEF and treatment. Since age and sex are already included in the multivariable model, we included creatinine to correct for differences in renal function rather than eGFR. Incidence rates of all outcomes are presented per 100 person-years. Risk of all-cause mortality, cause-specific mortality and HF hospitalizations were estimated as hazard ratios in Cox regression analyses. All-cause mortality was used as a competing risk when analyzing hospitalizations for HF. When analyzing CV and non-CV mortality, non-CV and unknown mortality and CV mortality and unknown mortality respectively were used as competing risks. In addition to the previously mentioned variables, multivariable survival analyses were corrected for treatment arm. We used restricted cubic splines to model age as a continuous variable versus clinical outcome. Lastly, we performed interaction analyses between age and BMI for all-cause mortality and the combined outcome of CV mortality or HF hospitalization at 5 years. In secondary analyses, we included source trial in our multivariable models. Clinical outcomes were assessed by cumulative incidence plots. In addition, because of the current guideline definition of HFpEF at LVEF≥50% and the age restriction of I-Preserve, we have performed two sensitivity analyses of the echocardiographic data: (1) restricting our analyses to patients with LVEF≥50% and (2) reanalyze the echocardiography data according to 4 subgroups (<65, 75-75, 75-85 and >85 years). All P values are 2 sided, and a value of $P<0.05$ was considered significant. All analyses were performed separately with Stata version 15 (StataCorp, College Station, TX).

Results

Baseline characteristics

Of the 8461 patients analyzed, 522 were ≤55 (6.2%), 1678 (19.8%) were between 56-64, 3402 (40.2%) were between 65-74 years, 2461 (29.1%) were between 75-84 years and 398 (4.7%) were ≥85 years of age. Compared to younger patients, older patients were more often white women, with a higher NYHA class, lower eGFR and worse overall signs and symptoms (**Table 1**). Diabetes mellitus, hypertension atrial fibrillation and a previous stroke were more prevalent with increasing age, while obesity (body mass index ≥30 kg/m^2) was more prevalent among younger patients. Younger patients were more often treated with beta-blockers and less often with diuretics.

After correcting for confounders including sex, body mass index (BMI) NYHA class, race, history of myocardial infarction, diabetes, hypertension, serum creatinine and LVEF, younger patients were more often obese (odds ratio [OR] 1.9; 95%CI 1.7-2.1), men (OR 1.9; 95%CI 1.7-2.2), and of Asian (OR 2.4; 95%CI 1.4-4.1) or Black (OR 2.8; 95%CI 2.3-3.5) race (**Figure 1**). In contrast, older patients had higher creatinine (OR 0.3 ;95%CI 0.2-0.4) and were in a higher NYHA class (NYHA class III/IV, OR 0.9; 95%CI 0.8-0.9, **Figure 1**).

Quality of life expressed by the KCCQ score in TOPCAT was worse in younger patients with HFpEF (**Online Table 1**) and a similar association was observed between the MLWHFQ score and age in CHARM-preserved (beta coefficient -0.24; P <0.001) and I-Preserve (beta coefficient -0.04; P = 0.024). This association remained significant after correction for sex, history of atrial fibrillation, diabetes and BMI (P <0.05 for all).

Echocardiographic Measurements

Overall, left ventricular (LV) volumes decreased with increasing age (**Table 2**). Younger patients with HFpEF had higher LV mass indexed to BSA compared to the elderly, with higher rates of left ventricular hypertrophy (≤55 years; 50% vs 41% in patients ≥85 years, P <0.001)

and abnormal relative wall thickness (≤55 years; 86% vs 68% in patients ≥85 years, P <0.001). Filling pressures (E/e') were slightly higher in younger patients (P= 0.022). Atrial size increased with increasing age. Overall, younger patients with HFpEF more often had concentric remodeling compared to older patients. After correcting for race, sex, BMI and history of diabetes, hypertension and atrial fibrillation, older age was associated with similar rates of abnormal relative wall thickness (OR 1.01; 95%CI 0.99-1.02) and abnormal filling pressures (E/e' >14; OR 1.01; 95%CI 0.99-1.03) but higher rates of LVH (OR 1.02; 95%CI 1.01-1.04). In sensitivity analyses according to 4 age groups (<65, 65-74, 75-84 and ≥85 years) and to patients with an LVEF≥50%, results were similar (**Online Tables 2 and 3**).

Clinical outcomes

Overall, 1644 (19%) patients died and 1480 (17%) patients were hospitalized for HF within 5 years.

Mortality: Among patients ≤55, 30 (6%) died after 5 years versus 190 (47%) among patients ≥85 years, equating to event rates of 1.9 (95%CI 1.3-2.7) and 16.7 (95%CI 14.5-19.2) per 100 patient years, respectively. The unadjusted rates for all-cause mortality, CV-mortality, non-CV mortality and hospitalizations for HF were higher in older patients (**Table 3**, **Figure 2**). Restricted cubic spline analyses for the association between age and all-cause mortality are shown in **Online Figure 1A.**

After multivariable adjustment, elderly (≥85 years) patients continued to have worse outcomes compared to younger patients (≤55 years): hazard ratio [HR] 6.9 (95%CI 4.2-11.4). The differential in risk between older and younger patients was greatest non-CV death (HR 10.5; 95%CI 3.7-29.4), compared with CV death (HR 4.6; 95%CI 2.5-8.4). When investigating causes of death, the ratio of non-CV death increased with increasing age (**Figure 3**). In very young

patients (≤55 years), SD was the single most important cause of death. Inclusion of source trial in multivariable analyses did not affect our results.

Composite of CV mortality/HF hospitalization: Among patients ≤55, 76 (15%) died or were admitted to hospital with worsening heart failure after 5 years versus 163 (41%) among patients ≥85 years, equating to event rates of 5.3 (95%CI 4.3-6.6) and 19.1 (95%CI 16.6-22.1) per 100 patient years, respectively. After multivariable correction, patients aged ≥85 years (SHR 2.1; 95%CI 1.5-2.9) had higher composite event rates in 5 years compared to patients aged ≤55 (**Table 3**). A restricted cubic spline analysis for the association between age and the composite outcome of CV mortality or HF hospitalization is shown in **Online Figure 1B**.

***Hospitalization for HF*:** In total, 59 (11%) of patients ≤55 years were hospitalization for HF within 5 years compared to 115 (29%) of patients ≥85 years. This equates to event rates of 4.0 (95%CI 3.1-5.1) and 12.0 (95%CI 10.0-14.4) per 100 patient years for patients ≤55 and ≥85 years respectively. A more u-shaped association appeared after multivariable adjustment, where patients 56-64 years were hospitalization for HF less often (SHR 0.7; 95%CI 0.5-0.9) and patients ≥85 years were hospitalized for HF more often (SHR 1.7; 9%CI 1.2-2.5). A restricted cubic spline analysis of the association between age and HF hospitalization is shown in **Online Figure 1C.**

Interaction with obesity: A significant interaction was found between age and BMI for both all-cause mortality and the composite outcome of CV mortality or HF hospitalization in univariable and multivariable analyses ($P_{interaction}$ for all <0.05). Obesity (BMI≥30 kg/m^2) was associated with lower rates of all-cause mortality in patients ≥65 years (HR 0.8; 95%CI 0.7-0.9), but not in patients <65 years (HR 1.4; 95%CI 1.1-1.8). Similarly, obesity was associated with higher rates of the combined outcome in patients <65 years (SHR 2.0; 95%CI 1.6-2.5), but not in

patients ≥65 years (SHR 1.0; 95%CI 0.9-1.1). Obesity remained significantly associated with higher rates of the composite outcome after multivariable correction for sex, creatinine, ethnicity, NYHA class, diabetes, hypertension, atrial fibrillation, LVEF and treatment arm (SHR 1.3; 95%CI 1.1-1.7) in patients <65 years, but not in patients ≥65 years (SHR 0.9; 95%CI 0.9-1.1).

Discussion

Younger patients with HFpEF were more often obese Black or Asian men with a lower comorbidity burden, yet had worse quality of life compared to older patients with HFpEF. Older patients with HFpEF were more often white women and had a higher comorbidity burden compared to younger patients. Non-CV death was a more important cause of death in elderly patients with HFpEF. In contrast, younger patients with HFpEF died more of CV causes, with SD being the most common cause of death.

Younger patients had a distinct clinical profile compared to older patients. In particular, younger patients were more than twice as likely to be obese compared to elderly patients, suggesting a predominant role of obesity in the pathogenesis of HFpEF in the young. Importantly, a recent study by Obokata et al. showed that obesity is a "true" HFpEF phenotype. Moreover, these obese patients were considerably younger than non-obese HFpEF patients(19). Similar results were also seen in ASIAN-HFpEF—younger patients were more often obese, while older patients had a higher comorbidity burden, particularly atrial fibrillation and worse renal function, which is also consistent with data from Massachusetts (3, 20). Our study extends the findings in the previous studies on HFpEF in the young from Asia and Massachusetts in several important ways including: (1) it is the first global multinational study of HFpEF in the young;(2) by having large numbers of adjudicated outcomes over long-term follow up we were able to examine mode of death; (3) we describe patient-reported quality of life measures and (4)

we report age-related differences in echocardiographic data on cardiac structure and function. Together with previous data, our study suggests a potential dichotomization of HFpEF phenotypes, with young obese HFpEF vs elderly HFpEF with a higher comorbidity load. That young obese HFpEF is a "true" HFpEF phenotype, is further supported by the increased LV volumes and increased prevalence of concentric remodeling in younger patients support the presence of adverse load following obesity and excess hypervolemia from plasma volume expansion (19, 20) as well as data from Olmsted County showing that obese patients with HFpEF were younger than non-obese patients with HFpEF(19, 21). Importantly, the latter study clearly demonstrated that these obese patients had "true" HFpEF, with raised left ventricular filling pressures in spite of lower NT-proBNP levels, and evidence of volume overload(19, 21). A separate prospective study from the Swedish Conscript Registry showed that obesity in early adulthood is associated with an increased risk for early onset HF. While the type of HF was not characterized in that study, our data suggest that an important proportion of those cases might have been HFpEF(22). Moreover, obesity as a risk factor for developing HF at a young age seems to be even more important in individuals of non-white ancestry, which is in line with our findings(23). This is further supported by the significant interaction between obesity and age for the composite outcome, where obesity was associated with worse clinical outcomes in younger, but not in older patients. In one small HFpEF study, each of caloric restriction and aerobic exercise training increased peak oxygen consumption. In addition, quality of life as measured by KCCQ improved in the diet arm, however the primary quality of life measure MLWHFQ did not improve with both exercise and diet (24). Beyond obesity, younger patients more often had DM independent of BMI compared to older patients. This suggests that beyond obesity alone, metabolic derangements following diabetes might be a possible risk factor for developing

HFpEF at a younger age. The link of obesity to diabetes, and the strong relationship of diabetes with worse outcome in HF, may be another important dimension of obesity in HF.

Younger patients with HFpEF had less objective evidence of fluid overload and were less often treated with diuretics despite having higher filling pressures (E/e'). Younger patients with HFrEF also show fewer signs of congestion (peripheral edema and basilar pulmonary crackles) and are less likely to be treated with diuretics. This may indicate that that fluid extravasation from the intravascular compartment does not occur as easily in younger compared with older patients with heart failure. However, a raised jugular venous pressure is reported as commonly in younger as older patients with HFrEF(6). This may mean that it is especially difficult to measure the jugular venous pressure in obese patients with HFpEF and echocardiographic measurement of filling pressures may be a particularly important tool in these patients for both diagnosis and clinical follow-up. In addition, younger patients with HFpEF might only display increased filling pressures at exertion (19), which emphasizes the importance of obesity as a risk factor for HFpEF and suggests that also exercise testing is of importance in these patients

Younger patients were less likely to be white compared to the elderly, although most patients in all age groups were white. This finding is in line with a recent report from the Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry, showed that Asian patients with HF are more than a decade younger than their western counterparts (11, 25, 26). In a particular study from ASIAN-HF investigating age-related differences in HFpEF, younger patients were more often obese men of Malay or Indian ethnicity. Furthermore, younger patients had similar cardiac structure and function, had better survival and similar quality of life compared to older patients (11). Our results confirm that ethnicity, sex and obesity play an important role in the young HFpEF phenotype. In addition, our study extends upon these previous findings by

showing that CV causes of death, particularly sudden death, is more important in younger patients with HFpEF. Furthermore, this previous study only included only patients from Asia. In contrast to ASIAN-HF, younger patients in our study had a higher prevalence of concentric hypertrophy and worse diastolic dysfunction compared to the elderly. This might be explained by the relatively large proportion of black patients among young patients with HFpEF; black patients have a higher afterload sensitivity as a stimulus for LV structural and functional remodeling, leading to greater diastolic dysfunction and more adverse remodeling (27). Indeed, this might explain the fact that incident HF before 50 years is more common among blacks compared to whites in the United States (23). Additional reports from the African continent described that African patients with HF are generally younger and more often have a hypertensive etiology of HF, suggesting that HFpEF has a potential higher prevalence in Africa (28–30).

When looking at quality of life, elderly patient had better quality of life compared to the younger patients, while there were no age related differences observed in quality of life across age strata in ASIAN-HF, power was considerably lower in the latter study (11). Several studies have reported that quality of life in HF varies by region (31, 32), ethnicity (33) and socioeconomic status (33, 34), which might explain the differences in association between age and quality of life in ASIAN-HF where patients were exclusively from Asia and the present study. Furthermore, our results are in line with a multinational study from the CHARM program, which reported similar differences in quality of life across age-strata in a combined cohort of patients with HFrEF and HFpEF (6). Perhaps some the most interesting findings in our study is the difference in mortality across age groups. Overall, older patients with HFpEF had higher mortality rates than younger patients. However, while the absolute mortality rate was lower in

younger patients with HFpEF, among patients who died younger patients with HFpEF died proportionally more frequently of CV causes than the elderly. Compared to HFrEF, patients with HFpEF are older and die more often from non-CV related causes(35–37). Indeed, age is an important predictor of non-CV death, compared with CV-death, in HF(38). Furthermore, older patients had a higher comorbidity burden, which might explain the higher proportion of non-CV death. In contrast to the elderly, younger patients with HFpEF died more of CV related causes, and particularly SD. However, without a terminal ECG rhythm strip it is not possible to differentiate sudden cardiac death (SCD) from other types of SD in this population e.g. cerebrovascular accident(36). A previous analysis of the DANISH study found that younger patients with non-ischemic HFrEF derived more benefit from cardiac defibrillator implantation(39). Similarly, a post-hoc analysis of the Surgical Treatment for Ischemic Heart Failure (STICH) trial, showed that particularly younger patients with HFrEF benefited more from coronary artery bypass grafting added to medical therapy compared to the elderly(40). Although both the DANISH and STICH trials did not include HFpEF, our current results suggest that the concept that younger patients might benefit from cardiovascular interventions deserves consideration in younger patients with HFpEF as well. Particularly, while the absolute event rate is lower in younger patients with HFpEF compared to the elderly, the number of life-years lost is considerably greater in the young.

Limitations

Our study has several limitations. First, this was a retrospective analysis. Secondly, we used clinical trial data and the patients enrolled were selected compared to patients with HFpEF more generally. Associations of age, other characteristics, and outcomes may or may not be causally linked. Importantly, I-Preserve and TOPCAT had lower age limits of 60 and 50 years,

respectively that might have underestimated the proportion of younger HFpEF patients in our analysis. The majority of our study population was of white ethnicity. It is not clear whether our results are generalizable to other ethnicities and more studies in non-white populations are needed. Lastly, data included in this study are from clinical trials and may not be representative of real-world HFpEF populations.

Conclusions

Patients with a HFpEF show distinct age dependent clinical profiles. Whereas younger patients are often obese non-white men, elderly patients are more often women with a plethora of comorbidities. Young patients die more of CV causes, particularly SD, while elderly patients die more from non-CV causes. Interventional trials targeting obesity and the prevention of sudden cardiac death may be of particular interest in younger patients with HFpEF.

PERSPECTIVES

Competency in Medical Knowledge: Younger patients with HFpEF are more often obese, non-white men, while older patients are more often white women with a higher prevalence of comorbidities. Despite fewer comorbidities, younger patients have worse quality of life, compared with older patients. Younger patients experienced proportionally more cardiovascular mortality and sudden death was the most common mode of death in younger patients. A higher proportion of older patients died from non-cardiovascular causes.

Translational Outlook: The global increase in obesity has major implications for the future risk of HFpEF at a younger age in Black and Asian populations. In addition to efforts to reduce obesity, specific therapies targeted at the risk of HFpEF in obese individuals are needed.

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Figure Legends

Figure 1: Forest plot depicting association between baseline clinical characteristics and odds of being <65 years versus ≥65 years. Clinical characteristics with a mean odds ratio and lower confidence bound >1 are significantly associated with being <65 years, while clinical characteristics with a mean odds ratio and lower confidence bound <1 are associated with being ≥65 years. Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York heart association.

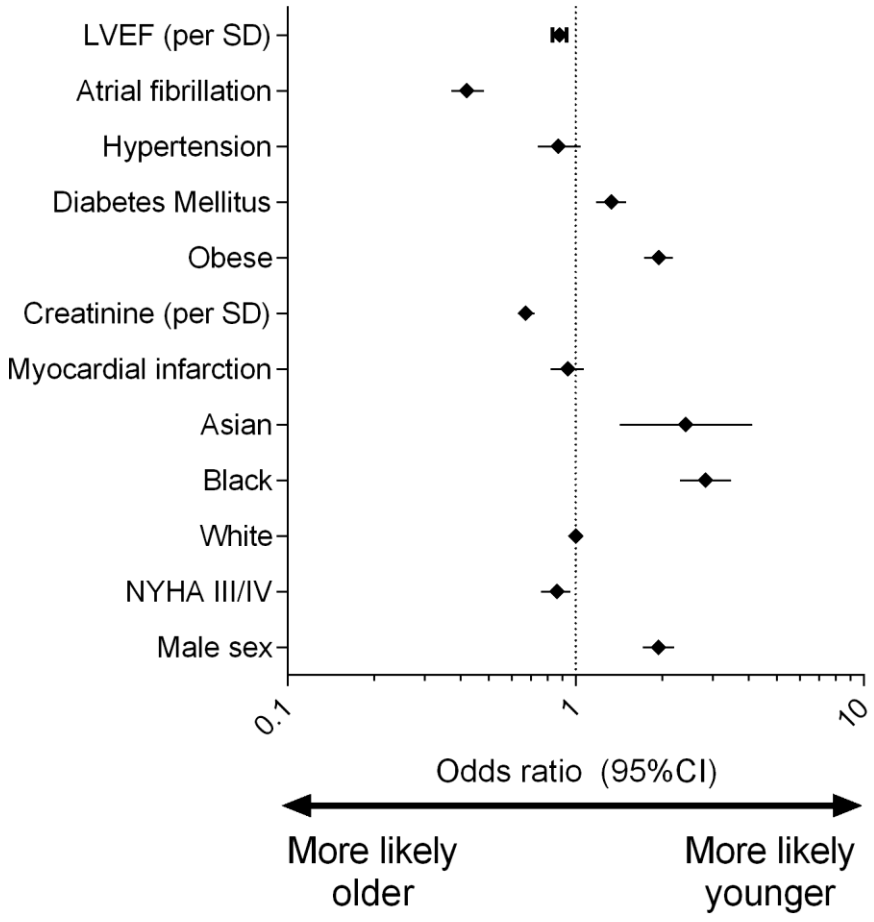

Figure 2: Cumulative incidence curves for all-cause mortality (A), CV mortality (B), a composite outcome of CV mortality or hospitalization for HF (C) and non-CV mortality (D) by age strata. Abbreviations: CV, cardiovascular; HF, heart failure.

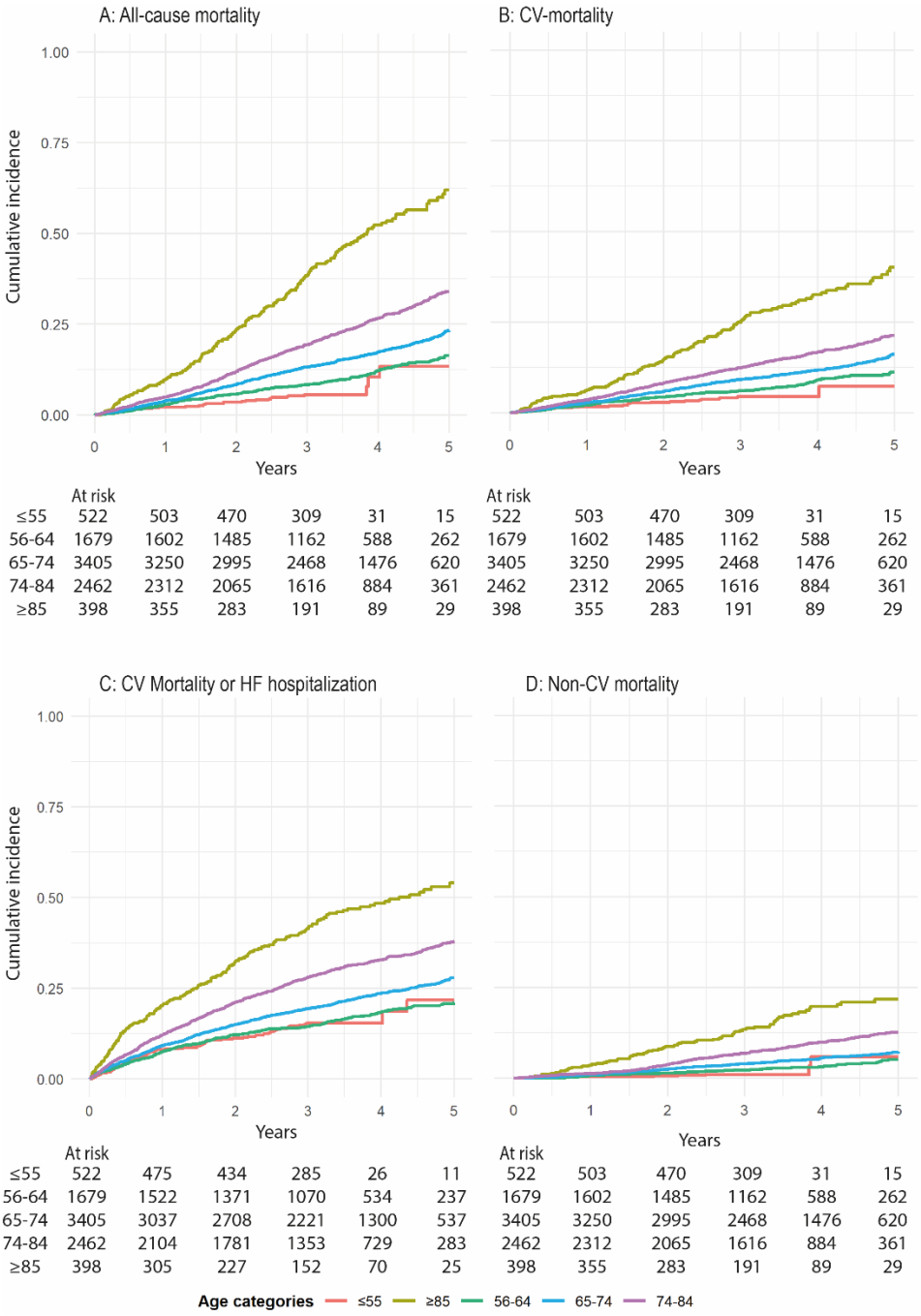

Figure 3: **Stacked bar graph showing adjudicated causes of death among patients who died across age strata.** Abbreviations: CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

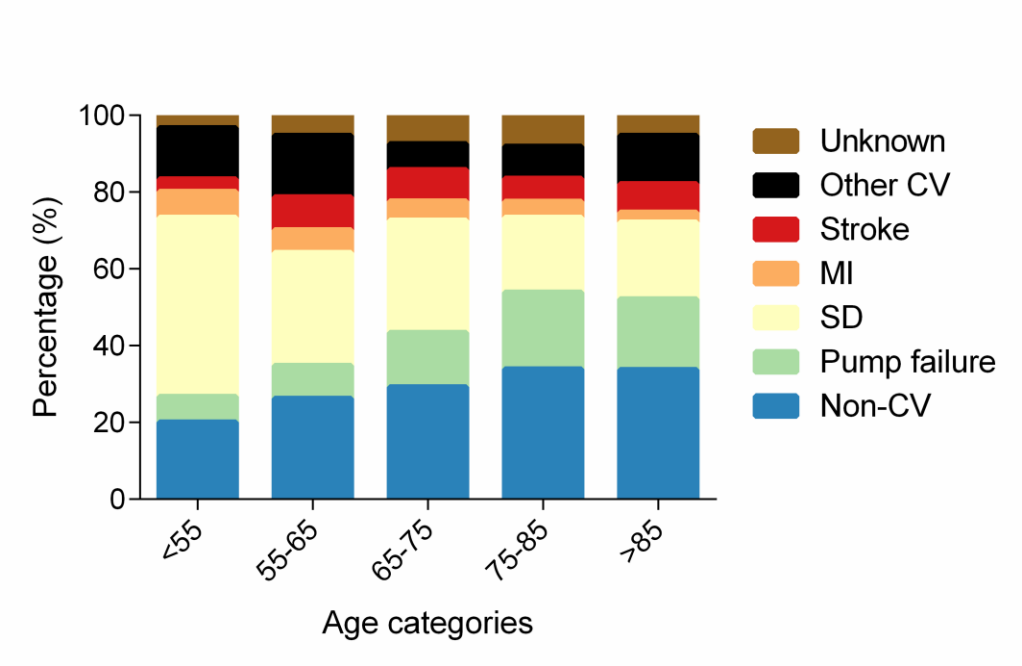

Figure 4: Central illustration describing age related differences in patients with HFpEF.

Abbreviations: CV, cardiovascular.

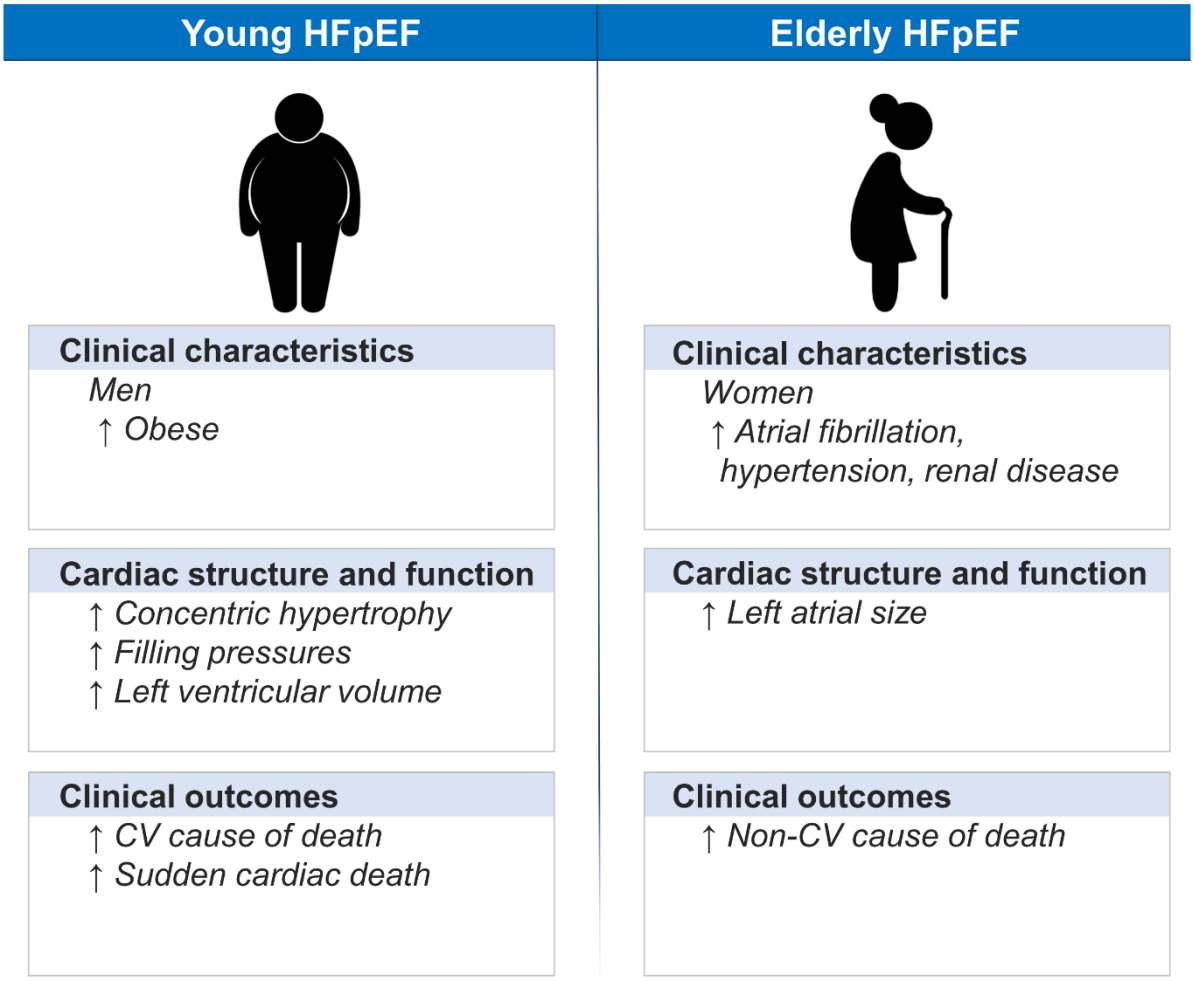

Table 1: Baseline characteristics

	≤55	*56-64*	*65-74*	*75-84*	*≥85*	**p-value**
N	522	1679	3405	2464	398	
Demographics						
Age (years)	49.9 (5.1)	61.1 (2.3)	69.6 (2.9)	78.6 (2.7)	87.2 (2.1)	NA
male	336 (64.4%)	928 (55.3%)	1555 (45.7%)	1039 (42.2%)	152 (38.2%)	<0.001
NYHA						
II	285 (68.3%)	529 (40.4%)	993 (34.8%)	580 (31.0%)	73 (29.8%)	<0.001
III	128 (30.7%)	757 (57.8%)	1812 (63.4%)	1227 (65.6%)	161 (65.7%)	
IV	4 (1.0%)	24 (1.8%)	53 (1.9%)	63 (3.4%)	11 (4.5%)	
Race						
White	408 (78.2%)	1444 (86.0%)	3093 (90.8%)	2282 (92.6%)	369 (92.7%)	<0.001
Black	85 (16.3%)	139 (8.3%)	162 (4.8%)	92 (3.7%)	14 (3.5%)	
Asian	15 (2.9%)	33 (2.0%)	41 (1.2%)	21 (0.9%)	8 (2.0%)	
Other	14 (2.7%)	63 (3.8%)	109 (3.2%)	69 (2.8%)	7 (1.8%)	
BMI	33.1 (8.2)	32.0 (7.2)	30.6 (5.9)	29.0 (5.6)	27.0 (5.3)	<0.001
Heart rate	72.7 (12.3)	71.1 (11.2)	70.5 (11.2)	71.1 (11.5)	70.6 (11.6)	<0.001
eGFR	86.3 (29.8)	78.1 (24.4)	71.5 (21.9)	63.9 (20.3)	57.2 (19.3)	<0.001
LVEF	56.0 (8.3)	57.4 (8.7)	58.4 (8.8)	58.6 (8.9)	59.5 (8.8)	<0.001
Signs and symptoms						
Shortness of breath	481 (92.1%)	1508 (94.9%)	2999 (94.2%)	2177 (94.4%)	344 (93.7%)	0.22
Rales	52 (10.0%)	305 (18.3%)	787 (23.2%)	613 (25.0%)	106 (26.8%)	<0.001
Increased JVP	47 (9.2%)	131 (7.9%)	289 (8.6%)	301 (12.4%)	70 (17.9%)	<0.001
Peripheral edema	181 (34.7%)	835 (49.8%)	1751 (51.4%)	1308 (53.0%)	216 (54.3%)	<0.001
Medical history						
BMI						
<18.5	1 (0.2%)	5 (0.3%)	12 (0.4%)	20 (0.8%)	11 (2.8%)	<0.001
18.5-25	63 (12.1%)	213 (12.7%)	480 (14.1%)	538 (22.0%)	146 (40.0%)	
25-30	167 (32.1%)	538 (32.1%)	1323 (38.9%)	963 (39.4%)	146 (36.7%)	

>30	290 (56%)	918 (54.9%)	1582 (46.6%)	924 (37.8%)	93 (23.5%)	
>35	167 (32.1%)	442 (26.4%)	678 (20.0%)	326 (13.4%)	31 (7.9%)	<0.001
PCI/CABG	140 (26.8%)	456 (27.2%)	706 (20.7%)	574 (23.2%)	68 (17.1%)	<0.001
Myocardial infarction	182 (34.9%)	499 (29.8%)	952 (27.9%)	677 (27.4%)	74 (18.6%)	<0.001
eGFR<60	48 (17.0%)	324 (25.1%)	928 (33.4%)	931 (45.2%)	195 (59.8%)	<0.001
Diabetes mellitus	165 (31.6%)	625 (37.3%)	1083 (31.8%)	706 (28.6%)	74 (18.6%)	<0.001
Valvular disease	7 (1.7%)	61 (4.7%)	193 (6.8%)	230 (12.3%)	40 (16.3%)	<0.001
Hypertension	353 (67.6%)	1350 (80.4%)	2900 (85.2%)	2021 (82.0%)	306 (76.9%)	<0.001
Atrial fibrillation	81 (15.5%)	350 (20.8%)	1057 (31.0%)	1048 (42.5%)	185 (46.5%)	<0.001
Stroke or Tia	32 (6.1%)	110 (6.6%)	326 (9.6%)	264 (10.7%)	47 (11.8%)	<0.001
Medication						
Beta-blocker	332 (63.6%)	1159 (69.1%)	2126 (62.5%)	1416 (57.5%)	199 (50.0%)	<0.001
Calcium channel blocker	160 (30.7%)	660 (39.4%)	1306 (38.4%)	895 (36.4%)	135 (33.9%)	0.001
Diuretic	355 (68.0%)	1297 (77.3%)	2801 (82.4%)	2111 (85.8%)	351 (88.2%)	<0.001
Laboratory						
Potassium (mmoL/L)	4.1 (3.8, 4.3)	4.3 (4.0, 4.6)	4.4 (4.1, 4.7)	4.3 (4.0, 4.7)	4.3 (4.0, 4.6)	<0.001
Sodium (mEq/L)	139.0 (138.0, 141.0)	140.0 (138.0, 142.0)	140.0 (138.0, 141.0)	140.0 (138.0, 141.0)	140.0 (138.0, 142.0)	0.15
Creatinine (mg/dL)	0.9 (0.8, 1.2)	0.9 (0.8, 1.2)	1.0 (0.8, 1.2)	1.1 (0.9, 1.3)	1.2 (0.9, 1.4)	<0.001

Table 2: Echocardiographic characteristics

	≤55	*56-64*	*65-74*	*75-84*	*≥85*	***p-value***
LV dimensions						
LVEDV	112.8 (84.9, 140.8)	100.9 (79.4, 125.4)	90.1 (68.5, 112.0)	83.2 (64.2, 104.8)	81.6 (64.2, 109.0)	**<0.001**
LVESV	44.0 (32.2, 58.0)	37.5 (27.6, 49.1)	32.7 (23.4, 43.8)	29.5 (22.2, 42.3)	30.7 (24.3, 44.8)	**<0.001**
LVS	1.2 (1.1, 1.4)	1.1 (0.9, 1.3)	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	1.1 (1.0, 1.3)	**<0.001**
PWT	1.2 (1.1, 1.3)	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)	1.0 (1.0, 1.2)	**<0.001**
Lvmass	222.9 (183.6, 280.6)	199.5 (147.2, 254.4)	175.4 (139.9, 222.4)	179.6 (144.8, 222.9)	173.4 (151.8, 219.7)	**<0.001**
Lvmassi	103.8 (84.8, 123.6)	94.4 (76.8, 116.2)	91.7 (75.1, 110.5)	97.4 (80.5, 117.9)	97.7 (82.8, 120.3)	**0.002**
*Lvmassi**	54.7 (45.5, 67.4)	48 (37.2, 60.3)	45.1 (36.6, 54.9)	46.5 (38.6, 58.8)	47.9 (37.9, 55.1)	**<0.001**
LVH (%)	50	35	32	42	41	**0.006**
*LVH (%)**	74	54	49	51	52	**<0.001**
RWT	0.5 (0.4, 0.6)	0.4 (0.4, 0.5)	0.4 (0.4, 0.5)	0.4 (0.4, 0.5)	0.5 (0.4, 0.5)	**<0.001**
RWT>0.42 (%)	86	60	49	57	68	**<0.001**
LVEF	55.0 (50.0, 60.0)	56.0 (50.0, 63.0)	58.0 (51.0, 64.0)	58.0 (51.0, 65.0)	60.0 (53.0, 65.0)	**<0.001**
Diastolic dysfunction						
Ewave	93.6 (67.0, 112.9)	83.7 (64.1, 108.1)	78.6 (60.9, 99.8)	82.9 (65.1, 101.5)	81.4 (66.6, 97.9)	**0.033**
Awave	68.3 (46.5, 83.4)	74.1 (59.2, 89.1)	80.6 (64.4, 96.0)	82.6 (61.5, 100.8)	80.5 (54.8, 97.5)	**<0.001**
E/e' lateral	14.1 (8.7, 16.9)	9.8 (7.3, 13.1)	9.4 (7.3, 12.2)	9.7 (7.3, 13.1)	10.0 (7.7, 14.1)	**0.022**
EA ratio	1.4 (1.0, 2.0)	1.0 (0.8, 1.5)	0.9 (0.7, 1.2)	0.9 (0.7, 1.4)	0.9 (0.7, 1.5)	**<0.001**
LAA	17.7 (15.7, 20.9)	20.2 (16.0, 24.2)	21.1 (17.5, 24.9)	22.1 (18.2, 25.7)	20.8 (17.8, 24.0)	**<0.001**
Geometry						**<0.001**
Normal (%)	10	31	38	30	26	
Concentric remodeling (%)	41	34	30	28	33	
Concentric hypertrophy (%)	45	26	20	29	36	

Eccentric hypertrophy (%)	5	9	12	13	5

*****LVmass indexed to height to the power of 1.7

Table 3: Association between age and outcomes (all-cause mortality, cardiovascular (CV) mortality, non-CV mortality and CV mortality or HF hospitalization).

				All-cause mortality	
			Univariable	***Model 1***	***Model 2***
	Cases/ N	Events/100 pt yrs (95%CI)	HR (95%CI) p-value	HR (95%CI) p-value	HR (95%CI) p-value
≤55	30/522	1.89 (1.32-2.70)	*reference*	*reference*	*reference*
56-64	187/1678	3.21 (2.78-3.70)	1.62 (1.10-2.39) 0.014	1.58 (0.97-2.58) 0.068	1.60 (0.98-2.62) 0.059
65-74	601/3405	4.89 (4.51-5.30)	2.45 (1.70-3.54) <0.001	2.22 (1.38-3.57) 0.001	2.28 (1.42-3.68) 0.001
75-84	636/2464	7.63 (7.01-7.24)	3.86 (2.68-5.57) <0.001	3.15 (1.94-5.08) <0.001	3.15 (1.95-5.08) <0.001
≥85	190/398	16.74 (14.52-19.29)	8.72 (5.93-12.82) <0.001	6.48 (3.93-10.69) <0.001	6.89 (4.17-11.37) <0.001
				CV mortality	
≤55	23/522	1.45 (0.96-2.18)	*reference*	*reference*	*reference*
56-64	133/1679	2.28 (1.93-2.70)	1.53 (0.98-2.38) 0.062	1.48 (0.82-2.65) 0.183	1.49 (0.83-2.66) 0.182
65-74	414/3405	3.38 (3.07-3.72)	2.22 (1.46-3.38) <0.001	1.96 (1.11-3.44) 0.020	2.00 (1.13-3.52) 0.017
75-84	414/2464	4.83 (4.38-5.32)	3.12 (2.05-4.76) <0.001	2.48 (1.41-4.38) 0.002	2.39 (1.35-4.24) 0.003
≥85	125/398	10.74 (9.00-12.83)	6.58 (4.21-10.28) <0.001	4.45 (2.46-8.08) <0.001	4.62 (2.53-8.44) <0.001
				Non-CV mortality	
≤55	6/522	0.38 (0.17-0.84)	*reference*	*reference*	*reference*
56-64	49/1679	0.84 (0.63-1.11)	2.12 (0.91-4.94) 0.083	1.96 (0.70-5.52) 0.200	1.98 (0.70-5.55) 0.196
65-74	176/3405	1.43 (1.23-1.65)	3.50 (1.55-7.91) 0.003	3.01 (1.10-8.21) 0.032	3.04 (1.11-8.29) 0.030
75-84	216/2464	2.58 (2.26-2.95)	6.19 (2.74-13.94) <0.001	4.95 (1.81-13.52) 0.002	4.87 (1.79-13.27) 0.002
≥85	64/398	5.64 (4.41-7.20)	12.31 (5.33-28.48) <0.001	10.71 (3.81-30.12) <0.001	10.45 (3.72-29.35) <0.001
				Hospitalization for HF	
≤55	59/522	4.00 (3.07-5.12)	*reference*	*reference*	*reference*
56-64	199/1679	3.64 (3.17-4.18)	0.97 (0.73-1.30) 0.853	0.75 (0.54-1.03) 0.071	0.70 (0.50-0.95) 0.024
65-74	535/3405	4.74 (4.35-5.16)	1.26 (0.96-1.65) 0.090	0.94 (0.70-1.28) 0.723	0.87 (0.64-1.17) 0.368
75-84	572/2464	7.79 (7.18-8.45)	1.97 (1.51-2.57) <0.001	1.39 (1.02-1.88) 0.035	1.24 (0.91-1.68) 0.173
≥85	115/398	11.98 (9.98-14.38)	2.66 (1.94-3.65) <0.001	1.78 (1.23-2.56) 0.002	1.70 (1.18-2.46) 0.005
				CV-mortality or hospitalization for HF	

≤55	79/522	5.31 (4.26-6.63)	*reference*	*reference*	*reference*
56-64	268/1679	5.23 (4.66-5.88)	1.02 (0.79-1.31) 0.900	0.80 (0.60-1.07) 0.129	0.77 (0.58-1.02) 0.070
65-74	792/3405	7.02 (6.54-7.52)	1.36 (1.08-1.72) 0.009	1.03 (0.79-1.35) 0.821	0.99 (0.75-1.30) 0.921
75-84	790/2464	10.76 (10.03-11.53)	2.02 (1.60-2.54) <0.001	1.40 (1.06-1.84) 0.016	1.30 (0.98-1.71) 0.066
≥85	184/398	19.17 (16.59-22.14)	3.35 (2.57-4.36) <0.001	2.11 (1.54-2.89) <0.001	2.10 (1.53-2.90) <0.001
			Sudden death		
≤55	13/522	0.82 (0.48-1.41)	*reference*	*reference*	*reference*
56-64	51/1679	0.88 (0.67-1.15)	1.05 (0.57-1.93) 0.882	1.32 (0.52-3.37) 0.563	1.34 (0.52-3.43) 0.539
65-74	173/3405	1.41 (1.22-1.64)	1.66 (0.94-2.92) 0.079	2.14 (0.87-5.29) 0.099	2.26 (0.91-5.60) 0.078
75-84	124/2464	1.49 (1.25-1.77)	1.67 (0.94-3.00) 0.078	1.99 (0.80-4.95) 0.137	2.10 (0.84-5.24) 0.110
≥85	36/398	3.17 (2.29-4.39)	3.12 (1.66-5.89) <0.001	3.55 (1.36-9.27) 0.010	4.07 (1.55-10.67) 0.004

Model 1: Sex, BMI, creatinine, race, NYHA class

Model 2: Model 1 + diabetes, atrial fibrillation, hypertension, LVEF and treatment arm