Journal of Cardiac Failure Vol. 00 No. 00 2023

Does Heterogeneity Exist in Treatment Associations With Renin–Angiotensin–System Inhibitors or Beta-blockers According to Phenotype Clusters in Heart Failure with Preserved Ejection Fraction?

ALICIA UIJL, PhD,[1,2,3] STEFAN KOUDSTAAL, MD, PhD,[4] DAVIDE STOLFO, MD, PhD,[3,5] ULF DAHLSTRÖM, MD, PhD,[6] ILONCA VAARTJES, PhD,[1] RICK E. GROBBEE, MD, PhD,[1] FOLKERT W. ASSELBERGS, MD, PhD,[2,7] LARS H. LUND, MD, PhD,[3,8] AND GIANLUIGI SAVARESE, MD, PhD[3]

Amsterdam, and Gouda, the Netherlands; Stockholm and Linköping, Sweden; Trieste, Italy; and UK

ABSTRACT

Background: We explored the association between use of renin–angiotensin system inhibitors and beta-blockers, with mortality/morbidity in 5 previously identified clusters of patients with heart failure with preserved ejection fraction (HFpEF).

Methods and Results: We analyzed 20,980 patients with HFpEF from the Swedish HF registry, phenotyped into young–low comorbidity burden (12%), atrial fibrillation–hypertensive (32%), older–atrial fibrillation (24%), obese–diabetic (15%), and a cardiorenal cluster (17%). In Cox proportional hazard models with inverse probability weighting, there was no heterogeneity in the association between renin–angiotensin system inhibitor use and cluster membership for any of the outcomes: cardiovascular (CV) mortality, all-cause mortality, HF hospitalisation, CV hospitalisation, or non-CV hospitalisation. In contrast, we found a statistical interaction between beta-blocker use and cluster membership for all-cause mortality ($P = .03$) and non-CV hospitalisation ($P = .001$). In the young–low comorbidity burden and atrial fibrillation–hypertensive cluster, beta-blocker use was associated with statistically significant lower all-cause mortality and non-CV hospitalisation and in the obese–diabetic cluster beta-blocker use was only associated with a statistically significant lower non-CV hospitalisation. The interaction between beta-blocker use and cluster membership for all-cause mortality could potentially be driven by patients with improved EF. However, patient numbers were diminished when excluding those with improved EF and the direction of the associations remained similar.

Conclusions: In patients with HFpEF, the association with all-cause mortality and non-CV hospitalisation was heterogeneous across clusters for beta-blockers. It remains to be elucidated how heterogeneity in HFpEF could influence personalized medicine and future clinical trial design. (*J Cardiac Fail 2023;00:1–11*)

Key Words: Phenotype clusters, personalized medicine, HFpEF, renin–angiotensin system inhibitors, beta-blockers.

From the [1]Julius Global Health, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, the Netherlands; [2]Amsterdam University Medical Centers, Department of Cardiology, University of Amsterdam, Amsterdam, the Netherlands; [3]Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [4]Department of Cardiology, Groene Hart Ziekenhuis, Gouda, the Netherlands; [5]Division of Cardiology, Cardiovascular Department, Azienda Sanitaria Universitaria Integrata di Trieste (ASUITS), Trieste, Italy; [6]Department of Cardiology and Department of Health, Medicine and Caring Sciences, Linkoping University, Linköping, Sweden; [7]Health Data Research UK London, Institute of Health Informatics, University College London, UK and [8]Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden.

Manuscript received February 3, 2023; revised manuscript received July 31, 2023; revised manuscript accepted August 6, 2023.

Reprint requests: Alicia Uijl, PhD, Department of Cardiology, Amsterdam University Medical Centers, Meibergdreef 9, 1105 AZ, the Netherlands. Tel: +31 638021986. E-mail: a.uijl@amsterdamumc.nl

1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2023.08.008

Heart failure with preserved ejection fraction (HFpEF) (EF ≥50%) has been reported with a prevalence of 20%−30% in contemporary registries,[1−3] although community studies can report a prevalence of ≤50%.[4,5] Unlike patients with HF with reduced EF (HFrEF) (EF ≤40%), who can benefit of several life-saving pharmacological and device treatments, only the sodium−glucose co-transporter 2 inhibitors empagliflozin and dapagliflozin have recently demonstrated to reduce mortality and morbidity in HFpEF.[6,7] Most randomized clinical trials (RCTs) investigating the efficacy of therapies for patients with HFpEF were overall neutral, but subsequent post hoc analyses identified potential treatment effects in specific subgroups of patients.[8,9]

There is growing awareness of the heterogeneity of the HFpEF patient population, which might explain the disappointing neutral results of several trials. This finding might pose the background for precision medicine in HFpEF. Clustering of patients based on clinical characteristics could be helpful, where the identification of similar patient subgroups could lead to a more homogeneous treatment response.[10]

In the Swedish HF registry (SwedeHF), we previously identified 5 distinct patient clusters in HFpEF, characterized by differences in demographics, clinical characteristics, HF treatments and outcomes, namely, a young−low comorbidity burden cluster, an atrial fibrillation (AF)−hypertensive cluster, an older−AF cluster, an obese−diabetic cluster, and a cardiorenal cluster.[11] These clusters were externally validated in the Chronic Heart Failure ESC guideline-based Cardiology practice Quality project (CHECK-HF) registry with major consistency and robustness.[11] However, it remains unknown if treatment effects might differ across patient clusters.

The aim of this study was to investigate whether a potential association between renin−angiotensin system (RAS) inhibitors and beta-blockers use and cardiovascular (CV) mortality, HF hospitalisation and all-cause mortality differs across these 5 HFpEF patient clusters.

Methods

Data Sources

The SwedeHF registry was widely implemented throughout Sweden in 2003.[1] The only inclusion criterion was clinician-judged HF until April 2017 and thereafter a diagnosis of HF according to the *International Statistical Classification of Diseases*, tenth revision. Patients are registered at discharge from the hospital or after an outpatient clinic visit. All residents in Sweden have unique personal identification numbers that allows linking disease-specific health registries and governmental health and statistical registries. For the current analysis, SwedeHF was linked to the National Patient Registry, Cause of Death registry and Statistics Sweden, which provided additional data on baseline comorbidities and the outcome HF hospitalisation, date and cause of death, and socioeconomic characteristics, respectively. All variable definitions are reported in Table S1.

Study Population

In the current study, we included 20,980 patients with a left ventricular EF of ≥50% registered between May 2000 and 31 December 2018 (n = 126,936 excluded). Registrations with missing information on medication use were excluded (n = 325). For patients with multiple registration, we only considered the first registration with available EF and data on use of medications (n = 8303 excluded). Patient selection is reported in Fig. S1.

Phenotypic Clusters

Patients were classified into 1 of the 5 phenotypic clusters, based on the highest probability of cluster membership from a latent class analysis model (*poLCA* package in R statistical software) in a subset of patients with HFpEF in SwedeHF between 2013 and 2016 (n = 6909). The model has been previously described in detail.[11] Briefly, latent class clusters were derived using maximum-likelihood estimation over 10 iterations to identify the most common patterns of the predefined variables.

Table S2 shows the probabilities of categorical variables in the model for the following variables: age (<65 years, 65−75 years, 75−85 years, and >85 years), sex (male/female), New York Heart Association (NYHA) functional class (I/II or III/IV), body mass index (<25, 25−30 and >30 kg/m^2), estimated glomerular filtration rat (<30, 30−60, and >60 mL/min/1.73 m^2); and the comorbidities: AF, chronic obstructive pulmonary disease, diabetes, hypertension, and ischemic heart disease (yes/no).

Statistical Analyses

Baseline continuous variables are presented as mean ± standard deviation or median with interquartile range (IQR); categorical data are presented as counts and percentages (%). Multiple imputation (*mice* package) was used to impute missing data in the baseline measurements (variables included in the multiple imputation reported in Table 1, full table in Table S3). There were 10,464 complete cases in the latent class model and 10,516 cluster memberships were imputed based on the pooled average of the probabilities from the latent class model in 10 imputed datasets.

Table 1. Baseline characteristics per cluster

	Overall	Cluster 1 (Young – Low Comorbidity Burden)	Cluster 2 (Hypertensive – AF)	Cluster 3 (Older – AF)	Cluster 4 (Obese – Diabetic)	Cluster 5 (Cardiorenal)	*P* Value
No. (%)	20,980	2591 (12.4)	6780 (32.3)	5001 (23.8)	3176 (15.1)	3432 (16.4)	
Age (years)*,†	79.0 [71.0–85.0]	59.0 [52.0–64.0]	78.0 [73.0–82.0]	88.0 [86.0–90.0]	71.0 [65.0–75.0]	82.0 [79.0–85.0]	<.001
Female (%)*,†	10872 (51.8)	1015 (39.2)	3212 (47.4)	3258 (65.1)	1055 (33.2)	2332 (67.9)	<.001
HF measurements							
NYHA functional class (III/IV) (%)*,†	4765 (37.3)	267 (14.3)	1093 (25.8)	1392 (50.0)	815 (42.1)	1198 (61.3)	<.001
NT-proBNP (pg/mL)	1875.0 [770.0–4000.0]	495.0 [150.0–1330.0]	1662.0 [761.25–3283.0]	3213.0 [1730.0–6467.0]	1310.0 [570.50–2966.0]	2510.0 [1300.0–4894.0]	<.001
Implantable devices (%)*,†,‡	470 (2.3)	150 (5.9)	173 (2.6)	36 (0.7)	77 (2.5)	34 (1.0)	<.001
Pacemaker (%)	10.2	3.9	9.3	13.9	7.7	13.4	<.001
Prior EF status (% HFrEF)	1279 (6.4)	475 (18.9)	399 (6.1)	96 (2.0)	212 (7.0)	97 (3.0)	<.001
Electrocardiogram at registration							<0.001
AF	8852 (43.4)	415 (17.0)	3147 (47.9)	2540 (52.0)	935 (30.2)	1815 (54.1)	
Sinus rhythm	9776 (48.0)	1893 (77.4)	2910 (44.3)	1826 (37.4)	1951 (63.0)	1196 (35.7)	
Pacemaker/other	1719 (8.4)	139 (5.7)	510 (7.8)	516 (10.6)	211 (6.8)	343 (10.2)	
Clinical measurements							
Systolic blood pressure (mm Hg)	132.7 (21.8)	126.4 (20.2)	131.7 (20.9)	133.3 (22.7)	136.4 (21.5)	135.3 (22.3)	<.001
Diastolic blood pressure (mm Hg)	73.3 (12.3)	75.2 (12.1)	74.0 (12.1)	71.8 (12.5)	73.8 (12.1)	72.4 (12.4)	<.001
Heart rate (bpm)*,†	72.0 [63.0–82.0]	69.0 [60.0–79.0]	71.0 [63.0–82.0]	73.0 [65.0–84.0]	71.0 [63.0–81.0]	72.0 [63.0–83.0]	<.001
BMI (kg/m^2)*,†	28.0 (6.2)	28.9 (6.8)	27.0 (5.4)	23.8 (3.5)	32.1 (6.4)	31.3 (5.5)	<.001
<25	4006 (34.2)	387 (30.7)	1325 (36.4)	1920 (67.3)	211 (11.0)	163 (7.9)	
25.0–29.9	3991 (34.0)	401 (31.8)	1506 (41.3)	824 (28.9)	553 (28.8)	707 (34.4)	
≥30	3731 (31.8)	472 (37.5)	812 (22.3)	108 (3.8)	1154 (60.2)	1185 (57.7)	
eGFR (mL/min/1.73 m^2)*,†	57.3 [41.3–75.3]	84.9 [70.9–96.0]	65.2 [51.9–79.1]	46.4 [34.5–58.6]	62.4 [43.8–79.5]	41.0 [30.0–51.6]	<.001
>60	9357 (45.7)	2236 (90.6)	4074 (61.7)	1108 (22.5)	1669 (53.6)	270 (8.0)	
30–60	9071 (44.3)	196 (7.9)	2505 (38.0)	2986 (60.5)	1127 (36.2)	2257 (66.8)	
<30	2062 (10.1)	35 (1.4)	19 (0.3)	838 (17.0)	320 (10.3)	850 (25.2)	
Comorbidities (%)							
Ischemic heart disease*,†	10021 (47.8)	640 (24.7)	2760 (40.7)	2663 (53.2)	1976 (62.2)	1982 (57.8)	<.001
Dilated cardiomyopathy	1083 (5.2)	545 (21.0)	272 (4.0)	75 (1.5)	145 (4.6)	46 (1.3)	<.001
AF*,†	13404 (63.9)	833 (32.1)	4750 (70.1)	3601 (72.0)	1550 (48.8)	2670 (77.8)	<0.01
Hypertension*,†	15620 (74.5)	1103 (42.6)	4545 (67.0)	3596 (71.9)	2969 (93.5)	3407 (99.3)	<.001
Valvular disease*,†	7202 (34.3)	663 (25.6)	2354 (34.7)	2226 (44.5)	812 (25.6)	1147 (33.4)	<.001
COPD*,†	3360 (16.0)	198 (7.6)	1340 (19.8)	495 (9.9)	707 (22.3)	620 (18.1)	<.001
Diabetes*,†	6000 (28.6)	146 (5.6)	216 (3.2)	435 (8.7)	2955 (93.0)	2248 (65.5)	<.001
Cancer*,†	3357 (16.0)	228 (8.8)	1179 (17.4)	934 (18.7)	455 (14.3)	561 (16.3)	<0.001
Medication use (%)							
Diuretic use*,†	17073 (81.4)	1416 (54.7)	5276 (77.8)	4446 (88.9)	2745 (86.4)	3190 (92.9)	<.001
RAS inhibitor use*,†	15284 (72.9)	2066 (79.7)	5147 (75.9)	3078 (61.5)	2558 (80.5)	2435 (70.9)	<.001
Beta-blocker use*,†	17078 (81.4)	2076 (80.1)	5516 (81.4)	3858 (77.1)	2701 (85.0)	2927 (85.3)	<.001
MRA use*,†	6225 (29.7)	728 (28.1)	2032 (30.0)	1361 (27.2)	1024 (32.2)	1080 (31.5)	<.001

Values are median [IQR] or median [Interquartile range] unless otherwise specified.

AF = atrial fibrillation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonists; NT-proBNP = N-terminal B-type natriuretic peptide; NYHA class = New York Heart Association functional class; RAS-inhibitor = renin–angiotensin system Inhibitors.

*Variables included in the multiple imputation, with in addition: year of inclusion and hemoglobin.

†Variables included in the calculation of the inverse probability weights, with in addition: year of inclusion and mean arterial pressure.

‡Implantable devices: implantable cardioverter defibrillator or cardiac resynchronization therapy.Extended baseline characteristics per cluster are shown in Supplementary Table S3.

Cox proportional hazard models were weighted with inverse probability weights (IPWs) to estimate the association between treatment use and outcomes per cluster. The IPW for treatment use of RAS inhibitor and beta-blockers were separately calculated based on the propensity score (PS). The IPW weights were 1/PS for the treated patients and 1/(1 − PS) for the untreated patients. To obtain the ,PS we fitted a logistic regression model in each imputed dataset including the variables reported in Table 1 as covariates, and then averaged the PS across the 10 imputed datasets. The proportional hazards assumption was verified by assessment of the Schoenfeld residuals.

The primary outcomes of this study were CV mortality, all-cause mortality and HF hospitalisation within 5 years. The composite of CV mortality and HF hospitalization, and separate outcomes CV and non-CV hospitalisation within 5 years were secondary outcomes. We used cause-specific Cox proportional hazard models for our primary outcome analysis censoring for non-CV and all-cause mortality, respectively.

We tested cluster heterogeneity for the associations between use of treatments and outcomes by an interaction term between medication use and cluster membership. Results are presented as hazard ratios (HR) with 95% confidence intervals (CIs).

We performed 3 sensitivity analyses, one where we analyzed only complete cases for the clusters (n = 10,464), a second to excluded patients with previous HFrEF diagnosis (n = 19,701), and a third analysis of the individual treatments in RAS inhibitor: angiotensin-converting enzyme (ACE) inhibitors (n = 20,963) and angiotensin receptor blockers (ARBs) (n = 20,883). All analyses were performed using R version 4.0.2.

Results

Baseline Characteristics

Baseline patient characteristics for the overall cohort and per cluster are shown in Table 1. Overall, the median age was 79 years old (IQR 71−85 years) and 52% were female. Comorbidities were common, of which hypertension (75%), AF (64%), and ischemic heart disease (48%) were the most prevalent. Beta-blockers and diuretics were the most frequently prescribed type of HF medication (both 81%), followed by RAS inhibitor (73%) and mineralocorticoid receptor antagonists (30%).

Patients were classified to 1 of the 5 clusters as follows: 2591 (12%) in the young−low comorbidity burden cluster, 6790 (32%) in the AF−hypertensive cluster, 5001 (24%) in the older−AF cluster, 3176 (15%) in the obese−diabetic cluster and 3432 (17%) in the cardiorenal cluster. Cluster profiles were comparable to those identified in the previous analysis of SwedeHF.[11]

Patients in the young−low comorbidity burden cluster were the youngest (median age 59 years, IQR 52−64 years), more likely male (61%), and had fewer comorbidities compared with the other clusters. However, they more frequently had implantable devices (implantable cardioverter defibrillator or cardiac resynchronization therapy), dilated cardiomyopathy, and 19% previously had a lower EF measurement below 40%. Patients in the AF−hypertensive cluster had a median age of 78 years (IQR 73−82 years) and 53% were male. This cluster was characterized by very high prevalence of AF (70%) and hypertension (67%). Patients in the older−AF cluster were the oldest (median age 88 years, IQR 86−90 years), more likely female (65%), and 72% had AF. These patients had the highest N-terminal B-type natriuretic peptide levels compared with the other clusters. Patients in the obese−diabetic cluster had a median age of 71 years (IQR 65−75 years) and were more likely male (67%). Most patients were overweight (29%) or obese (60%) and had diabetes (93%). Patients in the cardiorenal cluster were older (median age 82 years, IQR 79−85 years), more likely female (68%), and more often had NYHA functional class III or IV disease (61%) and several comorbidities. A large proportion of patients in this cluster had impaired kidney function (ie, 92% had estimated glomerular filtration rate of $<$60 mL/min/1.73 m^2).

Dose ranges of ACE inhibitors, ARB, and beta-blockers differed per cluster. The young cluster was prescribed higher doses and the elderly−AF cluster and cardiorenal cluster generally had lower doses; this difference was more notable for ACE inhibitors and ARB and less pronounced for beta-blockers (Fig. S2).

After weighting, there were no statistically significant differences in baseline characteristics between RAS inhibitor or beta-blocker users and nonusers (Fig. S3).

Primary Outcomes

CV Mortality. Over a median follow-up of 2.92 years (IQR 1.37−5.00 years), 5672 patients (27%) died of CV causes. RAS inhibitor use was associated with a statistically significant 13% lower risk of CV death (HR 0.87, 95% CI 0.82−0.93) in adjusted analyses. There was no statistically significant interaction between RAS inhibitor use and cluster membership (P value for interaction = 0.94) (Fig. 1).

Beta-blocker use was associated with a statistically significant 10% lower risk of CV death (HR 0.90, 95% CI 0.84−0.97) after adjustments, with no statistically significant interaction between beta-blocker

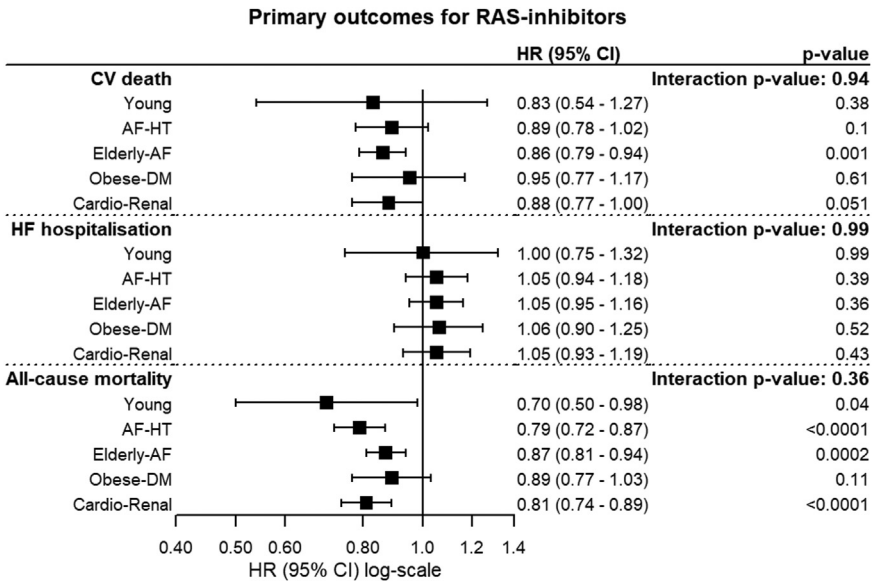

Fig. 1. The association between medication use with the primary outcomes per HFpEF cluster for RAS inhibitors. AF = atrial fibrillation; CV = cardiovascular; DM = diabetes; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HR = hazard ratio; HT = hypertension; RAS-inhibitors = renin–angiotensin system inhibitors.

use and cluster membership (*P* value for the interaction = 0.44) (Fig. 2).

HF Hospitalisation. In total, 6984 patients (33%) were hospitalized for HF. RAS inhibitor use was not associated with the risk of HF hospitalisation (HR 1.04, 95% CI 0.98–1.11) in adjusted analyses, and there was no statistically significant interaction between RAS inhibitor use and cluster membership (*P* value for the interaction = 0.99) (Fig. 1).

Similarly, beta-blocker use was not associated with the risk of HF hospitalisation (HR 0.95, 95% CI 0.88–1.02) after adjustments, and the interaction term between beta-blocker use and cluster membership did not reach statistical significance (*P* value = 0.38 for the interaction) (Fig. 2).

All-cause Mortality. In the overall cohort, 9852 patients (47%) died for any cause. RAS inhibitor use was associated with a statistically significant 17% lower risk of all-cause death (HR 0.83, 95% CI 0.79–0.87) after adjustments. There was no statistical interaction between RAS inhibitor and cluster membership (*P* value for the interaction = 0.36) (Fig. 1).

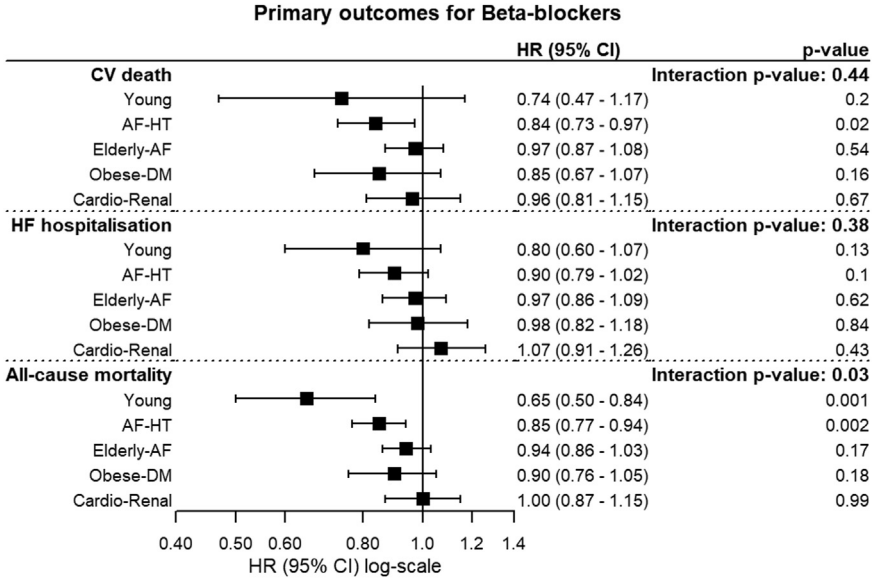

Fig. 2. The association between medication use with the primary outcomes per HFpEF cluster for beta-blockers. Abbreviations as in Fig 1.

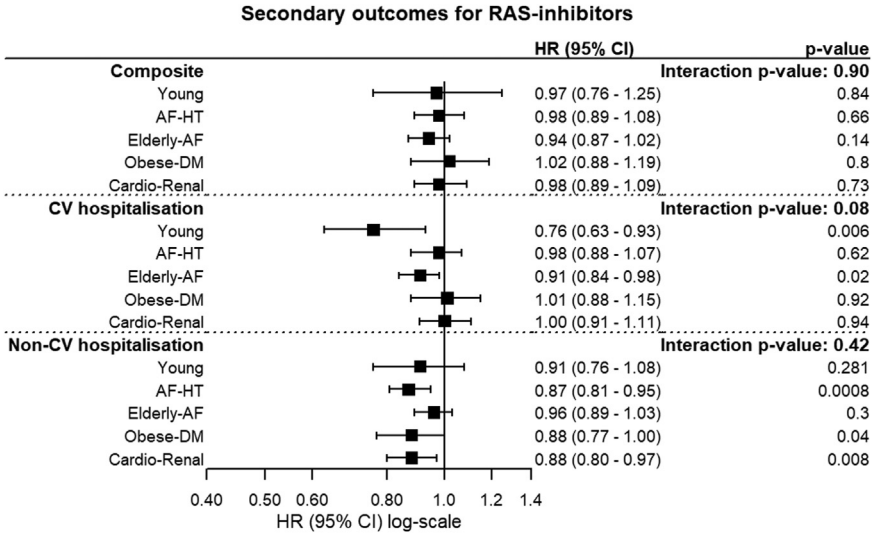

Fig. 3. The association between medication use with the secondary outcomes per HFpEF cluster for RAS inhibitors. Abbreviations as in Fig. 1.

Beta-blocker use was also associated with a statistically significant 10% lower risk of all-cause mortality (HR 0.90, 95% CI 0.85−0.95) in adjusted analyses. There was a statistically significant interaction between beta-blocker use and cluster membership (*P* value for the interaction = 0.03) (Fig. 2) for the association with all-cause mortality. In particular, beta-blocker use was associated with a lower all-cause mortality in the young−low comorbidity cluster (HR 0.65, 95% CI 0.50−0.84) and in the AF−hypertensive cluster (HR 0.85, 95% CI 0.77−0.94), but not within the other clusters.

Secondary Outcomes

Composite Outcome (CV Mortality or HF Hospitalization). In total, 9677 patients (46.1%) died of CV causes or reported an HF hospitalisation. RAS inhibitor use was not associated with a lower risk of the composite outcome (HR 0.97, 95% CI 0.92−1.02) after extensive adjustments and there was no statistically significant interaction between RAS inhibitor use and cluster membership (*P* value for the interaction = 0.90) (Fig. 3).

Consistently, beta-blocker use was also not associated with the risk of the composite outcome (HR 0.95, 95% CI 0.90−1.01) in adjusted analyses, and the interaction term between beta-blocker use and cluster membership was not significant (*P* value for the interaction = 0.19) (Fig. 4).

CV Hospitalisation. In total, there were 11,637 CV hospitalizations (55%). RAS inhibitor use was associated with a lower risk of CV hospitalisation

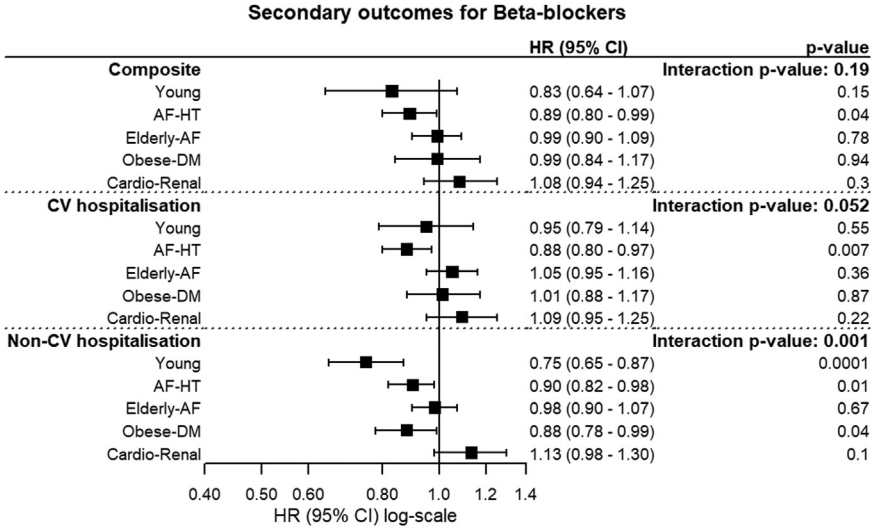

Fig. 4. The association between medication use with the secondary outcomes per HFpEF cluster for beta-blockers. Abbreviations as in Fig. 1.

(HR 0.94, 95% CI 0.90−0.99) in adjusted analyses, and there was no statistically significant interaction between RAS inhibitor use and cluster membership (*P* value for the interaction = 0.08) (Fig. 3).

Beta-blocker use was not associated with the risk of CV hospitalisation (HR 0.98, 95% CI 0.92−1.03) after adjustments, and the interaction term between beta-blocker use and cluster membership was not significant (*P* value = 0.052 for the interaction) (Fig. 4).

Non-CV Hospitalisation. In total, there were 14,021 non-CV hospitalizations (67%). RAS inhibitor use was associated with a lower risk of non-CV hospitalisation (HR 0.90, 95% CI 0.86−0.94) in adjusted analyses. There was no statistically significant interaction between RAS inhibitor use and cluster membership (*P* value for the interaction = 0.42) (Fig. 3).

Beta-blocker use was associated with the risk of non-CV hospitalisation (HR 0.92, 95% CI 0.88−0.97) after adjustments. The interaction term between beta-blocker use and cluster membership was significant (*P* value = 0.001 for the interaction) (Fig. 4). In the young, AF−hypertensive and obese−diabetic clusters, beta-blocker use was associated with fewer non-CV hospitalizations.

Sensitivity Analyses

In sensitivity analyses, we show that the complete cases analysis does not reach statistical significance for interaction for any of the outcomes (Table S4). When excluding the patients with improved EF (*n* = 1279), there is also no interaction between clusters and treatments for any of the outcomes except for non-CV hospitalisation with beta-blocker use (*P* = .005) (Table S5). Comparing ACE inhibitors and ARB separately, we find an interaction between ACE inhibitor use and cluster membership for CV mortality (*P* = .03), where the elderly−AF phenotype shows the most favorable outcomes with a HR 0.92 (95% CI 0.84−1.00) (Table S6).

Discussion

In this analysis from the SwedeHF registry, we examined the association between RAS inhibitor and beta-blockers and mortality and morbidity within different phenotypical clusters of HFpEF. Overall, beta-blockers and RAS inhibitor were associated with lower risks of all-cause and CV mortality, as well as non-CV hospitalisation. RAS inhibitor use was also associated with lower CV hospitalisation, whereas beta-blockers were not. Furthermore, using the clustering approach, we found heterogeneity in the association of beta-blockers with all-cause mortality and non-CV hospitalisation. In the young−low comorbidity burden and AF−hypertensive cluster, beta-blocker use was associated with both lower all-cause mortality and non-CV hospitalisation. In the obese−diabetic cluster, beta-blocker use was only associated with a lower non-CV hospitalisation.

Limited Therapeutic Options for Patients HFpEF

Although guidelines offer adequate therapies for patients with HFrEF, patients with HFpEF have few therapeutic options beyond comorbidity treatment and symptom control.[12] Recently, the EMPagliflozin outcomE tRial in Patients with chrOnic heaRt failure with preserved ejection fraction (EMPEROR-Preserved) and Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (PARAGON-HF) trials showed beneficial effects of sodium−glucose co-transporter 2 inhibitors and sacubitril/valsartan for patients with HFpEF, the latter only for patients at the lower end of the HFpEF EF spectrum.[13,14]

Trials using a phenotype approach in their design could help to identify potentially effective treatments, because HFpEF is characterized by high heterogeneity, and the same treatment might not be effective for all the diverse patients with HFpEF. Several studies have shown that there are distinct phenotypes within HFpEF that differ in demographics, clinical characteristics, HF pharmacotherapy, and outcomes, we have previously found 5 main phenotypes in SwedeHF: a young−low comorbidity burden cluster, an AF−hypertensive cluster, an older−AF cluster, an obese−diabetic cluster, and a cardiorenal cluster.[11] However, heterogeneity in potential treatment effectiveness based on belonging to a specific cluster has infrequently been investigated.[15-17]

RAS Inhibitors and HFpEF

Although previous RCTs for RAS inhibitor in HFpEF (Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity [CHARM-preserved], Perindopril in Elderly People with Chronic Heart Failure [PEP-CHF], and Irbesartan in Heart Failure with Preserved Ejection Fraction Study [I-PRESERVE])[18−20] were neutral for the primary outcomes, a meta-analysis showed a reduction in risk of CV mortality or HF hospitalisation at 1 year of follow-up, suggesting that the individual trials might have been underpowered.[21]

When investigating the association of RAS inhibitor with mortality and morbidity in HFpEF clusters, we showed that, regardless of HFpEF phenotypical cluster, RAS inhibitor are associated with both lower risk of all-cause and CV mortality. RAS inhibitors were also associated with CV and non-CV hospitalizations during a long-term follow-up study, but not with the composite outcome of CV mortality and HF hospitalisation. However, in a sensitivity analysis

there seems to be a benefit for the elderly−AF cluster with ACE inhibitor use for the CV mortality outcome.

Kao et al[15] (2015) found a potential benefit in terms of reduction in risk of all-cause mortality or CV hospitalisation (HR 0.72, $P = .046$) with irbesartan for one particular cluster in the I-PRESERVE trial, characterized by diabetes, obesity, coronary artery disease, and worse renal function. Yet, this finding was not validated in the CHARM-preserved.[15] A recent study by Gu et al[22] (2021) identified 3 clusters in HFpEF. In the cluster characterized by ischemic heart disease, diabetes, higher NYHA functional class, and higher B-type natriuretic peptide levels, the use of RAS inhibitor was associated with a lower risk of the composite endpoint of all-cause mortality and HF hospitalisation.[22] However, because both studies do not adjust for confounders, this association remains to hold in independent interaction analyses.

The PARAGON-HF trial might suggest that there is a heterogeneity in treatment effect for sacubitril/valsartan based on sex and EF, with only those at the lower end of the EF spectrum and women likely to benefit.[13] A RCT including stratification for phenotypic clusters might significantly contribute to reveal more therapeutic heterogeneity for sacubitril/valsartan in patients with HFpEF and could perhaps lead to an explanation on the association with HF hospitalisation, which we did not observe in the current study.

Beta-blockers and HFpEF

Few RCTs have studied beta-blockers in patient with HFpEF. Both the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure (SENIORS) trial (EF >35%) and the Japanese Diastolic Heart Failure Study (J-DHF) (EF >40%) showed no benefit of beta-blockers on mortality or HF hospitalisation.[23,24] In a meta-analysis of individual patient-level data from 11 RCTs, no beneficial effect on prognosis for HFpEF was observed. However, the number of patients with HFpEF with an EF of >50% was limited and therefore the analyses might have been underpowered.[25] Yet, a recent meta-analysis including 5 small beta-blocker trials with an EF of >40% showed that beta-blockers were associated with favorable outcomes in terms of NYHA functional class, exercise capacity, and B-type natriuretic peptide levels improvement in patients who had coronary artery disease or AF.[26] In addition, a small trial including patients with an EF of >40% and prior myocardial infarction showed that beta-blockers decreased all-cause mortality.[27] These findings suggest therapeutic heterogeneity for beta-blockers in patients with HFpEF. However, because these studies include patients with an EF of >40%, and not only patients with an EF of >50%, it remains to be elucidated if this association is driven by the inclusion of patients with HF with mildly reduced EF.

In our study, we show heterogeneity in the association of beta-blockers with all-cause mortality, with the young−low comorbidity burden cluster and AF−hypertensive cluster showing a significant lower risk of all-cause mortality. One potential mechanism that could explain this finding is the higher number of patients with dilated cardiomyopathy (21%), device therapy (6%), and previously lower EF (19%) in the young−low comorbidity burden cluster. It could be hypothesized that, at least to some extent, patients in this cluster could have HF with improved EF. Indeed, when we excluded patients with improved EF, which were mainly classified in the young−low comorbidity burden and AF−hypertensive clusters, the interaction term is not statistically significant anymore. Beta-blocker use was still associated with overall lower all-cause mortality, and, in an interaction analysis, the direction of the associations in the clusters is similar to the main analysis, yet not statistically significant ($P = .14$). It remains to be elucidated whether this was due to decreased power or an association driven by patients with improved EF. Therapy withdrawal in REcovered Dilated cardiomyopathy - Heart Failure (TRED-HF) study enrolling patients with dilated cardiomyopathy and improved EF showed that treatment withdrawal led to relapse; therefore, treatment discontinuation is not recommended in this setting.[28]

Beta-blockers are also used to treat hypertension, AF, and other cardiac comorbidities, which might explain potential beneficial effects of these treatments in the AF−hypertensive cluster. However, how there could be a potential benefit in this particular cluster compared with other clusters with comparable cardiac comorbidities is controversial. A study in patients with HFpEF and chronotropic incompetence actually showed that beta-blocker withdrawal increased the maximal functional capacity.[29] In addition, a secondary analysis of the Systolic Blood Pressure Intervention Trial (SPRINT) trial revealed that beta-blocker use was associated with a higher risk of incident HF in hypertensive subjects.[30] Recently, however, Karwath et al[31] showed that in patients with HFrEF and AF there also seems to be heterogeneity in treatment response in different clusters. These patients were younger and had a lower mortality risk, which could indicate less severe AF or a state before the onset of multimorbidity. Indeed, in our study the cardiorenal and elderly cluster, with similar distributions of AF, but higher

comorbidity burden, have worse survival rates than the AF−hypertensive cluster.

We showed that beta-blockers were associated with a lower risk of CV mortality in all patients with HFpEF. Gu et al (2021) found that in the cluster characterized by ischemic heart disease, diabetes, higher functional NYHA class and B-type natriuretic peptide levels, the use of beta-blockers was associated with a lower risk of both all-cause mortality and the composite endpoint of all-cause mortality and HF hospitalisation.[22] In contrast, another study also investigated both beta-blocker and RAS inhibitor use in HFpEF clusters, but found no association between treatment use and the outcome HF hospitalisation.[32] Our study also did not show an association between RAS inhibitor and beta-blockers with HF hospitalisation; therefore, it remains to be elucidated whether there could be treatment heterogeneity between clusters. Perhaps hospitalized patients have their management more optimized to decrease subsequent mortality.[33]

Last, we found a statistically significant interaction between cluster membership and beta-blocker use for non-CV hospitalisation. This outcome has not been studied previously and this interaction should be validated in future studies.

Strengths and Limitations

A strength of this study is the large and unselected HFpEF patient population captured in SwedeHF, which allowed for the detailed study of different phenotypes within this patient group and extensive adjustments for potential confounders. Another strength is that the clusters analyzed in our study were validated in other data sources, indicating consistency across different countries, types of studies (registry, cohort, and RCTs) and clustering methods.[15-17]

However, this study also has some limitations. RCTs remain the gold standard in estimating treatment effects, while we can only adjust for baseline imbalances in observational studies. Although we adjusted for many different variables by the IPW adjusted analyzes, residual confounding might still be present due to potential unmeasured or unknown confounders. In particular, frailty is common in HFpEF but not measured, and patients not receiving RAS inhibitor or BB might report tolerability issues owing to fact of being sicker. Although we use IPW adjustments, this study remains observational, and we are unable to assess causality. Thus, these findings may only be used as hypothesis generating for personalized medicine strategies and should be further confirmed in RCTs that are sufficiently powered but enroll a representative patient population. This population consists primarily of patients with a European ancestry; therefore, it remains to be elucidated whether these results apply to patients with other ethnic backgrounds. Amyloidosis and chronotropic incompetence were unknown in the study population; however, this factor could have influenced the results and should be further investigated. Last, for the association between RAS inhibitor or beta-blocker use and outcomes, we only analyzed baseline use of medications and did not take into account potential crossover, which may have led to an overestimate the association with the outcomes.

Conclusions

We found cluster heterogeneity in the association of beta-blockers with all-cause mortality, but not for RAS inhibitor. It remains to be elucidated how heterogeneity in HFpEF could influence personalized medicine and future clinical trial design.

Brief bullet points

- Overall associations in patients with HFpEF: Our analyses suggest that RAS inhibitor and beta-blocker use was associated with a significantly lower CV mortality, all-cause mortality, CV and non-CV hospitalisation, but not HF hospitalisation.
- RAS inhibitors and HFpEF clusters: There was no interaction between cluster membership and RAS inhibitor use. When ACE inhibitors and ARBs were investigated separately, there seems to be a benefit for the elderly−AF cluster with ACE inhibitor use for the CV mortality outcome.
- Beta-blockers and HFpEF clusters: we found a statistical interaction between beta-blocker use and cluster membership for all-cause mortality ($P = .03$) and non-CV hospitalisation ($P = .001$). In the young−low comorbidity burden and atrial fibrillation−hypertensive cluster, beta-blocker use was associated with lower all-cause mortality and non-CV hospitalisation and in the obese−diabetic cluster beta-blocker use was only associated with a lower non-CV hospitalisation. The interaction between beta-blocker use and cluster membership for all-cause mortality could potentially be driven by patients improved ejection fraction, this was not seen in non-CV hospitalisation.

Lay summary

In this study, we explored whether there were different associations between heart failure medications and clinical outcomes based on patient clusters

of heart failure with preserved ejection fraction. These patient clusters were assigned based on several patient characteristics, including age, sex and comorbidities. Overall, we found that heart failure drugs were associated with a lower risk of mortality. We found a difference between patient clusters, were patients assigned to the younger−lower comorbidity burden cluster or patients in the atrial fibrillation in combination with hypertension cluster had a lower risk of mortality using beta-blockers compared with the other patient clusters.

Proposed Social Media Text

Treatment interaction between phenotypical clusters with beta-blockers but not RAS-inhibitors were seen in patients with HFpEF in the Swedish Heart Failure Registry. Twitter Handle: @alicia_uijl

Declaration of Competing Interest

AU, SK, IV, DG, and FA have nothing to disclose.

DS reports personal fees from Novartis, Acceleron, and Merck, none related to the present work. UD reports grants from AstraZeneca, Boehringer Ingelheim, Pfizer, Vifor, Boston Scientific, and Roche Diagnostics and personal fees from Novartis, AstraZeneca, and Amgen, outside the submitted work. LHL reports personal fees from Merck, grants and personal fees from Boehringer Ingelheim, personal fees from Sanofi, grants and personal fees from Vifor-Fresenius, personal fees from AstraZeneca, grants and personal fees from Relypsa, personal fees from Bayer, grants from Boston Scientific, grants and personal fees from Novartis, personal fees from Pharmacosmos, personal fees from Abbott, grants and personal fees from Mundipharma, and personal fees from Medscape, outside the submitted work.

GS reports grants and personal fees from Vifor, grants and nonfinancial support from Boehringer Ingelheim, personal fees from Societa´ Prodotti Antibiotici, grants and personal fees from AstraZeneca, personal fees from Roche, personal fees from Servier, grants from Novartis, grants from Boston Scientific, personal fees from GENESIS, personal fees from Cytokinetics, personal fees from Medtronic, grants from Boston Scientific, grants from PHARMACOSMOS, grants from Merck, and grants from Bayer, outside the submitted work.

Funding

This work was supported by the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking BigData@Heart grant n° 116074. F. W. Asselbergs is supported by UCL Hospitals NIHR Biomedical Research Centre. I. Vaartjes is supported by the Dutch Heart Foundation, as part of "Facts and Figures."

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2023.08.008.

References

1. Savarese G, Vasko P, Jonsson Å, Edner M, Dahlström U, Lund LH. The Swedish Heart Failure Registry: a living, ongoing quality assurance and research in heart failure. Ups J Med Sci 2019;124:65–9. https://doi.org/10.1080/03009734.2018.1490831.
2. Brugts JJ, Linssen GCM, Hoes AW, Brunner-La Rocca HP. Real-world heart failure management in 10,910 patients with chronic heart failure in the Netherlands. Netherlands Hear J 2018;26:272–9. https://doi.org/10.1007/s12471-018-1103-7.
3. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola V-PP, et al. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2017;19:1574–85. https://doi.org/10.1002/ejhf.813.
4. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, et al. Systolic and diastolic heart failure in the community. JAMA 2006;296:2209–16. https://doi.org/10.1001/jama.296.18.2209.
5. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015;175:996. https://doi.org/10.1001/jamainternmed.2015.0924.
6. Rosano GMC, Moura B, Metra M, Böhm M, Bauersachs J, Gal T Ben, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2021;23:872–81. https://doi.org/10.1002/ejhf.2206.
7. Solomon SD, McMurray JJV, Claggett B, Boer RA de, DeMets D, Hernandez AF, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022;387:1089–98. https://doi.org/10.1056/NEJMoa2206286.
8. Solomon SD, Vaduganathan M, L-Claggett B, Packer M, Zile M, Swedberg K, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation 2020;141:352–61. https://doi.org/10.1161/CIRCULATIONAHA.119.044586.
9. Pfeffer MA, Claggett B, Assmann SF, Boineau R, Anand IS, Clausell N, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist

(TOPCAT) Trial. Circulation 2015;131:34–42. https://doi.org/10.1161/CIRCULATIONAHA.114.013255.
10. Shah SJ, Kitzman DW, Borlaug BA, Heerebeek L Van, Zile MR, Kass DA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation 2016;134:73–90. https://doi.org/10.1161/CIRCULATIONAHA.116.021884.
11. Uijl A, Savarese G, Vaartjes I, Dahlström U, Brugts JJ, Linssen GCMM, et al. Identification of distinct phenotypic clusters in heart failure with preserved ejection fraction. Eur J Heart Fail 2021;23:973–82. https://doi.org/10.1002/ejhf.2169.
12. McDonagh T, Metra M, Adamo M, Gardner R, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599–726. https://doi.org/10.1093/eurheartj/ehab368.
13. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609–20. https://doi.org/10.1056/NEJMoa1908655.
14. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med 2021;385:1451–61. https://doi.org/10.1056/NEJMoa2107038.
15. Kao DP, Lewsey JD, Anand IS, Massie BM, Zile MR, Carson PE, et al. Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response. Eur J Heart Fail 2015;17:925–35. https://doi.org/10.1002/ejhf.327.
16. Pandey A, Kagiyama N, Yanamala N, Segar MW, Cho JS, Tokodi M, et al. Deep-learning models for the echocardiographic assessment of diastolic dysfunction. JACC Cardiovasc Imaging 2021;14:1887–900. https://doi.org/10.1016/j.jcmg.2021.04.010.
17. Segar MW, Patel KV, Ayers C, Basit M, Tang WHW, Willett D, et al. Phenomapping of patients with heart failure with preserved ejection fraction using machine learning-based unsupervised cluster analysis. Eur J Heart Fail 2020;22:148–58. https://doi.org/10.1002/ejhf.1621.
18. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, et al., CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81. https://doi.org/10.1016/S0140-6736(03)14285-7.
19. Cleland J, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study. Eur Heart J 2006;27:2338–45. https://doi.org/10.1093/eurheartj/ehl250.
20. Massie B, Carson P, McMurray J, Komajda M, McKelvie R, Zile M, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456–67. https://doi.org/10.1056/NEJMoa0805450.
21. Meune C, Wahbi K, Duboc D, Weber S. Meta-analysis of renin-angiotensin-aldosterone blockade for heart failure in presence of preserved left ventricular function. J Cardiovasc Pharmacol Ther 2011;16:368–75. https://doi.org/10.1177/1074248410391667.
22. Gu J, an Pan J an JJ, Lin H, Zhang J, Feng J, Wang C, Qian C. Characteristics, prognosis and treatment response in distinct phenogroups of heart failure with preserved ejection fraction. Int J Cardiol 2021;323:148–54. https://doi.org/10.1016/j.ijcard.2020.08.065.
23. van Veldhuisen DJ, Cohen-Solal A, Böhm M, Anker SD, Babalis D, Roughton M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). J Am Coll Cardiol 2009;53:2150–8. https://doi.org/10.1016/j.jacc.2009.02.046.
24. Yamamoto K, Origasa H, Hori M. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail 2013;15:110–8. https://doi.org/10.1093/eurjhf/hfs141.
25. Cleland JGF, Bunting K V, Flather MD, Altman DG, Holmes J, Coats AJS, et al., Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. Eur Heart J 2018;39:26–35. https://doi.org/10.1093/eurheartj/ehx564.
26. Fukuta H, Goto T, Wakami K, Kamiya T, Ohte N. Effect of beta-blockers on heart failure severity in patients with heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Hear Fail Rev 2020 2020;26:165–71. https://doi.org/10.1007/s10741-020-10013-5.
27. Aronow WS, Ahn C, Kronzon I. Effect of propranolol versus no propranolol on total mortality plus nonfatal myocardial infarction in older patients with prior myocardial infarction, congestive heart failure, and left ventricular ejection fraction ≥40% treated with diuretics plus angiotensin-converting enzyme inhibitors. Am J Cardiol 1997;80:207–9. https://doi.org/10.1016/s0002-9149(97)00320-2.
28. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet 2019;393:61–73. https://doi.org/10.1016/S0140-6736(18)32484-X.
29. Palau P, Seller J, Domínguez E, Sastre C, Ramón JM, De R, Espriella L, et al. Effect of β-blocker withdrawal on functional capacity in heart failure and preserved ejection fraction. J Am Coll Cardiol 2021;78:2042–56. https://doi.org/10.1016/j.jacc.2021.08.073.
30. Silverman DN, de Lavallaz JdF, Plante TB, Infeld MM, Goyal P, Juraschek SP, et al. Beta-Blocker use in hypertension and heart failure (A Secondary Analysis of the Systolic Blood Pressure Intervention Trial). Am J Cardiol 2022;165:58–64. https://doi.org/10.1016/j.amjcard.2021.10.049.
31. Karwath A, Bunting KV, Gill SK, Tica O, Pendleton S, Aziz F, Barsky AD, et al. Redefining β-blocker response in heart failure patients with sinus rhythm and atrial fibrillation: a machine learning cluster analysis. Lancet 2021;398:1427–35. https://doi.org/10.1016/S0140-6736(21)01638-X.
32. Casebeer A, Horter L, Hayden J, Simmons J, Evers T. Phenotypic clustering of heart failure with preserved ejection fraction reveals different rates of hospitalization. J Cardiovasc Med 2021;22:45–52. https://doi.org/10.2459/JCM.0000000000001116.
33. Atzema CL, Austin PC, Yu B, Schull MJ, Jackevicius CA, Ivers NM, et al. Effect of early physician follow-up on mortality and subsequent hospital admissions after emergency care for heart failure: a retrospective cohort study. CMAJ 2018;190:E1468–77. https://doi.org/10.1503/cmaj.180786.