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Original research

Medications for specific phenotypes of heart failure with preserved ejection fraction classified by a machine learning-based clustering model

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ABSTRACT

Objective Our previously established machine learning-based clustering model classified heart failure with preserved ejection fraction (HFpEF) into four distinct phenotypes. Given the heterogeneous pathophysiology of HFpEF, specific medications may have favourable effects in specific phenotypes of HFpEF. We aimed to assess effectiveness of medications on clinical outcomes of the four phenotypes using a real-world HFpEF registry dataset.

Methods This study is a posthoc analysis of the PURSUIT-HFpEF registry, a prospective, multicentre, observational study. We evaluated the clinical effectiveness of the following four types of postdischarge medication in the four different phenotypes: angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARB), beta blockers, mineralocorticoid-receptor antagonists (MRA) and statins. The primary endpoint of this study was a composite of all-cause death and heart failure hospitalisation.

Results Of 1231 patients, 1100 (83 (IQR 77, 87) years, 604 females) were eligible for analysis. Median follow-up duration was 734 (398, 1108) days. The primary endpoint occurred in 528 patients (48.0%). Cox proportional hazard models with inverse-probability-of-treatment weighting showed the following significant effectiveness of medication on the primary endpoint: MRA for phenotype 2 (weighted HR (wHR) 0.40, 95% CI 0.21 to 0.75, p=0.005); ACEi or ARB for phenotype 3 (wHR 0.66 0.48 to 0.92, p=0.014) and statin therapy for phenotype 3 (wHR 0.43 (0.21 to 0.88), p=0.020). No other medications had significant treatment effects in the four phenotypes.

Conclusions Machine learning-based clustering may have the potential to identify populations in which specific medications may be effective. This study suggests the effectiveness of MRA, ACEi or ARB and statin for specific phenotypes of HFpEF.

Trial registration number UMIN000021831.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While the pathophysiological heterogeneity of heart failure with preserved ejection fraction (HFpEF) hinders the conventional 'one-size-fits-all' approach, it conversely suggests the possible efficacy of specific medication for specific phenotypes. Our previously established machine-learning-based subclassification algorithm provides four distinct phenotypes of acute decompensated HFpEF.

WHAT THIS STUDY ADDS

⇒ We applied the subclassification algorithm to the real-world data and found that some specific medications (mineralocorticoid-receptor antagonists, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers and statins) are effective for specific phenotypes of HFpEF.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Machine learning-based clustering may have the potential to identify populations in which specific medications may be effective. Clinical application of the machine-learning-based patient selection in combined with the specific treatment strategy will be a part of the precision medicine of HFpEF and should be further investigated.

BACKGROUND

Heart failure with preserved ejection fraction (HFpEF) is a leading cause of morbidity and mortality throughout the world. Although HFpEF currently represents 50% of all cases of HF, few evidence-based medical therapies for HFpEF have been established. Trials evaluating angiotensin-receptor blockers (ARB), angiotensin receptor–neprilysin inhibitors (ARNI), mineralocorticoid-receptor antagonists (MRA) and beta blockers failed to show efficacy in patients with HFpEF.[1–4] Sodium–glucose cotransporter 2 (SGLT2) inhibitors are the only proved medications for HFpEF to date.[5 6] One reason for these

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unsuccessful results may be the multifactorial pathophysiology of the disease, which involves impairments in cardiac, vascular and peripheral reserve caused by common risk factors such as ageing, adiposity, hypertension and metabolic stress.[7] While this pathophysiological heterogeneity hinders the conventional 'one-size-fits-all' approach, it conversely suggests the possible efficacy of specific treatment strategies for specific phenotypes.

To identify some distinct phenogroups, we previously applied a machine-learning-based clustering technique (latent class analysis) to acute HFpEF and established a clustering model.[8 9] These studies demonstrated that cases of heterogeneous acute HFpEF can be classified into four distinct phenotypes, each with a different clinical prognosis.[8 9] These phenotypes were labelled based on group characteristics as phenotype 1, 'rhythm trouble'; phenotype 2, 'ventricular-arterial uncoupling'; phenotype 3, 'low output and systemic congestion' and phenotype 4, 'systemic failure', respectively. We hypothesised that specific medications may have favourable effects on clinical outcomes in specific phenotypes.

Here, we aimed to assess the effectiveness of medications on clinical outcomes of these four phenotypes using a real-world HFpEF registry dataset.

METHODS

Study subjects

This study is a posthoc subanalysis of the Prospective mUlti-centeR obServational stUdy of patIenTs with Heart Failure with preserved Ejection Fraction (PURSUIT-HFpEF) study, an ongoing, prospective, multireferral centre, observational study (UMIN-CTR ID: UMIN000021831).[8 10 11] Consecutive patients with acute decompensated heart failure and preserved left ventricular ejection fraction (≥50%) were prospectively registered from 26 hospitals located in Kansai region of Japan. Acute decompensated heart failure was diagnosed on the basis of the following criteria: (1) clinical symptoms and signs according to the Framingham Heart Study criteria and (2) a serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of ≥400 pg/mL or brain natriuretic peptide (BNP) level of ≥100 pg/mL. Basic patient characteristics, echocardiography, laboratory tests and lists of medications were obtained on admission, at discharge and at each annual follow-up time point. In this study, we used the latest dataset, which was fixed in April 2022. Patients who survived to discharge and had at least one outpatient clinical follow-up were eligible for this analysis. The study conformed to the ethical guidelines outlined in the Declaration of Helsinki and the study protocol was approved by the ethics committee of each participating hospital. All patients provided written informed consent for participation in this study.

Patient and public involvement

This research was conducted without patient involvement.

Medications

We evaluated four types of postdischarge medication in this analysis: angiotensin-converting enzyme inhibitors (ACEi) or ARB, beta blockers, MRA and statins. These data were collected at hospital discharge. Analysis was performed under the intention-to-treat framework.

Study endpoint

The primary endpoint of this study is a composite of all-cause death and heart failure hospitalisation. Study follow-up started at the time of hospital discharge. In the PURSUIT-HFpEF study, all patients were followed up in each hospital after discharge. Clinical follow-up data were obtained by dedicated coordinators and investigators by direct contact with patients and their physicians at the hospital or in an outpatient setting, or by telephone interview with their families or by mail.

Statistical analysis

In this study, we evaluated the effect of medications prescribed at discharge on postdischarge clinical outcomes in each machine learning-based phenotype. Analysis flow is presented in figure 1. Four types of postdischarge medication were evaluated in four phenotypes individually.

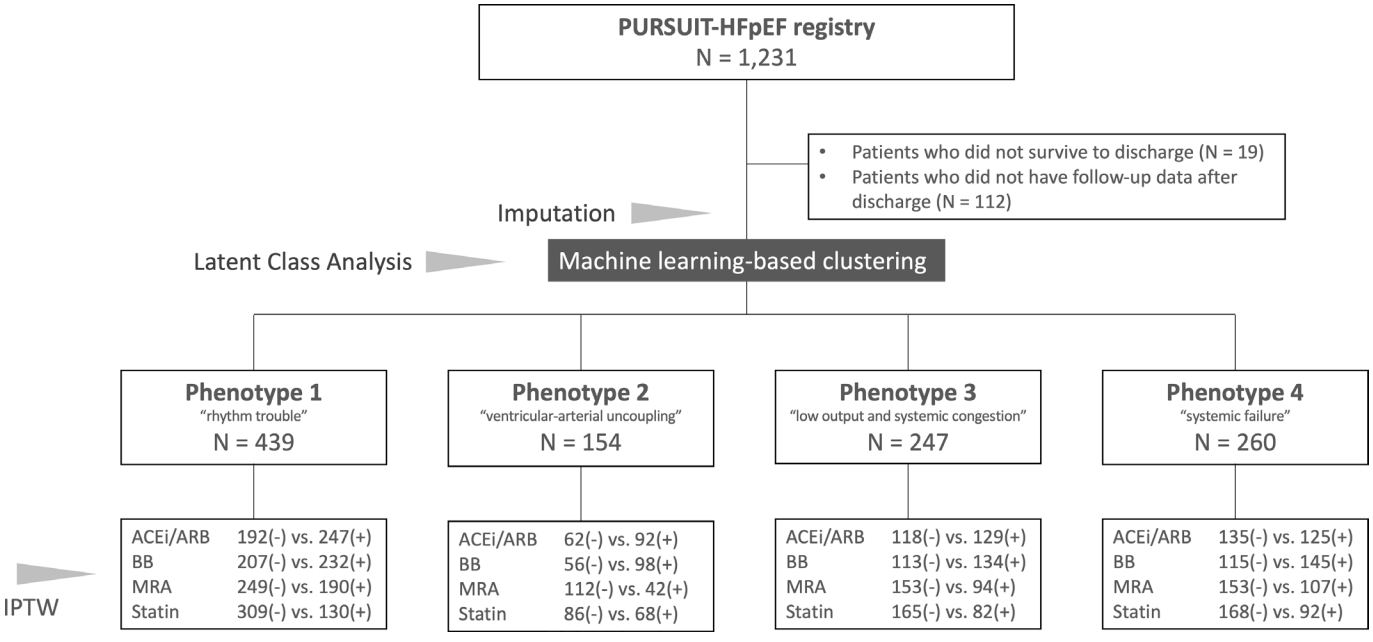

Figure 1 Analysis flowchart. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; MRA, mineralocorticoid-receptor antagonist; IPTW, inverse-probability-of-treatment weighting.

All statistical analyses were performed with R software (V.4.1.1; R Foundation for Statistical Computing, Vienna, Austria). P values less than 0.05 were considered statistically significant. Data with list-wise deletion are presented. Categorical variables are expressed as counts (percentages) and compared with the χ^2 test or Fisher exact test. Continuous variables are expressed as mean (SD) or median (IQR) and compared using analysis of variance with the Tukey-Kramer test and Kruskal-Wallis test with Steel-Dwass test as appropriate. The normality of distribution of continuous data was examined with the Shapiro-Wilk test.

Imputation for missing data

Because the exclusion of cases with missing data can cause bias in analysis and loss of power in detecting statistical differences, missing values in the variables used in the following analyses were imputed by random forest imputation using the 'missForest' package prior to analysis.

Application of the machine-learning clustering model

We previously applied the latent class analysis ('VarSelLCM' package in R 4.0.5) to the PURSUIT-HFpEF dataset (fixed in April 2021) and established a machine learning-based clustering model with following 16 variables: C reactive protein, creatinine, gamma-glutamyl transferase, BNP, white blood cells, systolic blood pressure, fasting blood sugar, triglyceride, clinical scenario classification, infection-triggered acute decompensated HF, estimated glomerular filtration rate, platelets, neutrophils, GWTG-HF (Get With The Guidelines-Heart Failure) risk score, chronic kidney disease (CKD) and CONUT (Controlling Nutritional Status) score.[12] In the present study, we applied this clustering model[9] to the updated dataset (fixed in April 2022) and classified them into four subgroups, namely phenotype 1, 'rhythm trouble'; phenotype 2, 'ventricular-arterial uncoupling'; phenotype 3, 'low output and systemic congestion' and phenotype 4, 'systemic failure'. The latent class analysis is described in detail elsewhere.[8 9]

Table 1 Clinical characteristics of the machine learning-based phenotypes

	Phenotype 1	Phenotype 2	Phenotype 3	Phenotype 4	
	Rhythm trouble	Ventricular-arterial uncoupling	Low output and systemic congestion	Systemic failure	P value
Patient number	439	154	247	260	
Age, years	83.0 (77.0–87.0)	79.0 (72.0–84.0)	83.0 (79.0–87.0)	83.0 (77.0–88.0)	<0.001
Female sex	264 (60.1%)	79 (51.3%)	122 (49.4%)	139 (53.5%)	0.030
Body mass index	23.5 (20.7–26.6)	24.2 (21.3–27.8)	24.5 (21.7–27.0)	23.7 (21.2–26.8)	0.116
Systolic blood pressure, mm Hg	155.0 (138.0–171.0)	184.0 (166.0–207.0)	128.0 (115.5–139.0)	141.0 (124.0–159.3)	<0.001
Diastolic blood pressure, mm Hg	84.0 (70.0–96.8)	92.0 (77.0–115.0)	70.0 (60.0–81.5)	76.0 (64.0–89.0)	<0.001
Heart rate, bpm	82.0 (66.0–10.0)	87.0 (73.0–107.3)	75.0 (60.0–92.0)	88.0 (72.0–102.0)	<0.001
Atrial fibrillation	211 (48.1%)	26 (16.9%)	134 (54.3%)	130 (50.0%)	<0.001
Hypertension	363 (82.7%)	147 (95.5%)	200 (81.0%)	223 (85.8%)	<0.001
Diabetes mellitus	101 (23.0%)	83 (53.9%)	82 (33.2%)	98 (37.7%)	<0.001
Dyslipidaemia	168 (38.3%)	87 (56.5%)	106 (42.9%)	107 (41.2%)	0.001
Coronary artery disease	60 (13.7%)	39 (25.3%)	47 (19.0%)	44 (16.9%)	0.009
Prior myocardial infarction	23 (5.2%)	15 (9.7%)	18 (7.3%)	18 (6.9%)	0.271
COPD	25 (5.7%)	8 (5.2%)	21 (8.5%)	23 (8.8%)	0.247
Peripheral artery disease	17 (4.0%)	16 (10.7%)	13 (5.4%)	14 (5.5%)	0.024
Chronic kidney disease	81 (18.5%)	109 (70.8%)	151 (61.1%)	104 (40.0%)	<0.001
Cancer	59 (13.6%)	16 (10.5%)	24 (10.0%)	38 (14.8%)	0.294
Previous HF hospitalisation	77 (17.5%)	32 (20.8%)	102 (41.3%)	60 (23.1%)	<0.001
Trigger of acute decompensated HF					
Infection	21 (4.8%)	15 (9.7%)	16 (6.5%)	135 (51.9%)	<0.001
Uncontrollable blood pressure	73 (16.6%)	57 (37.0%)	9 (3.6%)	27 (10.4%)	<0.001
Arrhythmia	151 (34.4%)	28 (18.2%)	83 (33.6%)	45 (17.3%)	<0.001
Clinical frailty scale ≥5	126 (28.7%)	38 (24.7%)	71 (28.7%)	93 (35.8%)	0.081
NT-proBNP, pg/mL	2677.9 (1578.0–4131.0)	8063.7 (3276.8–19 104.0)	4138.0 (2260.0–6900.0)	4519.0 (2500.0–7222.8)	<0.001
C reactive protein, mg/dL	0.28 (0.10–0.58)	0.49 (0.17–1.50)	0.40 (0.17–1.15)	4.72 (2.41–9.34)	<0.001
Left ventricular mass index	97.5 (84.3–115.7)	115.2 (97.5–139.2)	98.4 (79.7–117.2)	98.4 (82.3–113.4)	<0.001
Estimated pulmonary artery systolic pressure, mm Hg	43.0 (34.0–53.8)	39.3 (32.8–49.1)	46.0 (36.6–58.9)	45.0 (34.9–54.0)	0.002
CONUT score[12]	3.00 (2.00–4.00)	3.00 (2.00–4.20)	4.00 (3.00–5.64)	5.00 (3.99–7.00)	<0.001
Medication at discharge					
ACEi/ARB	247 (56.3%)	92 (59.7%)	129 (52.2%)	125 (48.1%)	0.074
Beta blockers	232 (52.8%)	98 (63.6%)	134 (54.3%)	145 (55.8%)	0.137
MRA	190 (43.3%)	42 (27.3%)	94 (38.1%)	107 (41.2%)	0.005
Statins	130 (29.6%)	68 (44.2%)	82 (33.2%)	92 (35.4%)	0.011
CCB	204 (46.5%)	118 (76.6%)	91 (36.8%)	122 (46.9%)	<0.001
Diuretics	344 (78.4%)	113 (73.4%)	224 (90.7%)	217 (83.5%)	<0.001

Data are expressed as median (IQR) or number (percentage).
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CONUT score, controlling nutritional status score; COPD, chronic obstructive pulmonary disease; HF, heart failure; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Treatment effect in each phenotype

We estimated propensity scores by fitting a multivariable logistic regression model with variables listed in online supplemental table 1. Four different models for the four types of medications were individually created based on clinical consensus among the investigators. The area under the receiver operating characteristics curve is summarised in online supplemental table 2 for the four different models in each phenotype (16 models in total). We established weighted Cox proportional-hazards regression models with inverse-probability-of-treatment weighting (IPTW) to eliminate potential confounding factors associated with the observational nature of the study. The weights for patients who were prescribed a medication of interest were the inverse of the propensity score, and the weights for patients who were not were the inverse of (1 – propensity score). The results are summarised as weighted hazard ratios (wHRs) and 95% CIs. The proportional hazards assumption of the treatment of interest for the primary endpoint was confirmed by Schoenfeld residuals. To measure the balance, we checked the standardised mean differences before and after matching. A standardised mean difference (SMD) within 25% is considered a negligible imbalance between groups.[13] Differences in survival curves between the patient groups were estimated using the weighted Kaplan-Meier method and analysed using the log-rank test ('jskm' package).

RESULTS

Study subjects

An analysis flowchart is presented in figure 1. Of 1231 patients, 1100 patients were eligible for analysis. Median age was 83 (IQR 77, 87) years, and 604 patients (54.9%) were female. Median follow-up duration was 734 (398, 1108) days. The primary endpoint occurred in 528 patients (48.0%). The patients were classified by the machine learning-based clustering model into four phenotypes. Characteristics of the phenotypes were consistent with those we previously reported (table 1).[8 9]

Effectiveness of medications

In each of the four phenotypes, patients with versus without a medication of interest (four medications) were compared. Comparisons of patients' characteristics without and with the medication of interest in each phenotype are tabulated in

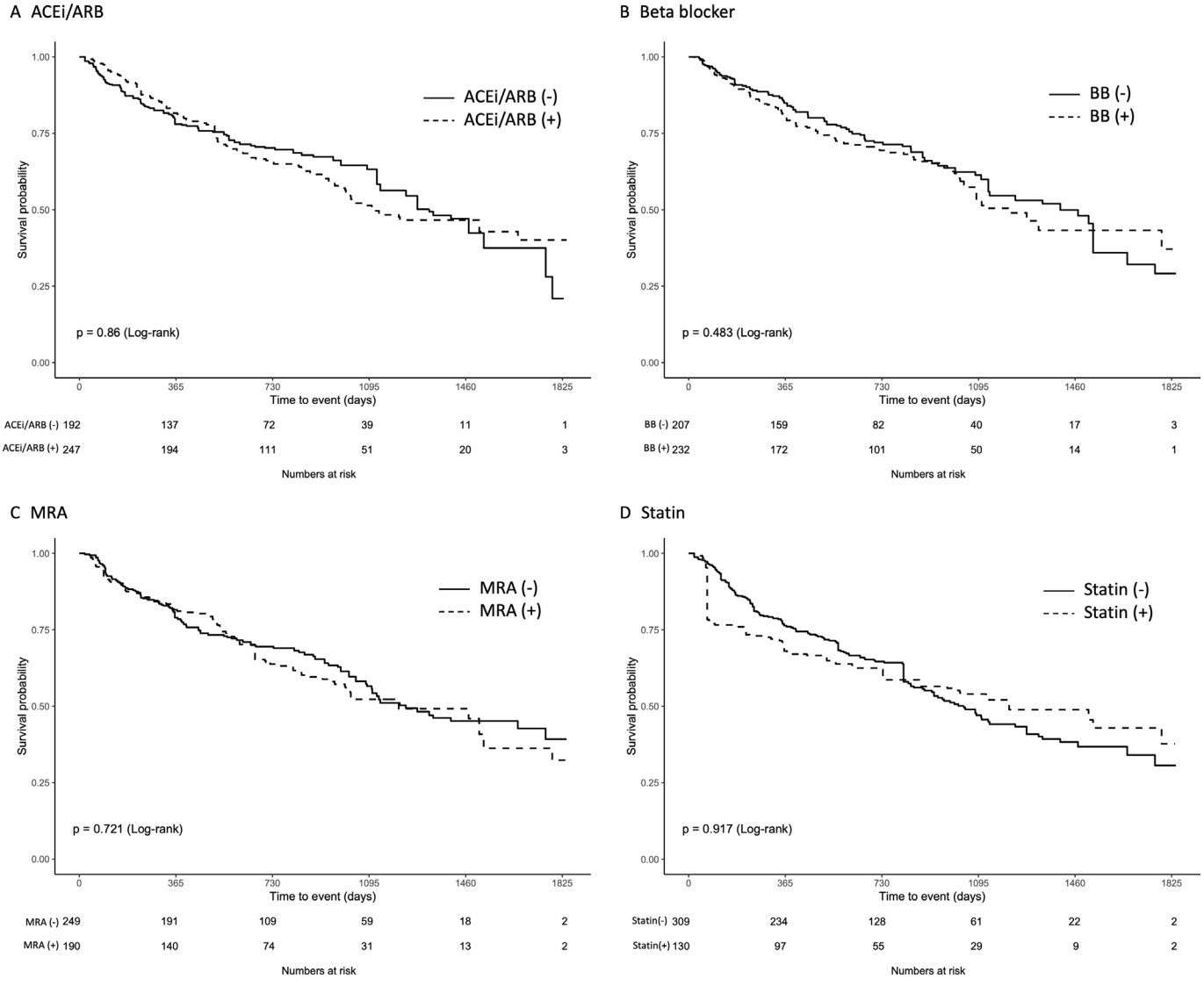

Figure 2 Weighted Kaplan-Meier curves for phenotype 1. Survival analysis for a composite of all-cause death and HF hospitalisation using the weighted Kaplan-Meier method for ACEi/ARB (A), BB (B), MRA (C) and statins (D) in phenotype 1. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; MRA, mineralocorticoid-receptor antagonist; HF, heart failure.

online supplemental tables 3–18. Balance in patient characteristics before and after IPTW is summarised in online supplemental tables 19–34. In most comparisons after IPTW, patients were overall well-balanced (SMD<0.25). Crude incidence of the primary endpoint, all-cause death and HF hospitalisation in each treatment group is tabulated in online supplemental tables 35–37, respectively. Weighted Kaplan-Meier curves are illustrated in figures 2–5 for phenotypes 1–4, respectively. Cox proportional hazard models with IPTW showed the following significant effectiveness of medication on the primary endpoint table 2): MRA for phenotype 2 (wHR 0.40, 95% CI 0.21 to 0.75, p=0.005); ACEi or ARB for phenotype 3 (wHR 0.66, 95% CI 0.48 to 0.92, p=0.014) and statin therapy for phenotype 3 (wHR 0.43, 95% CI 0.21 to 0.88, p=0.020). The weighted Kaplan-Meier curve suggested a possible harmful effect of beta blockers for phenotype 4 (wHR 1.33, 95% CI 0.89 to 1.99, p=0.161). No other medications had significant treatment effects in the four phenotypes. Significant effectiveness of the medications was not seen when patients were not classified into the phenotypes (weighted Kaplan-Meier curves in the overall cohort: online supplemental figure 1), suggesting the importance of this phenotyping.

DISCUSSION

We previously established a subclassification machine-learning-based algorithm and reported four distinct phenotypes of acute decompensated HFpEF.[8 9] In the present study, we assessed the impact of medications at discharge on subsequent clinical outcomes in each phenotype. The findings can be summarised (graphical abstract) as follows: (1) machine learning-based clustering may have the potential to identify populations in which specific medications may be effective; (2) none of the four medications evaluated in this analysis had a significant effect on clinical outcomes in phenotype 1; (3) MRA significantly improved clinical outcomes in phenotype 2; (4) ACEi or ARB and statin therapy significantly improved clinical outcomes in phenotype 3 and (5) beta blockers tended to worsen the clinical outcomes in phenotype 4.

Phenotype 1

Phenotype 1 is dubbed ‘rhythm trouble’. This phenotype has a low comorbidity burden. The reason for the worsening of

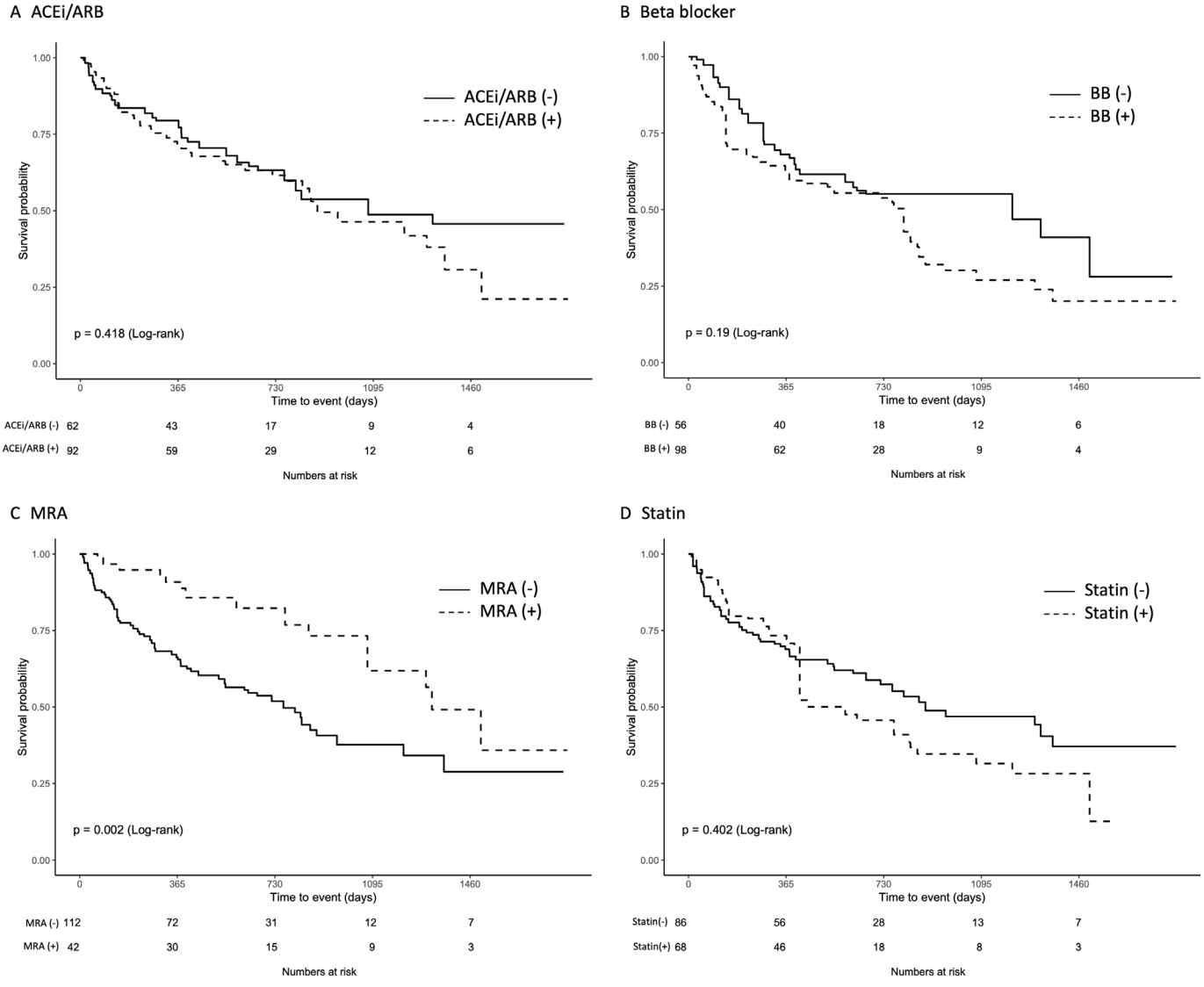

Figure 3 Weighted Kaplan-Meier curves for phenotype 2. Survival analysis for a composite of all-cause death and HF hospitalisation using the weighted Kaplan-Meier method for ACEi/ARB (A), BB (B), MRA (C) and statins (D) in phenotype 2. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; MRA, mineralocorticoid-receptor antagonist; HF, heart failure.

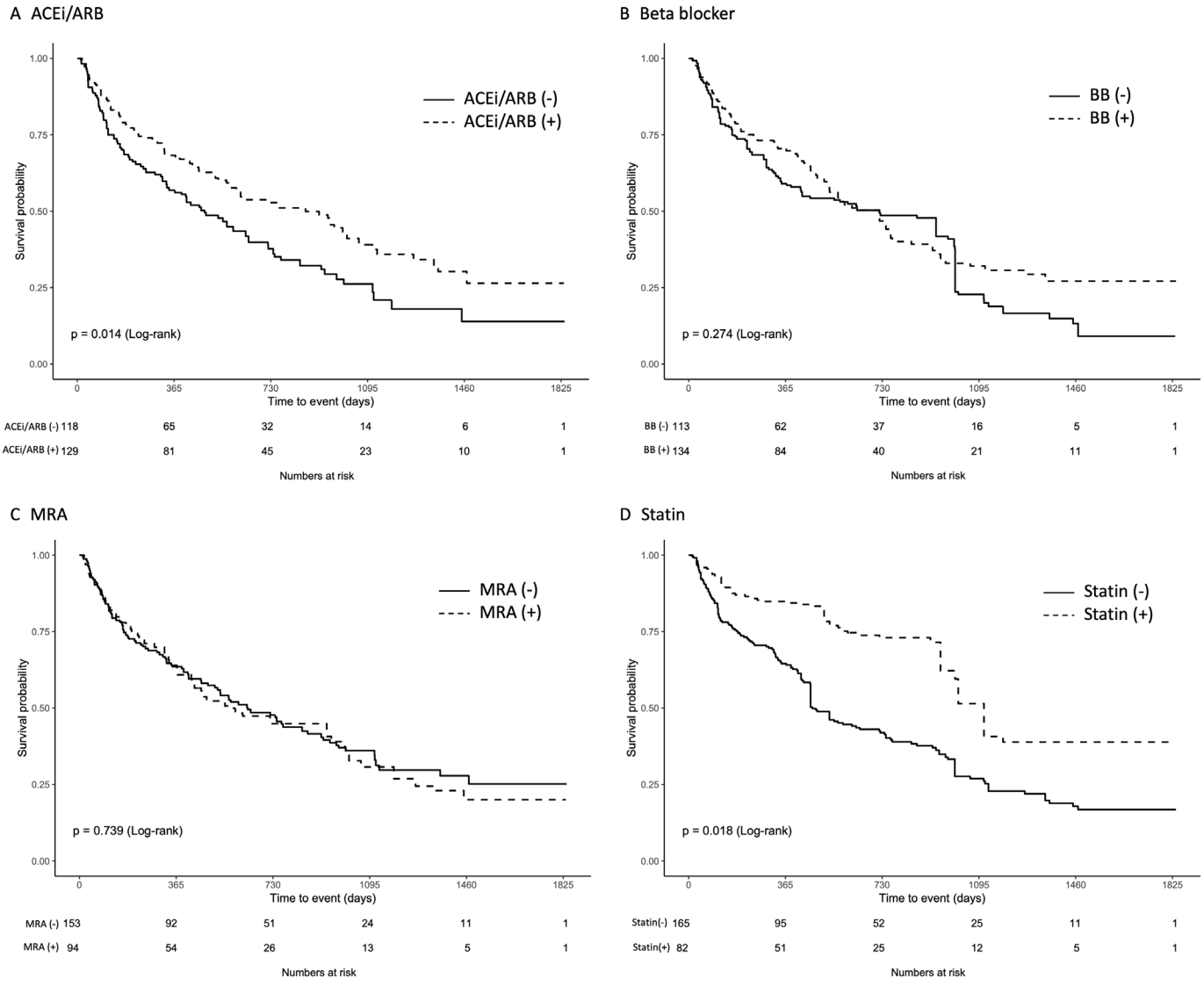

Figure 4 Weighted Kaplan-Meier curves for phenotype 3. Survival analysis for a composite of all-cause death and HF hospitalisation using the weighted Kaplan-Meier method for ACEi/ARB (A), BB (B), MRA (C) and statins (D) in phenotype 3. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; MRA, mineralocorticoid-receptor antagonist; HF, heart failure.

heart failure is mainly atrial fibrillation. Prognosis is the most benign among the four phenotypes.[8] Neither ACEi/ARB, beta blockers, MRA nor statins, which are all thought to have favourable neurohormonal and anti-inflammatory effects, showed any positive impacts in this phenotype. As expected based on the characteristics of the phenotype, aggressive rhythm control, including antiarrhythmic drugs and catheter ablation, may work exclusively with this phenotype.

MRA for phenotype 2

MRA improved clinical outcomes in phenotype 2. This phenotype shows cardiac hypertrophy and hypertension, a typical feature of HFpEF, and is therefore dubbed 'ventricular-arterial uncoupling'.[8] Studies of the pathophysiology of HFpEF have historically focused on this phenotype. Inflammation is considered a major player in the pathophysiology of classical HFpEF.[14] Our team previously demonstrated with animal models that blockade of mineralocorticoid receptor with eplerenone prevented the transition to overt HFpEF in association with the attenuation of structural alteration and diastolic dysfunction independent of blood pressure lowering.[15] Myocardial mineralocorticoid receptor level but not corticosterone level significantly increased in HFpEF rats, suggesting that the upregulation of mineralocorticoid receptor may play a central role in the pathogenesis of HFpEF.[15] This may partially explain why MRA but not ACEi/ARB significantly improved clinical outcomes in the present phenotype: MRA may effectively block the upregulated myocardial mineralocorticoid receptor in this phenotype.

MRA was evaluated in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. Although the main study did not show its efficacy in the overall cohort, many posthoc studies tried to identify subgroups in which spironolactone was beneficial.[2] For instance, this treatment showed significant interaction with sex, with a reduction in all-cause mortality associated with spironolactone therapy in women.[16] Further, spironolactone showed substantial benefit in the group with lower natriuretic peptide levels in TOPCAT.[17] These data are inconsistent with our findings, because our phenotype 2 shows a balanced male-to-female ratio and higher level of natriuretic peptides. On the other hand, another sub-study using machine leaning showed similar results. Cohen *et al* divided patients into three phenogroups using latent class analysis,[18] and found that MRA was exclusively effective

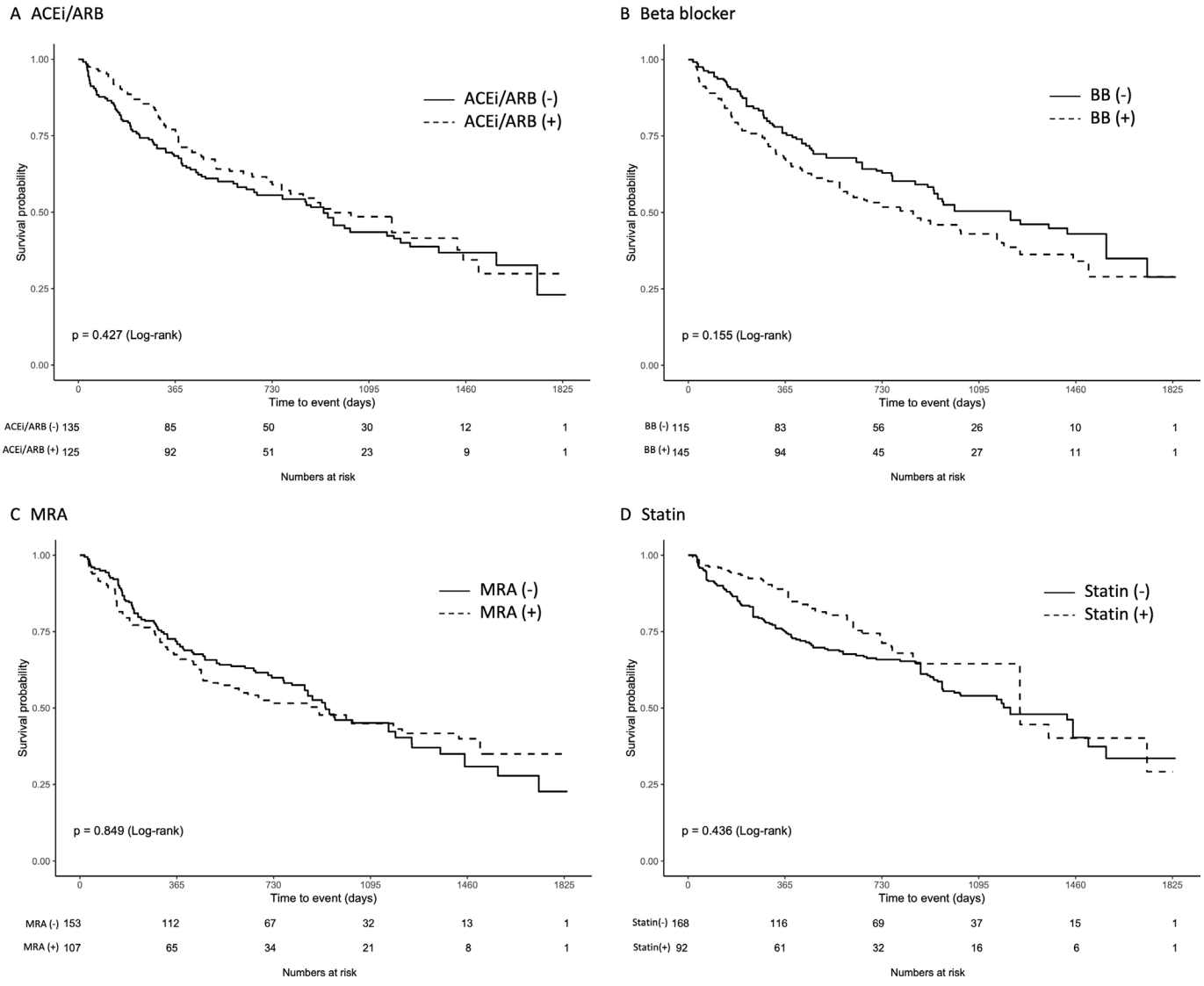

Figure 5 Weighted Kaplan Meier curves for phenotype 4. Survival analysis for a composite of all-cause death and HF hospitalisation using the weighted Kaplan-Meier method for ACEi/ARB (A), BB (B), MRA (C) and statin (D) in phenotype 4. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; MRA, mineralocorticoid-receptor antagonist; HF, heart failure.

in the phenogroup characterised by obesity, diabetes, CKD, concentric LV hypertrophy, high renin and biomarkers of tumour necrosis factor-alpha-mediated inflammation, liver fibrosis and tissue remodelling. This phenogroup in the TOPCAT trial is similar to phenotype 2 in our study, and our data further support the findings of the TOPCAT trial.[18]

ACEi/ARB and statins for phenotype 3

ACEi/ARB improved clinical outcomes in this phenotype. This phenotype included relatively high rates of CKD and frail patients, although not highest. ACEi and ARB are the best-studied antihypertensive agents and provide significant renal and cardiovascular protection for patients with CKD.[19] Our team recently reported the effectiveness of ACEi/ARB specifically for frail patients.[20] Although the high rates of CKD and frailty do not individually explain the effectiveness of the drug, the effect can be multifactorial.

Statin therapy significantly improved clinical outcomes in phenotype 3. This phenotype is labelled 'low output and systemic congestion', because it is characterised by elevated levels of

Table 2 Clinical impact of medications in each phenotype

	Phenotype 1		Phenotype 2		Phenotype 3		Phenotype 4	
	wHR (95% CI)	P value	wHR (95% CI)	P value	wHR (95% CI)	P value	wHR (95% CI)	P value
ACEi/ARB	1.03 (0.71 to 1.51)	0.860	1.24 (0.73 to 2.09)	0.425	0.66 (0.48 to 0.92)	0.014	0.86 (0.59 to 1.25)	0.432
Beta blockers	1.13 (0.81 to 1.58)	0.482	1.45 (0.83 to 2.52)	0.193	0.82 (0.58 to 1.17)	0.279	1.33 (0.89 to 1.99)	0.161
MRA	1.07 (0.75 to 1.53)	0.720	0.40 (0.21 to 0.75)	0.005	1.06 (0.76 to 1.49)	0.737	1.04 (0.70 to 1.54)	0.847
Statins	1.04 (0.48 to 2.26)	0.915	1.26 (0.74 to 2.15)	0.388	0.43 (0.21 to 0.88)	0.020	0.69 (0.27 to 1.79)	0.447

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid-receptor antagonist; wHR, weighted HR.

gamma-glutamyl transferase and bilirubin, low blood pressure and a low heart rate.[8] Since this phenotype shows a relatively low burden of comorbidities (hypertension, diabetes and dyslipidaemia), the effectiveness of statin therapy was unexpected. Although statin therapy in HFpEF has never been evaluated in a randomised trial, a few observational studies have reported its effectiveness in these patients.[21 22] Several potential mechanisms may explain the beneficial effect of statins in the HFpEF population: improvement of endothelial function, increase in arterial distensibility, regression of cardiac hypertrophy and fibrosis and anti-inflammatory and immunomodulatory effects.[7 23 24] Nevertheless, these mechanisms do not explain the specific effectiveness of these drugs in this phenotype. A retrospective study suggested the possible effectiveness of statin therapy in patients with severe pulmonary hypertension (pulmonary artery systolic pressure ≥60 mm Hg) and preserved ejection fraction.[25] The specific effect of statins on pulmonary hypertension may partially explain the effectiveness in this phenotype, given that phenotype 3 had the highest level of pulmonary artery systolic pressure. However, the precise mechanism remains unknown and warrants investigation.

For both medications, our findings remain limited to hypothesis generation, and the precise mechanisms remain unknown. Furthermore, considering the specific characteristics of this phenotype ('low output and systemic congestion'), we hypothesise that inodilators such as phosphodiesterase III inhibitors might provide auspicious treatment for this phenotype. The findings should be reconfirmed and further investigated in large-scale prospective studies.

Beta blockers for phenotype 4

Beta blockers tended to worsen clinical outcomes in phenotype 4. Although allowing that the sample size was underpowered, the weighted Kaplan-Meier curve suggested a possible harmful effect. This phenotype is labelled 'systemic failure'.[8] Specific features of this phenotype include the worst nutritional status, highest level of frailty and infection-triggered HF worsening. Several studies have reported harmful effects for beta blockers on HFpEF.[26 27] In general, mechanistically, the incremental risk of beta blockers may be explained by an increase in central blood pressure by reflected pressure waves.[28] Prolonged diastolic filling increases ventricular volumes and pressures, increasing ventricular load.[29] This in turn leads to the increase in BNP and NT-proBNP levels. However, the reason why beta blockers worsened outcomes exclusively in phenotype 4 remains to be clarified. We speculate that cardiac sympathetic activity in this phenotype may be more attenuated than in the other phenotypes, and patients may be more prone to chronotropic incompetence because they include a higher proportion of elderly with a higher frailty score and a worse nutritional status. The use of beta blockers may further attenuate the cardiac sympathetic activity in these patients and worsen their chronotropic incompetence, which might have resulted in worse prognosis.

Study limitations

Several limitations of this study should be acknowledged. First, this study is a posthoc retrospective analysis. Some of the comparisons were obviously underpowered. The findings are all hypothesis-generating and should be interpreted with caution. Second, we assessed only four types of drugs. Data non-availability for ARNI, the limited use of SGLT2 inhibitors (1.7%), and no data of drug dosage in this registry did not allow us to evaluate their clinical impacts. Third, other possible treatment strategies for HFpEF including cardiac rehabilitation and patient self-management were not evaluated in this study. Fourth, mechanisms of these favourable and unfavourable treatment effects are still unknown. Further basic studies appear necessary. Fifth, validity of the clustering model remains uncertain. Because the latent class analysis is a kind of unsupervised machine learning techniques, external validation study is theoretically not applicable. The possible effects of specific medications in the specific phenotypes can only be confirmed by prospective randomised study using the clustering model, which will further confirm the 'clinical' validity of the model. Last, the generalisability of the findings to other regions and ethnicities is limited by differences in race, social healthcare system and diet. For instance, obesity is an important HFpEF feature in European and US populations,[18] but does not stand out in Asian populations; to the contrary, frailty appears an important feature in Asian HFpEF.[30] Clinical application of machine-learning-based patient selection in combined with the specific treatment strategy can be a part of the precision medicine of HFpEF. However, such approach needs further regional optimisation.

CONCLUSION

Machine learning-based clustering may have the potential to identify populations in which specific medications may be effective. This study suggested the effectiveness of MRA, ACEi or ARB and statins for specific phenotypes of HFpEF.

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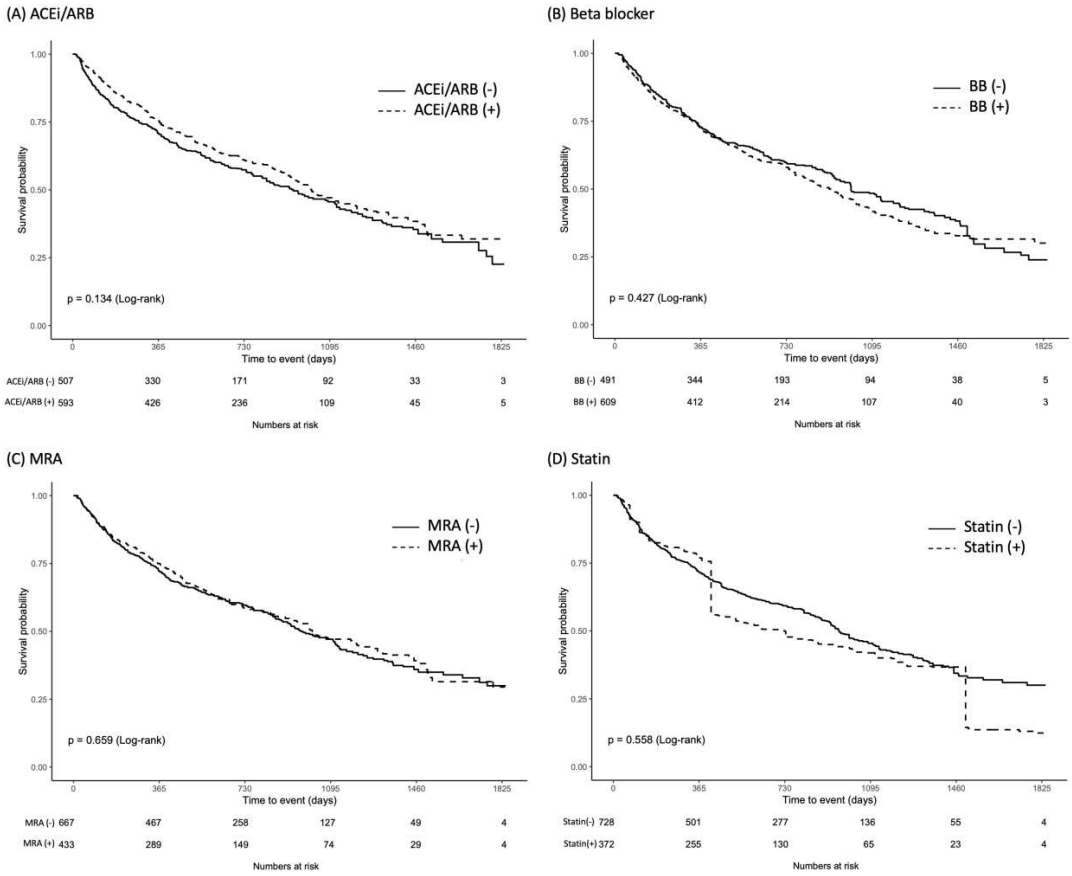
Online appendix

Supplemental Figure 1. Weighted Kaplan-Meier curves in the overall cohort

Survival analysis for a composite of all-cause death and HF hospitalization using the weighted Kaplan-Meier method for ACEi/ARB (A), BB (B), MRA (C), and statin (D) in the overall cohort. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; MRA, mineralocorticoid-receptor antagonist; HF, heart failure.



Supplemental Table 1. Variables included in the multivariable logistic regression model for the calculation of propensity score

ACEi/ARB	**Beta blockers**	**MRA**	**Statins**
Age	Age	Age	Age
Male sex	Male sex	Male sex	Male sex
Hypertension	Hypertension	Hypertension	BMI
Systolic blood pressure	Systolic blood pressure	Systolic blood pressure	Dyslipidemia
Diabetes mellitus	LVMI	Potassium	LDL cholesterol
CKD	Diabetes mellitus	Prior myocardial infarction	Hypertension
Prior myocardial infarction	COPD	CKD	Systolic blood pressure
LVMI	Coronary artery disease	NT-proBNP level	Diabetes mellitus
History of HF hospitalization	Prior myocardial infarction	ACEi or ARB	Coronary artery disease
NT-proBNP level	Heart rate	Beta blocker	Prior myocardial infarction
Beta blocker	Atrial fibrillation	CCB	PCI
MRA	Sick sinus syndrome	Diuretics	CABG
CCB	AV block		
Diuretics	History of HF hospitalization		
	NT-proBNP level		
	ACEi or ARB		
	MRA		
	CCB		
	Diuretics		

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid-receptor antagonist; HF, heart failure; CCB, calcium channel blocker; CKD, chronic kidney disease; LVMI, left ventricular mass index; COPD, chronic obstructive pulmonary disease; LDL, low density lipoprotein; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AV block, atrioventricular block; CONUT score, controlling nutritional status score.

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Supplemental Table 2. Area under the curve of the multivariable logistic regression models for the calculation of propensity score

	Phenotype 1	Phenotype 2	Phenotype 3	Phenotype 4
ACEi/ARB	0.75: 0.71-0.80	0.67: 0.58-0.75	0.66: 0.60-0.73	0.71: 0.65-0.78
Beta blockers	0.77: 0.73-0.82	0.78: 0.70-0.85	0.78: 0.72-0.84	0.73: 0.67-0.80
MRA	0.73: 0.69-0.78	0.75: 0.67-0.83	0.66: 0.59-0.73	0.72: 0.66-0.78
Statins	0.88: 0.84-0.92	0.77: 0.69-0.84	0.92: 0.88-0.96	0.93: 0.89-0.96

Area under the curve (AUC) with 95% confidence interval of each multivariable logistic regression model for the calculation of propensity score is summarized. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid-receptor antagonist.

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Supplemental Table 3. Baseline characteristics of patients (ACEi or ARB in phenotype 1)

	ACEi or ARB (-)	ACEi or ARB (+)	P value
Patient number	192	247	
Age, years	84.0 [78.0, 88.0]	82.0 [76.0, 86.0]	0.044
Female sex	125 (65.1%)	139 (56.3%)	0.076
Body mass index	22.7 [20.3, 25.7]	24.1 [21.2, 26.9]	0.007
Systolic blood pressure, mmHg	148.0 [130.0, 161.2]	160.0 [145.5, 178.5]	<0.001
Heart rate, bpm	82.0 [69.8, 102.2]	80.0 [63.5, 100.0]	0.074
Atrial fibrillation	95 (49.5%)	116 (47.0%)	0.669
Hypertension	133 (69.3%)	230 (93.1%)	<0.001
Diabetes mellitus	41 (21.4%)	60 (24.3%)	0.541
Dyslipidemia	65 (33.9%)	103 (41.7%)	0.114
Coronary artery disease	19 (9.9%)	41 (16.6%)	0.059
Prior myocardial infarction	6 (3.1%)	17 (6.9%)	0.124
Chronic kidney disease	39 (20.3%)	42 (17.0%)	0.446
Clinical frailty scale ≥5	59 (30.7%)	67 (27.1%)	0.471
NT-proBNP, pg/mL	2749.5 [1605.2, 3924.5]	2651.0 [1538.0, 4210.0]	0.744
ACEi or ARB	0 (0.0%)	247 (100.0%)	<0.001
Beta blocker	95 (49.5%)	137 (55.5%)	0.250
MRA	88 (45.8%)	102 (41.3%)	0.393
Statin	48 (25.0%)	82 (33.2%)	0.078
CCB	62 (32.3%)	142 (57.5%)	<0.001
Diuretics	151 (78.6%)	193 (78.1%)	0.991

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 4. Baseline characteristics of patients (Beta blocker in phenotype 1)

	Beta blocker (-)	Beta blocker (+)	P value
Patient number	207	232	
Age, years	83.0 [78.0, 88.0]	82.0 [76.0, 86.0]	0.020
Female sex	122 (58.9%)	142 (61.2%)	0.699
Body mass index	23.4 [20.6, 26.5]	23.5 [20.8, 26.6]	0.792
Systolic blood pressure, mmHg	158.0 [142.0, 175.0]	152.0 [133.0, 168.0]	0.018
Heart rate, bpm	74.0 [55.5, 85.0]	90.5 [75.0, 112.0]	<0.001
Atrial fibrillation	84 (40.6%)	127 (54.7%)	0.004
Hypertension	169 (81.6%)	194 (83.6%)	0.674
Diabetes mellitus	44 (21.3%)	57 (24.6%)	0.478
Dyslipidemia	72 (34.8%)	96 (41.4%)	0.186
Coronary artery disease	16 (7.7%)	44 (19.0%)	0.001
Prior myocardial infarction	6 (2.9%)	17 (7.3%)	0.062
Chronic kidney disease	31 (15.0%)	50 (21.6%)	0.099
Clinical frailty scale ≥5	65 (31.4%)	61 (26.3%)	0.282
NT-proBNP, pg/mL	2628.9 [1465.0, 3817.6]	2767.5 [1747.5, 4363.4]	0.072
ACEi or ARB	110 (53.1%)	137 (59.1%)	0.250
Beta blocker	0 (0.0%)	232 (100.0%)	<0.001
MRA	74 (35.7%)	116 (50.0%)	0.004
Statin	56 (27.1%)	74 (31.9%)	0.315
CCB	103 (49.8%)	101 (43.5%)	0.227
Diuretics	154 (74.4%)	190 (81.9%)	0.074

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 5. Baseline characteristics of patients (MRA in phenotype 1)

	MRA (-)	MRA (+)	P value
Patient number	249	190	
Age, years	83.0 [76.0, 87.0]	83.0 [77.0, 87.0]	0.971
Female sex	148 (59.4%)	116 (61.1%)	0.807
Body mass index	23.1 [20.3, 26.5]	24.0 [21.2, 26.7]	0.085
Systolic blood pressure, mmHg	157.0 [142.0, 175.0]	150.5 [132.0, 166.0]	0.001
Heart rate, bpm	80.0 [63.0, 96.0]	85.0 [71.0, 103.0]	0.001
Atrial fibrillation	100 (40.2%)	111 (58.4%)	<0.001
Hypertension	204 (81.9%)	159 (83.7%)	0.723
Diabetes mellitus	53 (21.3%)	48 (25.3%)	0.386
Dyslipidemia	96 (38.6%)	72 (37.9%)	0.967
Coronary artery disease	31 (12.4%)	29 (15.3%)	0.478
Prior myocardial infarction	11 (4.4%)	12 (6.3%)	0.504
Chronic kidney disease	52 (20.9%)	29 (15.3%)	0.168
Clinical frailty scale ≥5	71 (28.5%)	55 (28.9%)	>0.999
NT-proBNP, pg/mL	2770.0 [1600.0, 4279.0]	2518.4 [1538.0, 3877.6]	0.189
ACEi or ARB	145 (58.2%)	102 (53.7%)	0.393
Beta blocker	116 (46.6%)	116 (61.1%)	0.004
MRA	0 (0.0%)	190 (100.0%)	<0.001
Statin	67 (26.9%)	63 (33.2%)	0.188
CCB	130 (52.2%)	74 (38.9%)	0.008
Diuretics	171 (68.7%)	173 (91.1%)	<0.001

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 6. Baseline characteristics of patients (Statin in phenotype 1)

	Statin (-)	Statin (+)	P value
Patient number	309	130	
Age, years	82.0 [77.0, 87.0]	83.0 [77.2, 86.0]	0.543
Female sex	186 (60.2%)	78 (60.0%)	>0.999
Body mass index	23.2 [20.4, 26.4]	24.2 [21.7, 27.1]	0.019
Systolic blood pressure, mmHg	155.0 [138.0, 171.0]	156.0 [140.0, 171.8]	0.455
Heart rate, bpm	82.0 [67.0, 100.0]	78.0 [60.5, 103.0]	0.375
Atrial fibrillation	155 (50.2%)	56 (43.1%)	0.211
Hypertension	245 (79.3%)	118 (90.8%)	0.006
Diabetes mellitus	53 (17.2%)	48 (36.9%)	<0.001
Dyslipidemia	66 (21.4%)	102 (78.5%)	<0.001
Coronary artery disease	25 (8.1%)	35 (26.9%)	<0.001
Prior myocardial infarction	9 (2.9%)	14 (10.8%)	0.002
Chronic kidney disease	55 (17.8%)	26 (20.0%)	0.683
Clinical frailty scale ≥5	94 (30.4%)	32 (24.6%)	0.266
NT-proBNP, pg/mL	2686.0 [1510.0, 4009.6]	2673.9 [1702.5, 4371.2]	0.348
ACEi or ARB	165 (53.4%)	82 (63.1%)	0.078
Beta blocker	158 (51.1%)	74 (56.9%)	0.315
MRA	127 (41.1%)	63 (48.5%)	0.188
Statin	0 (0.0%)	130 (100.0%)	<0.001
CCB	134 (43.4%)	70 (53.8%)	0.057
Diuretics	242 (78.3%)	102 (78.5%)	>0.999

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 7. Baseline characteristics of patients (ACEi or ARB in phenotype 2)

	ACEi or ARB (-)	ACEi or ARB (+)	P value
Patient number	62	92	
Age, years	79.0 [72.2, 83.0]	78.0 [71.8, 84.2]	0.935
Female sex	31 (50.0%)	48 (52.2%)	0.920
Body mass index	24.2 [21.9, 27.5]	24.4 [21.0, 28.0]	0.966
Systolic blood pressure, mmHg	183.5 [161.8, 201.0]	185.5 [168.0, 211.0]	0.448
Heart rate, bpm	84.5 [65.8, 108.8]	88.0 [74.0, 104.2]	0.299
Atrial fibrillation	11 (17.7%)	15 (16.3%)	0.989
Hypertension	58 (93.5%)	89 (96.7%)	0.591
Diabetes mellitus	34 (54.8%)	49 (53.3%)	0.978
Dyslipidemia	40 (64.5%)	47 (51.1%)	0.138
Coronary artery disease	15 (24.2%)	24 (26.1%)	0.939
Prior myocardial infarction	6 (9.7%)	9 (9.8%)	>0.999
Chronic kidney disease	49 (79.0%)	60 (65.2%)	0.095
Clinical frailty scale ≥5	15 (24.2%)	23 (25.0%)	>0.999
NT-proBNP, pg/mL	8257.4 [3579.8, 20391.0]	7903.7 [2869.0, 17057.6]	0.462
ACEi or ARB	0 (0.0%)	92 (100.0%)	<0.001
Beta blocker	36 (58.1%)	62 (67.4%)	0.313
MRA	13 (21.0%)	29 (31.5%)	0.208
Statin	27 (43.5%)	41 (44.6%)	>0.999
CCB	43 (69.4%)	75 (81.5%)	0.120
Diuretics	45 (72.6%)	68 (73.9%)	>0.999

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 8. Baseline characteristics of patients (Beta blocker in phenotype 2)

	Beta blocker (-)	Beta blocker (+)	P value
Patient number	56	98	
Age, years	79.5 [73.8, 84.2]	78.0 [71.0, 84.0]	0.349
Female sex	31 (55.4%)	48 (49.0%)	0.552
Body mass index	24.3 [21.0, 27.7]	24.2 [21.7, 27.7]	0.734
Systolic blood pressure, mmHg	175.5 [155.5, 199.0]	188.5 [173.0, 212.8]	0.002
Heart rate, bpm	83.5 [63.2, 94.0]	91.0 [74.2, 109.8]	0.023
Atrial fibrillation	7 (12.5%)	19 (19.4%)	0.382
Hypertension	50 (89.3%)	97 (99.0%)	0.017
Diabetes mellitus	28 (50.0%)	55 (56.1%)	0.572
Dyslipidemia	31 (55.4%)	56 (57.1%)	0.963
Coronary artery disease	8 (14.3%)	31 (31.6%)	0.029
Prior myocardial infarction	2 (3.6%)	13 (13.3%)	0.095
Chronic kidney disease	37 (66.1%)	72 (73.5%)	0.431
Clinical frailty scale ≥5	17 (30.4%)	21 (21.4%)	0.297
NT-proBNP, pg/mL	7147.5 [2800.0, 18317.8]	8412.0 [3591.1, 19104.0]	0.413
ACEi or ARB	30 (53.6%)	62 (63.3%)	0.313
Beta blocker	0 (0.0%)	98 (100.0%)	<0.001
MRA	12 (21.4%)	30 (30.6%)	0.297
Statin	23 (41.1%)	45 (45.9%)	0.679
CCB	40 (71.4%)	78 (79.6%)	0.340
Diuretics	37 (66.1%)	76 (77.6%)	0.174

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 9. Baseline characteristics of patients (MRA in phenotype 2)

	MRA (-)	MRA (+)	P value
Patient number	112	42	
Age, years	79.0 [72.0, 83.0]	81.0 [72.0, 85.0]	0.425
Female sex	57 (50.9%)	22 (52.4%)	>0.999
Body mass index	24.2 [21.4, 28.0]	23.8 [21.2, 27.5]	0.926
Systolic blood pressure, mmHg	183.0 [165.5, 204.2]	193.5 [168.2, 212.5]	0.384
Heart rate, bpm	87.0 [73.8, 105.8]	83.0 [73.0, 108.2]	0.908
Atrial fibrillation	21 (18.8%)	5 (11.9%)	0.442
Hypertension	106 (94.6%)	41 (97.6%)	0.722
Diabetes mellitus	59 (52.7%)	24 (57.1%)	0.754
Dyslipidemia	64 (57.1%)	23 (54.8%)	0.934
Coronary artery disease	28 (25.0%)	11 (26.2%)	>0.999
Prior myocardial infarction	10 (8.9%)	5 (11.9%)	0.803
Chronic kidney disease	83 (74.1%)	26 (61.9%)	0.199
Clinical frailty scale ≥5	28 (25.0%)	10 (23.8%)	>0.999
NT-proBNP, pg/mL	7978.7 [3195.0, 21192.5]	8075.0 [3635.8, 11249.8]	0.362
ACEi or ARB	63 (56.2%)	29 (69.0%)	0.208
Beta blocker	68 (60.7%)	30 (71.4%)	0.297
MRA	0 (0.0%)	42 (100.0%)	<0.001
Statin	45 (40.2%)	23 (54.8%)	0.150
CCB	88 (78.6%)	30 (71.4%)	0.472
Diuretics	74 (66.1%)	39 (92.9%)	0.002

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 10. Baseline characteristics of patients (Statin in phenotype 2)

	Statin (-)	Statin (+)	P value
Patient number	86	68	
Age, years	81.0 [73.2, 84.0]	77.0 [71.8, 84.0]	0.187
Female sex	40 (46.5%)	39 (57.4%)	0.240
Body mass index	23.8 [20.8, 26.7]	25.4 [22.1, 28.6]	0.135
Systolic blood pressure, mmHg	185.5 [164.0, 203.5]	183.0 [167.8, 212.2]	0.705
Heart rate, bpm	84.5 [72.2, 101.8]	90.0 [73.0, 109.2]	0.242
Atrial fibrillation	16 (18.6%)	10 (14.7%)	0.671
Hypertension	83 (96.5%)	64 (94.1%)	0.750
Diabetes mellitus	42 (48.8%)	41 (60.3%)	0.210
Dyslipidemia	36 (41.9%)	51 (75.0%)	<0.001
Coronary artery disease	16 (18.6%)	23 (33.8%)	0.049
Prior myocardial infarction	8 (9.3%)	7 (10.3%)	>0.999
Chronic kidney disease	63 (73.3%)	46 (67.6%)	0.561
Clinical frailty scale ≥5	24 (27.9%)	14 (20.6%)	0.391
NT-proBNP, pg/mL	7860.5 [3281.3, 18547.8]	8268.7 [3390.2, 19226.5]	0.681
ACEi or ARB	51 (59.3%)	41 (60.3%)	>0.999
Beta blocker	53 (61.6%)	45 (66.2%)	0.679
MRA	19 (22.1%)	23 (33.8%)	0.150
Statin	0 (0.0%)	68 (100.0%)	<0.001
CCB	66 (76.7%)	52 (76.5%)	>0.999
Diuretics	59 (68.6%)	54 (79.4%)	0.186

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 11. Baseline characteristics of patients (ACEi or ARB in phenotype 3)

	ACEi or ARB (-)	ACEi or ARB (+)	P value
Patient number	118	129	
Age, years	83.5 [80.0, 87.0]	83.0 [79.0, 88.0]	0.447
Female sex	68 (57.6%)	54 (41.9%)	0.019
Body mass index	23.9 [21.0, 25.9]	25.0 [22.3, 28.0]	0.008
Systolic blood pressure, mmHg	124.0 [111.0, 136.8]	131.0 [118.0, 142.0]	0.003
Heart rate, bpm	78.0 [61.0, 92.0]	74.0 [60.0, 92.0]	0.460
Atrial fibrillation	59 (50.0%)	75 (58.1%)	0.248
Hypertension	92 (78.0%)	108 (83.7%)	0.323
Diabetes mellitus	36 (30.5%)	46 (35.7%)	0.469
Dyslipidemia	42 (35.6%)	64 (49.6%)	0.036
Coronary artery disease	16 (13.6%)	31 (24.0%)	0.053
Prior myocardial infarction	7 (5.9%)	11 (8.5%)	0.590
Chronic kidney disease	67 (56.8%)	84 (65.1%)	0.226
Clinical frailty scale ≥5	43 (36.4%)	28 (21.7%)	0.016
NT-proBNP, pg/mL	4222.3 [2429.2, 6885.0]	3820.0 [2045.9, 6900.0]	0.421
ACEi or ARB	0 (0.0%)	129 (100.0%)	<0.001
Beta blocker	69 (58.5%)	65 (50.4%)	0.252
MRA	44 (37.3%)	50 (38.8%)	0.915
Statin	30 (25.4%)	52 (40.3%)	0.019
CCB	33 (28.0%)	58 (45.0%)	0.008
Diuretics	106 (89.8%)	118 (91.5%)	0.822

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 12. Baseline characteristics of patients (Beta blocker in phenotype 3)

	Beta blocker (-)	Beta blocker (+)	P value
Patient number	113	134	
Age, years	84.0 [79.0, 88.0]	83.0 [78.2, 86.0]	0.163
Female sex	52 (46.0%)	70 (52.2%)	0.397
Body mass index	24.4 [21.7, 26.9]	24.6 [21.7, 27.1]	0.804
Systolic blood pressure, mmHg	128.0 [113.0, 140.0]	130.0 [117.2, 138.0]	0.413
Heart rate, bpm	68.0 [54.0, 81.0]	82.0 [66.0, 100.0]	<0.001
Atrial fibrillation	52 (46.0%)	82 (61.2%)	0.024
Hypertension	94 (83.2%)	106 (79.1%)	0.515
Diabetes mellitus	43 (38.1%)	39 (29.1%)	0.176
Dyslipidemia	50 (44.2%)	56 (41.8%)	0.795
Coronary artery disease	16 (14.2%)	31 (23.1%)	0.104
Prior myocardial infarction	5 (4.4%)	13 (9.7%)	0.179
Chronic kidney disease	71 (62.8%)	80 (59.7%)	0.710
Clinical frailty scale ≥5	35 (31.0%)	36 (26.9%)	0.569
NT-proBNP, pg/mL	3962.0 [2180.0, 6250.0]	4339.8 [2397.2, 7264.2]	0.213
ACEi or ARB	64 (56.6%)	65 (48.5%)	0.252
Beta blocker	0 (0.0%)	134 (100.0%)	<0.001
MRA	38 (33.6%)	56 (41.8%)	0.236
Statin	36 (31.9%)	46 (34.3%)	0.783
CCB	54 (47.8%)	37 (27.6%)	0.002
Diuretics	103 (91.2%)	121 (90.3%)	0.992

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 13. Baseline characteristics of patients (MRA in phenotype 3)

	MRA (-)	MRA (+)	P value
Patient number	153	94	
Age, years	83.0 [79.0, 87.0]	83.0 [79.0, 87.0]	0.966
Female sex	78 (51.0%)	44 (46.8%)	0.613
Body mass index	24.4 [21.4, 26.9]	24.5 [22.3, 27.0]	0.351
Systolic blood pressure, mmHg	130.0 [116.0, 140.0]	127.0 [115.0, 136.8]	0.179
Heart rate, bpm	72.0 [59.0, 89.0]	80.0 [63.2, 95.0]	0.032
Atrial fibrillation	71 (46.4%)	63 (67.0%)	0.002
Hypertension	132 (86.3%)	68 (72.3%)	0.011
Diabetes mellitus	52 (34.0%)	30 (31.9%)	0.844
Dyslipidemia	68 (44.4%)	38 (40.4%)	0.626
Coronary artery disease	28 (18.3%)	19 (20.2%)	0.838
Prior myocardial infarction	13 (8.5%)	5 (5.3%)	0.496
Chronic kidney disease	95 (62.1%)	56 (59.6%)	0.795
Clinical frailty scale ≥5	40 (26.1%)	31 (33.0%)	0.314
NT-proBNP, pg/mL	3996.3 [2300.0, 6900.0]	4188.3 [2245.0, 6900.0]	0.974
ACEi or ARB	79 (51.6%)	50 (53.2%)	0.915
Beta blocker	78 (51.0%)	56 (59.6%)	0.236
MRA	0 (0.0%)	94 (100.0%)	<0.001
Statin	53 (34.6%)	29 (30.9%)	0.635
CCB	63 (41.2%)	28 (29.8%)	0.096
Diuretics	136 (88.9%)	88 (93.6%)	0.310

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 14. Baseline characteristics of patients (Statin in phenotype 3)

	Statin (-)	Statin (+)	P value
Patient number	165	82	
Age, years	83.0 [78.0, 88.0]	83.0 [79.0, 85.0]	0.311
Female sex	81 (49.1%)	41 (50.0%)	>0.999
Body mass index	24.0 [21.6, 26.5]	25.3 [22.1, 28.4]	0.013
Systolic blood pressure, mmHg	129.0 [116.0, 140.0]	127.5 [115.2, 138.0]	0.790
Heart rate, bpm	75.0 [60.0, 92.0]	75.5 [60.0, 92.0]	0.872
Atrial fibrillation	85 (51.5%)	49 (59.8%)	0.276
Hypertension	128 (77.6%)	72 (87.8%)	0.079
Diabetes mellitus	47 (28.5%)	35 (42.7%)	0.037
Dyslipidemia	33 (20.0%)	73 (89.0%)	<0.001
Coronary artery disease	20 (12.1%)	27 (32.9%)	<0.001
Prior myocardial infarction	6 (3.6%)	12 (14.6%)	0.004
Chronic kidney disease	97 (58.8%)	54 (65.9%)	0.350
Clinical frailty scale ≥5	54 (32.7%)	17 (20.7%)	0.070
NT-proBNP, pg/mL	4230.0 [2209.0, 6960.0]	3669.6 [2333.0, 6002.3]	0.433
ACEi or ARB	77 (46.7%)	52 (63.4%)	0.019
Beta blocker	88 (53.3%)	46 (56.1%)	0.783
MRA	65 (39.4%)	29 (35.4%)	0.635
Statin	0 (0.0%)	82 (100.0%)	<0.001
CCB	52 (31.5%)	39 (47.6%)	0.020
Diuretics	148 (89.7%)	76 (92.7%)	0.597

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Supplemental Table 15. Baseline characteristics of patients (ACEi or ARB in phenotype 4)

	ACEi or ARB (-)	ACEi or ARB (+)	P value
Patient number	135	125	
Age, years	84.0 [77.0, 90.0]	83.0 [77.0, 86.0]	0.057
Female sex	78 (57.8%)	61 (48.8%)	0.185
Body mass index	23.6 [20.9, 26.6]	24.2 [21.9, 27.7]	0.148
Systolic blood pressure, mmHg	136.0 [120.0, 150.5]	146.0 [129.0, 168.0]	<0.001
Heart rate, bpm	87.0 [71.5, 100.0]	90.0 [72.0, 103.0]	0.554
Atrial fibrillation	65 (48.1%)	65 (52.0%)	0.620
Hypertension	107 (79.3%)	116 (92.8%)	0.003
Diabetes mellitus	43 (31.9%)	55 (44.0%)	0.059
Dyslipidemia	48 (35.6%)	59 (47.2%)	0.075
Coronary artery disease	19 (14.1%)	25 (20.0%)	0.268
Prior myocardial infarction	9 (6.7%)	9 (7.2%)	>0.999
Chronic kidney disease	58 (43.0%)	46 (36.8%)	0.375
Clinical frailty scale ≥5	67 (49.6%)	26 (20.8%)	<0.001
NT-proBNP, pg/mL	4622.0 [2800.0, 7526.5]	4150.0 [2090.0, 7007.0]	0.254
ACEi or ARB	0 (0.0%)	125 (100.0%)	<0.001
Beta blocker	77 (57.0%)	68 (54.4%)	0.762
MRA	61 (45.2%)	46 (36.8%)	0.213
Statin	38 (28.1%)	54 (43.2%)	0.016
CCB	49 (36.3%)	73 (58.4%)	0.001
Diuretics	111 (82.2%)	106 (84.8%)	0.695

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 16. Baseline characteristics of patients (Beta blocker in phenotype 4)

	Beta blocker (-)	Beta blocker (+)	P value
Patient number	115	145	
Age, years	84.0 [78.0, 88.0]	83.0 [77.0, 88.0]	0.253
Female sex	63 (54.8%)	76 (52.4%)	0.799
Body mass index	23.7 [21.2, 27.2]	23.7 [21.7, 26.6]	0.854
Systolic blood pressure, mmHg	142.0 [130.0, 160.0]	138.0 [121.0, 157.0]	0.081
Heart rate, bpm	81.0 [66.0, 96.5]	92.0 [76.0, 110.0]	<0.001
Atrial fibrillation	55 (47.8%)	75 (51.7%)	0.617
Hypertension	100 (87.0%)	123 (84.8%)	0.757
Diabetes mellitus	46 (40.0%)	52 (35.9%)	0.579
Dyslipidemia	44 (38.3%)	63 (43.4%)	0.473
Coronary artery disease	18 (15.7%)	26 (17.9%)	0.749
Prior myocardial infarction	8 (7.0%)	10 (6.9%)	>0.999
Chronic kidney disease	37 (32.2%)	67 (46.2%)	0.030
Clinical frailty scale ≥5	45 (39.1%)	48 (33.1%)	0.381
NT-proBNP, pg/mL	3790.0 [1820.0, 6552.5]	5084.0 [2850.0, 7530.0]	0.008
ACEi or ARB	57 (49.6%)	68 (46.9%)	0.762
Beta blocker	0 (0.0%)	145 (100.0%)	<0.001
MRA	48 (41.7%)	59 (40.7%)	0.965
Statin	35 (30.4%)	57 (39.3%)	0.175
CCB	60 (52.2%)	62 (42.8%)	0.166
Diuretics	93 (80.9%)	124 (85.5%)	0.404

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 17. Baseline characteristics of patients (MRA in phenotype 4)

	MRA (-)	MRA (+)	P value
Patient number	153	107	
Age, years	83.0 [77.0, 87.0]	84.0 [77.0, 89.0]	0.065
Female sex	80 (52.3%)	59 (55.1%)	0.743
Body mass index	23.8 [21.2, 26.9]	23.5 [21.2, 26.8]	0.730
Systolic blood pressure, mmHg	142.0 [126.0, 162.0]	140.0 [122.5, 156.0]	0.324
Heart rate, bpm	86.0 [68.0, 100.0]	91.0 [77.0, 106.0]	0.038
Atrial fibrillation	78 (51.0%)	52 (48.6%)	0.801
Hypertension	133 (86.9%)	90 (84.1%)	0.646
Diabetes mellitus	60 (39.2%)	38 (35.5%)	0.634
Dyslipidemia	61 (39.9%)	46 (43.0%)	0.707
Coronary artery disease	24 (15.7%)	20 (18.7%)	0.640
Prior myocardial infarction	9 (5.9%)	9 (8.4%)	0.588
Chronic kidney disease	66 (43.1%)	38 (35.5%)	0.269
Clinical frailty scale ≥5	50 (32.7%)	43 (40.2%)	0.266
NT-proBNP, pg/mL	4622.0 [2300.0, 7523.0]	4478.6 [2523.5, 7050.0]	0.853
ACEi or ARB	79 (51.6%)	46 (43.0%)	0.213
Beta blocker	86 (56.2%)	59 (55.1%)	0.965
MRA	0 (0.0%)	107 (100.0%)	<0.001
Statin	48 (31.4%)	44 (41.1%)	0.137
CCB	79 (51.6%)	43 (40.2%)	0.090
Diuretics	115 (75.2%)	102 (95.3%)	<0.001

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Supplemental Table 18. Baseline characteristics of patients (Statin in phenotype 4)

	Statin (-)	Statin (+)	P value
Patient number	168	92	
Age, years	84.0 [77.0, 89.0]	83.0 [77.0, 86.0]	0.192
Female sex	87 (51.8%)	52 (56.5%)	0.547
Body mass index	23.0 [20.9, 25.6]	25.6 [22.5, 28.6]	<0.001
Systolic blood pressure, mmHg	139.5 [124.0, 157.0]	145.0 [128.5, 163.8]	0.218
Heart rate, bpm	88.0 [72.0, 103.0]	87.0 [71.8, 99.2]	0.765
Atrial fibrillation	92 (54.8%)	38 (41.3%)	0.052
Hypertension	135 (80.4%)	88 (95.7%)	0.001
Diabetes mellitus	55 (32.7%)	43 (46.7%)	0.036
Dyslipidemia	27 (16.1%)	80 (87.0%)	<0.001
Coronary artery disease	20 (11.9%)	24 (26.1%)	0.006
Prior myocardial infarction	8 (4.8%)	10 (10.9%)	0.110
Chronic kidney disease	66 (39.3%)	38 (41.3%)	0.853
Clinical frailty scale ≥5	66 (39.3%)	27 (29.3%)	0.143
NT-proBNP, pg/mL	4616.0 [2589.2, 7222.8]	4384.7 [2157.5, 6972.0]	0.410
ACEi or ARB	71 (42.3%)	54 (58.7%)	0.016
Beta blocker	88 (52.4%)	57 (62.0%)	0.175
MRA	63 (37.5%)	44 (47.8%)	0.137
Statin	0 (0.0%)	92 (100.0%)	<0.001
CCB	73 (43.5%)	49 (53.3%)	0.166
Diuretics	133 (79.2%)	84 (91.3%)	0.019

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; MRA, mineralocorticoid-receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide.

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Supplemental Table 19. Baseline characteristics of patients before and after IPTW (ACEi or ARB in phenotype 1)

	Original cohort			IPTW		
	ACEi or ARB (-)	ACEi or ARB (+)	SMD	ACEi or ARB (-)	ACEi or ARB (+)	SMD
Patient number	192	247		449	443	
Age, years	84.0 [78.0, 88.0]	82.0 [76.0, 86.0]	0.088	83.0 [77.0, 88.0]	82.4 [77.0, 87.0]	0.028
Female sex	125 (65.1%)	139 (56.3%)	0.181	263 (59%)	255 (58%)	0.023
Hypertension	133 (69.3%)	230 (93.1%)	0.641	373 (83%)	362 (82%)	0.035
Systolic blood pressure, mmHg	148.0 [130.0, 161.2]	160.0 [145.5, 178.5]	0.569	156.0 [136.3, 174.0]	155.0 [137.0, 170.0]	0.072
Diabetes mellitus	41 (21.4%)	60 (24.3%)	0.07	105 (23%)	104 (24%)	0.003
Chronic kidney disease	39 (20.3%)	42 (17.0%)	0.085	83 (18%)	79 (18%)	0.014
Prior myocardial infarction	6 (3.1%)	17 (6.9%)	0.173	25 (6%)	24 (5%)	0.004
Left ventricular mass index	92.9 [77.7, 109.0]	104.5 [87.9, 121.8]	0.325	95.4 [80.9, 115.1]	99.9 [83.6, 116.0]	0.068
Previous HF hospitalization	36 (18.8%)	41 (16.6%)	0.056	76 (17%)	76 (17%)	0.007
NT-proBNP, pg/mL	2749.5 [1605.2, 3924.5]	2651.0 [1538.0, 4210.0]	0.015	2601.2 [1693.4, 3851.9]	2624.8 [1593.2, 4187.0]	0.017
Beta blocker	95 (49.5%)	137 (55.5%)	0.12	258 (57%)	236 (53%)	0.082
MRA	88 (45.8%)	102 (41.3%)	0.092	188 (42%)	201 (45%)	0.068
CCB	62 (32.3%)	142 (57.5%)	0.524	225 (50%)	208 (47%)	0.063
Diuretics	151 (78.6%)	193 (78.1%)	0.012	363 (81%)	357 (81%)	0.010

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 20. Baseline characteristics of patients before and after IPTW (Beta blocker in phenotype 1)

	Original cohort			IPTW		
	Beta blocker (-)	Beta blocker (+)	SMD	Beta blocker (-)	Beta blocker (+)	SMD
Patient number	207	232		437	442	
Age, years	83.0 [78.0, 88.0]	82.0 [76.0, 86.0]	0.123	82.0 [76.6, 88.0]	82.0 [75.0, 86.0]	0.002
Female sex	122 (58.9%)	142 (61.2%)	0.046	246 (56%)	243 (55%)	0.023
Hypertension	169 (81.6%)	194 (83.6%)	0.052	369 (84%)	372 (84%)	0.003
Systolic blood pressure, mmHg	158.0 [142.0, 175.0]	152.0 [133.0, 168.0]	0.146	156.5 [140.0, 173.0]	154.6 [136.4, 170.0]	0.027
Left ventricular mass index	96.9 [83.0, 114.9]	99.5 [85.0, 117.0]	0.091	97.1 [86.3, 115.4]	99.5 [83.2, 120.7]	0.009
Diabetes mellitus	44 (21.3%)	57 (24.6%)	0.079	103 (23%)	103 (23%)	0.003
COPD	11 (5.3%)	14 (6.0%)	0.031	23 (5%)	21 (5%)	0.022
Coronary artery disease	16 (7.7%)	44 (19.0%)	0.335	43 (10%)	59 (13%)	0.106
Prior myocardial infarction	6 (2.9%)	17 (7.3%)	0.202	14 (3%)	23 (5%)	0.095
Heart rate, bpm	74.0 [55.5, 85.0]	90.5 [75.0, 112.0]	0.831	82.0 [66.0, 101.0]	80.0 [65.7, 100.0]	0.043
Atrial fibrillation	84 (40.6%)	127 (54.7%)	0.286	207 (47%)	202 (46%)	0.035
Sick sinus syndrome	19 (9.2%)	14 (6.0%)	0.119	30 (7%)	33 (8%)	0.029
AV block	26 (12.6%)	15 (6.5%)	0.209	42 (10%)	47 (11%)	0.029
Previous HF hospitalization	28 (13.5%)	49 (21.1%)	0.202	68 (16%)	76 (17%)	0.043
NT-proBNP, pg/mL	2628.9 [1465.0, 3817.6]	2767.5 [1747.5, 4363.4]	0.183	2775.2 [1510.0, 4377.0]	2631.3 [1710.0, 4117.4]	0.017
ACEi or ARB	110 (53.1%)	137 (59.1%)	0.119	247 (57%)	237 (54%)	0.059
MRA	74 (35.7%)	116 (50.0%)	0.291	194 (44%)	189 (43%)	0.030
CCB	103 (49.8%)	101 (43.5%)	0.125	210 (48%)	216 (49%)	0.016

Diuretics	154 (74.4%)	190 (81.9%)	0.182	342 (78%)	336 (76%)	0.052

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

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Supplemental Table 21. Baseline characteristics of patients before and after IPTW (MRA in phenotype 1)

	Original cohort			IPTW		
	MRA (-)	MRA (+)	SMD	MRA (-)	MRA (+)	SMD
Patient number	249	190		439	448	
Age, years	83.0 [76.0, 87.0]	83.0 [77.0, 87.0]	0.102	83.0 [77.0, 87.0]	81.0 [75.0, 86.0]	0.051
Female sex	148 (59.4%)	116 (61.1%)	0.033	265 (60%)	258 (58%)	0.057
Hypertension	204 (81.9%)	159 (83.7%)	0.047	366 (83%)	357 (80%)	0.098
Systolic blood pressure, mmHg	157.0 [142.0, 175.0]	150.5 [132.0, 166.0]	0.309	156.0 [140.4, 171.0]	154.0 [137.5, 172.0]	0.003
Potassium	4.1 [3.8, 4.4]	3.9 [3.7, 4.3]	0.291	4.1 [3.7, 4.3]	4.0 [3.7, 4.4]	0.041
Prior myocardial infarction	11 (4.4%)	12 (6.3%)	0.084	26 (6%)	22 (5%)	0.045
Chronic kidney disease	52 (20.9%)	29 (15.3%)	0.146	80 (18%)	88 (20%)	0.037
NT-proBNP, pg/mL	2770.0 [1600.0, 4279.0]	2518.4 [1538.0, 3877.6]	0.13	2729.3 [1590.4, 4101.8]	2895.9 [1622.2, 4269.7]	0.058
ACEi or ARB	145 (58.2%)	102 (53.7%)	0.092	255 (58%)	250 (56%)	0.048
Beta blocker	116 (46.6%)	116 (61.1%)	0.293	235 (53%)	235 (52%)	0.020
CCB	130 (52.2%)	74 (38.9%)	0.269	204 (47%)	205 (46%)	0.016
Diuretics	171 (68.7%)	173 (91.1%)	0.581	345 (78%)	347 (77%)	0.025

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 22. Baseline characteristics of patients before and after IPTW (Statin in phenotype 1)

	Original cohort			IPTW		
	Statin (-)	Statin (+)	SMD	Statin (-)	Statin (+)	SMD
Patient number	309	130		448	463	
Age, years	82.0 [77.0, 87.0]	83.0 [77.2, 86.0]	0.106	82.0 [77.0, 87.0]	84.0 [78.0, 90.0]	0.233
Female sex	186 (60.2%)	78 (60.0%)	0.004	262 (58%)	218 (47%)	0.229
Body mass index	23.2 [20.4, 26.4]	24.2 [21.7, 27.1]	0.236	23.2 [20.3, 26.5]	22.6 [20.8, 25.8]	0.055
Dyslipidemia	66 (21.4%)	102 (78.5%)	1.391	173 (39%)	169 (37%)	0.044
LDL cholesterol, mg/dL	102.0 [86.0, 115.2]	83.0 [69.0, 94.8]	0.643	97.0 [77.0, 111.1]	94.0 [82.8, 130.5]	0.277
Hypertension	245 (79.3%)	118 (90.8%)	0.326	374 (83%)	406 (88%)	0.123
Systolic blood pressure, mmHg	155.0 [138.0, 171.0]	156.0 [140.0, 171.8]	0.074	156.0 [138.0, 170.7]	160.0 [145.0, 172.0]	0.164
Diabetes mellitus	53 (17.2%)	48 (36.9%)	0.457	121 (27%)	120 (26%)	0.024
Coronary artery disease	25 (8.1%)	35 (26.9%)	0.512	72 (16%)	72 (16%)	0.011
Prior myocardial infarction	9 (2.9%)	14 (10.8%)	0.315	24 (5%)	25 (5%)	0.002
PCI	14 (4.5%)	25 (19.2%)	0.467	35 (8%)	51 (11%)	0.110
CABG	2 (0.6%)	10 (7.7%)	0.358	10 (2%)	24 (5%)	0.158

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 23. Baseline characteristics of patients before and after IPTW (ACEi or ARB in phenotype 2)

	Original cohort			IPTW		
	ACEi or ARB (-)	ACEi or ARB (+)	SMD	ACEi or ARB (-)	ACEi or ARB (+)	SMD
Patient number	62	92		156	153	
Age, years	79.0 [72.2, 83.0]	78.0 [71.8, 84.2]	0.023	79.0 [72.0, 83.0]	78.0 [71.9, 84.0]	0.043
Female sex	31 (50.0%)	48 (52.2%)	0.043	76 (49%)	76 (50%)	0.014
Hypertension	58 (93.5%)	89 (96.7%)	0.149	149 (96%)	147 (96%)	0.007
Systolic blood pressure, mmHg	183.5 [161.8, 201.0]	185.5 [168.0, 211.0]	0.104	184.4 [164.0, 201.0]	183.6 [166.8, 208.1]	0.004
Diabetes mellitus	34 (54.8%)	49 (53.3%)	0.032	76 (49%)	80 (52%)	0.068
Chronic kidney disease	49 (79.0%)	60 (65.2%)	0.312	110 (71%)	108 (71%)	0.001
Prior myocardial infarction	6 (9.7%)	9 (9.8%)	0.004	14 (9%)	15 (10%)	0.024
Left ventricular mass index	118.8 [101.4, 143.7]	113.4 [93.7, 137.0]	0.187	113.9 [97.2, 140.0]	115.0 [97.2, 138.2]	0.016
Previous HF hospitalization	13 (21.0%)	19 (20.7%)	0.008	28 (18%)	30 (19%)	0.036
NT-proBNP, pg/mL	8257.4 [3579.8, 20391.0]	7903.7 [2869.0, 17057.6]	0.181	7778.8 [3549.2, 14559.4]	8260.5 [2914.5, 19359.7]	0.030
Beta blocker	36 (58.1%)	62 (67.4%)	0.194	98 (63%)	99 (65%)	0.034
MRA	13 (21.0%)	29 (31.5%)	0.242	43 (28%)	42 (28%)	<0.001
CCB	43 (69.4%)	75 (81.5%)	0.286	120 (77%)	118 (77%)	0.007
Diuretics	45 (72.6%)	68 (73.9%)	0.03	112 (72%)	112 (73%)	0.033

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 24. Baseline characteristics of patients before and after IPTW (Beta blocker in phenotype 2)

	Original cohort			IPTW		
	Beta blocker (-)	Beta blocker (+)	SMD	Beta blocker (-)	Beta blocker (+)	SMD
Patient number	56	98		143	159	
Age, years	79.5 [73.8, 84.2]	78.0 [71.0, 84.0]	0.133	79.0 [73.0, 84.7]	79.3 [71.0, 84.0]	0.027
Female sex	31 (55.4%)	48 (49.0%)	0.128	77 (54%)	84 (53%)	0.015
Hypertension	50 (89.3%)	97 (99.0%)	0.422	135 (95%)	147 (92%)	0.102
Systolic blood pressure, mmHg	175.5 [155.5, 199.0]	188.5 [173.0, 212.8]	0.504	188.1 [159.0, 215.5]	181.3 [170.0, 203.7]	0.020
Left ventricular mass index	111.8 [92.4, 134.3]	117.9 [100.0, 139.8]	0.122	111.6 [92.5, 137.8]	113.4 [98.7, 139.2]	0.038
Diabetes mellitus	28 (50.0%)	55 (56.1%)	0.123	73 (51%)	92 (58%)	0.139
COPD	4 (7.1%)	4 (4.1%)	0.133	7 (5%)	6 (4%)	0.037
Coronary artery disease	8 (14.3%)	31 (31.6%)	0.422	35 (24%)	48 (30%)	0.135
Prior myocardial infarction	2 (3.6%)	13 (13.3%)	0.355	12 (9%)	15 (9%)	0.026
Heart rate, bpm	83.5 [63.2, 94.0]	91.0 [74.2, 109.8]	0.436	86.6 [70.0, 109.6]	84.5 [70.7, 103.1]	0.014
Atrial fibrillation	7 (12.5%)	19 (19.4%)	0.189	17 (12%)	24 (15%)	0.097
Sick sinus syndrome	2 (3.6%)	5 (5.1%)	0.075	5 (4%)	7 (4%)	0.017
AV block	3 (5.4%)	9 (9.2%)	0.148	7 (5%)	11 (7%)	0.089
Previous HF hospitalization	13 (23.2%)	19 (19.4%)	0.094	37 (26%)	30 (19%)	0.173
NT-proBNP, pg/mL	7147.5 [2800.0, 18317.8]	8412.0 [3591.1, 19104.0]	0.058	6518.5 [2800.0, 16211.3]	9465.1 [3598.1, 19596.2]	0.010
ACEi or ARB	30 (53.6%)	62 (63.3%)	0.198	93 (66%)	93 (58%)	0.148
MRA	12 (21.4%)	30 (30.6%)	0.21	28 (19%)	40 (25%)	0.136
CCB	40 (71.4%)	78 (79.6%)	0.191	107 (75%)	118 (74%)	0.022

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Diuretics	37 (66.1%)	76 (77.6%)	0.257	101 (71%)	110 (70%)	0.022

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 25. Baseline characteristics of patients before and after IPTW (MRA in phenotype 2)

	Original cohort			IPTW		
	MRA (-)	MRA (+)	SMD	MRA (-)	MRA (+)	SMD
Patient number	112	42		155	147	
Age, years	79.0 [72.0, 83.0]	81.0 [72.0, 85.0]	0.114	79.0 [72.0, 83.0]	78.0 [72.0, 85.0]	0.046
Female sex	57 (50.9%)	22 (52.4%)	0.03	80 (51%)	84 (57%)	0.111
Hypertension	106 (94.6%)	41 (97.6%)	0.155	148 (96%)	144 (98%)	0.127
Systolic blood pressure, mmHg	183.0 [165.5, 204.2]	193.5 [168.2, 212.5]	0.166	183.5 [166.0, 207.0]	172.5 [163.9, 202.1]	0.146
Potassium	4.3 [3.9, 4.7]	4.1 [3.7, 4.5]	0.329	4.3 [3.8, 4.6]	4.4 [3.9, 5.0]	0.208
Prior myocardial infarction	10 (8.9%)	5 (11.9%)	0.098	15 (9%)	11 (8%)	0.070
Chronic kidney disease	83 (74.1%)	26 (61.9%)	0.264	108 (70%)	104 (71%)	0.022
NT-proBNP, pg/mL	7978.7 [3195.0, 21192.5]	8075.0 [3635.8, 11249.8]	0.387	6430.0 [2800.0, 17875.9]	8488.3 [3650.7, 9273.0]	0.314
ACEi or ARB	63 (56.2%)	29 (69.0%)	0.267	94 (60%)	101 (69%)	0.176
Beta blocker	68 (60.7%)	30 (71.4%)	0.228	98 (63%)	101 (69%)	0.112
CCB	88 (78.6%)	30 (71.4%)	0.166	118 (76%)	114 (78%)	0.037
Diuretics	74 (66.1%)	39 (92.9%)	0.703	114 (74%)	110 (75%)	0.029

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 26. Baseline characteristics of patients before and after IPTW (Statin in phenotype 2)

	Original cohort			IPTW		
	Statin (-)	Statin (+)	SMD	Statin (-)	Statin (+)	SMD
Patient number	86	68		151	163	
Age, years	81.0 [73.2, 84.0]	77.0 [71.8, 84.0]	0.244	78.0 [71.0, 83.0]	78.6 [69.0, 85.2]	0.223
Female sex	40 (46.5%)	39 (57.4%)	0.218	75 (49%)	82 (50%)	0.014
Body mass index	23.8 [20.8, 26.7]	25.4 [22.1, 28.6]	0.198	23.6 [20.5, 26.7]	24.2 [20.6, 28.7]	0.024
Dyslipidemia	36 (41.9%)	51 (75.0%)	0.714	84 (56%)	87 (53%)	0.050
LDL cholesterol, mg/dL	98.8 [81.5, 117.5]	80.0 [63.8, 97.2]	0.441	94.7 [78.0, 115.1]	88.4 [72.0, 128.3]	0.285
Hypertension	83 (96.5%)	64 (94.1%)	0.113	144 (95%)	155 (95%)	0.031
Systolic blood pressure, mmHg	185.5 [164.0, 203.5]	183.0 [167.8, 212.2]	0.08	186.0 [164.0, 204.0]	178.0 [170.2, 206.8]	0.042
Diabetes mellitus	42 (48.8%)	41 (60.3%)	0.232	80 (53%)	77 (47%)	0.123
Coronary artery disease	16 (18.6%)	23 (33.8%)	0.351	39 (26%)	40 (25%)	0.029
Prior myocardial infarction	8 (9.3%)	7 (10.3%)	0.033	16 (11%)	14 (9%)	0.076
PCI	16 (18.6%)	21 (30.9%)	0.287	36 (24%)	35 (22%)	0.050
CABG	3 (3.5%)	3 (4.4%)	0.047	5 (3%)	5 (3%)	0.003

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 27. Baseline characteristics of patients before and after IPTW (ACEi or ARB in phenotype 3)

	Original cohort			IPTW		
	ACEi or ARB (-)	ACEi or ARB (+)	SMD	ACEi or ARB (-)	ACEi or ARB (+)	SMD
Patient number	118	129		248	246	
Age, years	83.5 [80.0, 87.0]	83.0 [79.0, 88.0]	0.065	83.0 [79.0, 87.0]	83.0 [79.0, 87.8]	0.017
Female sex	68 (57.6%)	54 (41.9%)	0.319	121 (49%)	119 (48%)	0.008
Hypertension	92 (78.0%)	108 (83.7%)	0.147	202 (81%)	200 (81%)	0.002
Systolic blood pressure, mmHg	124.0 [111.0, 136.8]	131.0 [118.0, 142.0]	0.373	128.0 [113.0, 139.1]	129.0 [117.8, 139.0]	0.004
Diabetes mellitus	36 (30.5%)	46 (35.7%)	0.11	82 (33%)	80 (32%)	0.015
Chronic kidney disease	67 (56.8%)	84 (65.1%)	0.172	156 (63%)	155 (63%)	0.003
Prior myocardial infarction	7 (5.9%)	11 (8.5%)	0.1	14 (6%)	16 (7%)	0.033
Left ventricular mass index	94.6 [74.1, 113.6]	103.2 [83.2, 120.9]	0.234	98.1 [77.8, 116.0]	99.3 [81.5, 118.6]	0.021
Previous HF hospitalization	48 (40.7%)	54 (41.9%)	0.024	104 (42%)	103 (42%)	0.002
NT-proBNP, pg/mL	4222.3 [2429.2, 6885.0]	3820.0 [2045.9, 6900.0]	0.007	4209.2 [2420.3, 6868.4]	4062.6 [2020.7, 6953.5]	0.015
Beta blocker	69 (58.5%)	65 (50.4%)	0.163	134 (54%)	133 (54%)	0.004
MRA	44 (37.3%)	50 (38.8%)	0.03	93 (37%)	93 (38%)	0.011
CCB	33 (28.0%)	58 (45.0%)	0.359	89 (36%)	90 (37%)	0.016
Diuretics	106 (89.8%)	118 (91.5%)	0.056	226 (91%)	224 (91%)	0.010

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 28. Baseline characteristics of patients before and after IPTW (Beta blocker in phenotype 3)

	Original cohort			IPTW		
	Beta blocker (-)	Beta blocker (+)	SMD	Beta blocker (-)	Beta blocker (+)	SMD
Patient number	113	134		261	240	
Age, years	84.0 [79.0, 88.0]	83.0 [78.2, 86.0]	0.174	83.0 [76.0, 87.0]	83.0 [78.0, 87.0]	0.146
Female sex	52 (46.0%)	70 (52.2%)	0.125	153 (59%)	128 (53%)	0.106
Hypertension	94 (83.2%)	106 (79.1%)	0.104	193 (74%)	194 (81%)	0.168
Systolic blood pressure, mmHg	128.0 [113.0, 140.0]	130.0 [117.2, 138.0]	0.067	124.0 [111.0, 136.0]	128.0 [117.0, 138.0]	0.138
Left ventricular mass index	102.1 [84.8, 116.8]	97.6 [75.4, 117.3]	0.119	101.6 [80.5, 116.7]	101.4 [78.7, 120.0]	0.048
Diabetes mellitus	43 (38.1%)	39 (29.1%)	0.19	85 (32%)	80 (33%)	0.024
COPD	6 (5.3%)	15 (11.2%)	0.215	13 (5%)	19 (8%)	0.118
Coronary artery disease	16 (14.2%)	31 (23.1%)	0.232	71 (27%)	49 (20%)	0.156
Prior myocardial infarction	5 (4.4%)	13 (9.7%)	0.207	43 (17%)	20 (9%)	0.246
Heart rate, bpm	68.0 [54.0, 81.0]	82.0 [66.0, 100.0]	0.622	74.0 [56.8, 98.3]	77.8 [61.9, 92.0]	0.036
Atrial fibrillation	52 (46.0%)	82 (61.2%)	0.308	130 (50%)	132 (55%)	0.107
Sick sinus syndrome	14 (12.4%)	14 (10.4%)	0.061	38 (15%)	33 (14%)	0.022
AV block	16 (14.2%)	10 (7.5%)	0.217	29 (11%)	24 (10%)	0.038
Previous HF hospitalization	35 (31.0%)	67 (50.0%)	0.395	105 (40%)	106 (44%)	0.087
NT-proBNP, pg/mL	3962.0 [2180.0, 6250.0]	4339.8 [2397.2, 7264.2]	0.075	4220.0 [2292.7, 6305.8]	4313.8 [2366.3, 7334.5]	0.035
ACEi or ARB	64 (56.6%)	65 (48.5%)	0.163	125 (48%)	125 (52%)	0.079
MRA	38 (33.6%)	56 (41.8%)	0.169	93 (36%)	89 (37%)	0.033
CCB	54 (47.8%)	37 (27.6%)	0.426	87 (33%)	85 (35%)	0.044

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Diuretics	103 (91.2%)	121 (90.3%)	0.029	244 (93%)	220 (92%)	0.067

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 29. Baseline characteristics of patients before and after IPTW (MRA in phenotype 3)

	Original cohort			IPTW		
	MRA (-)	MRA (+)	SMD	MRA (-)	MRA (+)	SMD
Patient number	153	94		249	241	
Age, years	83.0 [79.0, 87.0]	83.0 [79.0, 87.0]	0.01	83.0 [79.0, 87.0]	83.0 [78.9, 87.0]	0.014
Female sex	78 (51.0%)	44 (46.8%)	0.084	124 (50%)	118 (49%)	0.014
Hypertension	132 (86.3%)	68 (72.3%)	0.349	201 (81%)	193 (80%)	0.012
Systolic blood pressure, mmHg	130.0 [116.0, 140.0]	127.0 [115.0, 136.8]	0.14	128.0 [113.0, 139.5]	127.0 [113.8, 138.0]	0.032
Potassium	4.3 [3.9, 4.7]	4.3 [3.7, 4.5]	0.311	4.2 [3.9, 4.6]	4.3 [3.9, 4.6]	0.072
Prior myocardial infarction	13 (8.5%)	5 (5.3%)	0.126	18 (7%)	18 (8%)	0.013
Chronic kidney disease	95 (62.1%)	56 (59.6%)	0.052	150 (60%)	144 (60%)	0.015
NT-proBNP, pg/mL	3996.3 [2300.0, 6900.0]	4188.3 [2245.0, 6900.0]	0.029	3993.2 [2192.6, 6655.8]	4243.3 [2218.1, 7217.1]	0.014
ACEi or ARB	79 (51.6%)	50 (53.2%)	0.031	130 (52%)	127 (53%)	0.010
Beta blocker	78 (51.0%)	56 (59.6%)	0.173	135 (54%)	133 (55%)	0.017
CCB	63 (41.2%)	28 (29.8%)	0.24	91 (36%)	85 (35%)	0.022
Diuretics	136 (88.9%)	88 (93.6%)	0.168	227 (91%)	223 (92%)	0.051

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 30. Baseline characteristics of patients before and after IPTW (Statin in phenotype 3)

	Original cohort			IPTW		
	Statin (-)	Statin (+)	SMD	Statin (-)	Statin (+)	SMD
Patient number	165	82		245	268	
Age, years	83.0 [78.0, 88.0]	83.0 [79.0, 85.0]	0.113	83.0 [78.0, 89.0]	83.0 [79.0, 83.0]	0.169
Female sex	81 (49.1%)	41 (50.0%)	0.018	119 (49%)	146 (55%)	0.123
Body mass index	24.0 [21.6, 26.5]	25.3 [22.1, 28.4]	0.383	24.5 [22.1, 26.6]	24.1 [22.1, 25.8]	0.015
Dyslipidemia	33 (20.0%)	73 (89.0%)	1.923	103 (42%)	106 (40%)	0.055
LDL cholesterol, mg/dL	93.0 [80.7, 108.0]	75.5 [63.0, 85.7]	0.668	87.7 [69.4, 104.4]	93.0 [68.3, 117.6]	0.188
Hypertension	128 (77.6%)	72 (87.8%)	0.273	202 (82%)	228 (85%)	0.073
Systolic blood pressure, mmHg	129.0 [116.0, 140.0]	127.5 [115.2, 138.0]	0.037	128.0 [112.4, 139.3]	131.0 [113.6, 138.0]	0.051
Diabetes mellitus	47 (28.5%)	35 (42.7%)	0.3	68 (28%)	68 (25%)	0.054
Coronary artery disease	20 (12.1%)	27 (32.9%)	0.514	34 (14%)	37 (14%)	0.009
Prior myocardial infarction	6 (3.6%)	12 (14.6%)	0.389	11 (5%)	14 (5%)	0.031
PCI	16 (9.7%)	20 (24.4%)	0.398	29 (12%)	30 (11%)	0.020
CABG	3 (1.8%)	7 (8.5%)	0.307	4 (2%)	8 (3%)	0.088

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 31. Baseline characteristics of patients before and after IPTW (ACEi or ARB in phenotype 4)

	Original cohort			IPTW		
	ACEi or ARB (-)	ACEi or ARB (+)	SMD	ACEi or ARB (-)	ACEi or ARB (+)	SMD
Patient number	135	125		258	268	
Age, years	84.0 [77.0, 90.0]	83.0 [77.0, 86.0]	0.178	84.0 [77.0, 89.0]	83.0 [78.4, 87.0]	0.009
Female sex	78 (57.8%)	61 (48.8%)	0.181	141 (55%)	149 (56%)	0.017
Hypertension	107 (79.3%)	116 (92.8%)	0.398	220 (85%)	220 (82%)	0.088
Systolic blood pressure, mmHg	136.0 [120.0, 150.5]	146.0 [129.0, 168.0]	0.468	141.0 [125.7, 157.0]	136.6 [122.0, 159.0]	0.073
Diabetes mellitus	43 (31.9%)	55 (44.0%)	0.252	94 (36%)	94 (35%)	0.025
Chronic kidney disease	58 (43.0%)	46 (36.8%)	0.126	100 (39%)	96 (36%)	0.067
Prior myocardial infarction	9 (6.7%)	9 (7.2%)	0.021	17 (7%)	16 (6%)	0.021
Left ventricular mass index	97.3 [79.7, 113.7]	99.4 [84.5, 113.4]	0.107	97.8 [82.4, 115.4]	98.2 [82.9, 109.9]	0.047
Previous HF hospitalization	35 (25.9%)	25 (20.0%)	0.141	59 (23%)	65 (24%)	0.032
NT-proBNP, pg/mL	4622.0 [2800.0, 7526.5]	4150.0 [2090.0, 7007.0]	0.2	4437.2 [2614.3, 7166.1]	5084.0 [2373.9, 7326.3]	0.029
Beta blocker	77 (57.0%)	68 (54.4%)	0.053	146 (57%)	158 (59%)	0.045
MRA	61 (45.2%)	46 (36.8%)	0.171	105 (41%)	119 (44%)	0.078
CCB	49 (36.3%)	73 (58.4%)	0.454	120 (47%)	119 (44%)	0.045
Diuretics	111 (82.2%)	106 (84.8%)	0.07	216 (84%)	221 (82%)	0.041

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 32. Baseline characteristics of patients before and after IPTW (Beta blocker in phenotype 4)

	Original cohort			IPTW		
	Beta blocker (-)	Beta blocker (+)	SMD	Beta blocker (-)	Beta blocker (+)	SMD
Patient number	115	145		275	254	
Age, years	84.0 [78.0, 88.0]	83.0 [77.0, 88.0]	0.196	81.9 [75.0, 86.1]	83.0 [77.0, 88.0]	0.101
Female sex	63 (54.8%)	76 (52.4%)	0.048	153 (56%)	139 (55%)	0.027
Hypertension	100 (87.0%)	123 (84.8%)	0.061	223 (81%)	217 (85%)	0.118
Systolic blood pressure, mmHg	142.0 [130.0, 160.0]	138.0 [121.0, 157.0]	0.218	136.1 [123.0, 155.5]	142.3 [122.0, 160.0]	0.075
Left ventricular mass index	100.3 [82.4, 121.5]	94.7 [80.7, 110.5]	0.203	98.2 [75.1, 112.4]	96.9 [83.9, 111.0]	0.079
Diabetes mellitus	46 (40.0%)	52 (35.9%)	0.085	106 (39%)	95 (37%)	0.024
COPD	13 (11.3%)	10 (6.9%)	0.154	20 (7%)	20 (8%)	0.032
Coronary artery disease	18 (15.7%)	26 (17.9%)	0.061	50 (18%)	44 (17%)	0.023
Prior myocardial infarction	8 (7.0%)	10 (6.9%)	0.002	21 (8%)	19 (7%)	0.014
Heart rate, bpm	81.0 [66.0, 96.5]	92.0 [76.0, 110.0]	0.471	90.0 [72.0, 103.2]	89.0 [75.0, 104.5]	0.097
Atrial fibrillation	55 (47.8%)	75 (51.7%)	0.078	140 (51%)	124 (49%)	0.047
Sick sinus syndrome	10 (8.7%)	10 (6.9%)	0.067	18 (6%)	18 (7%)	0.030
AV block	6 (5.2%)	3 (2.1%)	0.169	10 (3%)	9 (3%)	0.005
Previous HF hospitalization	19 (16.5%)	41 (28.3%)	0.285	56 (20%)	58 (23%)	0.055
NT-proBNP, pg/mL	3790.0 [1820.0, 6552.5]	5084.0 [2850.0, 7530.0]	0.202	4362.8 [1857.0, 6866.7]	4755.1 [2733.3, 7190.4]	0.057
ACEi or ARB	57 (49.6%)	68 (46.9%)	0.053	118 (43%)	118 (46%)	0.064
MRA	48 (41.7%)	59 (40.7%)	0.021	113 (41%)	107 (42%)	0.016
CCB	60 (52.2%)	62 (42.8%)	0.189	117 (43%)	120 (47%)	0.089

Diuretics	93 (80.9%)	124 (85.5%)	0.125	219 (80%)	212 (84%)	0.098

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 33. Baseline characteristics of patients before and after IPTW (MRA in phenotype 4)

	Original cohort			IPTW		
	MRA (-)	MRA (+)	SMD	MRA (-)	MRA (+)	SMD
Patient number	153	107		260	256	
Age, years	83.0 [77.0, 87.0]	84.0 [77.0, 89.0]	0.19	83.0 [78.0, 88.0]	84.0 [75.0, 89.0]	0.017
Female sex	80 (52.3%)	59 (55.1%)	0.057	140 (54%)	146 (57%)	0.056
Hypertension	133 (86.9%)	90 (84.1%)	0.08	222 (86%)	218 (85%)	0.015
Systolic blood pressure, mmHg	142.0 [126.0, 162.0]	140.0 [122.5, 156.0]	0.135	141.0 [123.7, 158.7]	141.0 [120.1, 157.8]	0.016
Potassium	4.2 [3.8, 4.6]	4.0 [3.6, 4.3]	0.278	4.1 [3.7, 4.5]	4.1 [3.6, 4.5]	0.009
Prior myocardial infarction	9 (5.9%)	9 (8.4%)	0.098	17 (6%)	15 (6%)	0.022
Chronic kidney disease	66 (43.1%)	38 (35.5%)	0.157	104 (40%)	98 (38%)	0.041
NT-proBNP, pg/mL	4622.0 [2300.0, 7523.0]	4478.6 [2523.5, 7050.0]	0.001	4474.0 [2299.9, 7371.6]	4406.1 [2465.8, 7304.9]	0.003
ACEi or ARB	79 (51.6%)	46 (43.0%)	0.174	124 (48%)	118 (46%)	0.036
Beta blocker	86 (56.2%)	59 (55.1%)	0.022	147 (57%)	149 (58%)	0.029
CCB	79 (51.6%)	43 (40.2%)	0.231	125 (48%)	123 (48%)	0.002
Diuretics	115 (75.2%)	102 (95.3%)	0.593	217 (83%)	219 (86%)	0.059

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 34. Baseline characteristics of patients before and after IPTW (Statin in phenotype 4)

	Original cohort			IPTW		
	Statin (-)	Statin (+)	SMD	Statin (-)	Statin (+)	SMD
Patient number	168	92		287	353	
Age, years	84.0 [77.0, 89.0]	83.0 [77.0, 86.0]	0.025	85.0 [78.1, 89.0]	88.0 [79.0, 88.0]	0.138
Female sex	87 (51.8%)	52 (56.5%)	0.095	182 (63%)	280 (79%)	0.359
Body mass index	23.0 [20.9, 25.6]	25.6 [22.5, 28.6]	0.57	24.4 [21.8, 28.2]	20.4 [20.4, 24.7]	0.427
Dyslipidemia	27 (16.1%)	80 (87.0%)	2.012	135 (47%)	109 (31%)	0.338
LDL cholesterol, mg/dL	98.0 [81.8, 111.0]	79.7 [67.0, 94.1]	0.603	91.0 [76.7, 105.9]	130.8 [83.5, 145.0]	0.719
Hypertension	135 (80.4%)	88 (95.7%)	0.484	251 (88%)	339 (96%)	0.321
Systolic blood pressure, mmHg	139.5 [124.0, 157.0]	145.0 [128.5, 163.8]	0.14	143.7 [123.2, 151.0]	175.6 [141.1, 183.0]	0.701
Diabetes mellitus	55 (32.7%)	43 (46.7%)	0.289	128 (45%)	235 (66%)	0.451
Coronary artery disease	20 (11.9%)	24 (26.1%)	0.368	81 (28%)	37 (11%)	0.457
Prior myocardial infarction	8 (4.8%)	10 (10.9%)	0.229	12 (4%)	12 (3%)	0.038
PCI	15 (8.9%)	23 (25.0%)	0.438	34 (12%)	34 (10%)	0.072
CABG	3 (1.8%)	8 (8.7%)	0.314	52 (18%)	13 (4%)	0.472

Data are expressed as median [interquartile range] or number (percentage). Abbreviations: IPTW, inverse-probability-of-treatment weighting; SMD, standardized mean difference.

Supplemental Table 35. Incidence of the primary endpoint (a composite of all-cause death and HF hospitalization)

	Phenotype 1		Phenotype 2		Phenotype 3		Phenotype 4	
	Event number	Incidence (per 100 py)	Event number	Incidence (per 100 py)	Event number	Incidence (per 100 py)	Event number	Incidence (per 100 py)
ACEi/ARB (-)	76/192	21.4	29/62	29.0	79/118	48.4	76/135	32.1
ACEi/ARB (+)	91/247	18.4	44/92	30.2	74/129	33.7	59/125	24.8
Beta blockers (-)	74/207	18.3	24/56	23.7	71/113	41.8	58/115	25.4
Beta blockers (+)	93/232	20.8	49/98	33.9	82/134	38.6	77/145	31.3
MRA (-)	94/249	18.8	59/112	34.6	94/153	39.2	76/153	25.5
MRA (+)	73/190	20.8	14/42	18.6	59/94	41.3	59/107	33.5
Statins (-)	122/309	20.5	42/86	28.5	108/165	42.2	87/168	27.5
Statins (+)	45/130	17.7	31/68	31.5	45/82	35.4	48/92	30.4

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid-receptor antagonist; py, person-year.

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Supplemental Table 36. Incidence of all-cause death

	Phenotype 1		Phenotype 2		Phenotype 3		Phenotype 4	
	Event number	Incidence (per 100 py)	Event number	Incidence (per 100 py)	Event number	Incidence (per 100 py)	Event number	Incidence (per 100 py)
ACEi/ARB (-)	44/192	10.4	19/62	15.4	50/118	20.9	53/135	18.6
ACEi/ARB (+)	48/247	8.3	24/92	11.5	44/129	14.6	33/125	11.1
Beta blockers (-)	45/207	9.9	13/56	9.8	39/113	16.1	37/115	13.8
Beta blockers (+)	47/232	8.6	30/98	15.0	55/134	18.5	49/145	15.7
MRA (-)	52/249	8.9	36/112	15.1	60/153	18.1	46/153	12.8
MRA (+)	40/190	9.4	7/42	7.5	34/94	16.3	40/107	18.0
Statins (-)	67/309	9.6	24/86	12.4	67/165	18.4	60/168	16.3
Statins (+)	25/130	8.1	19/68	13.7	27/82	15.3	26/92	12.2

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid-receptor antagonist; py, person-year.

Supplemental Table 37. Incidence of HF hospitalization

	Phenotype 1		Phenotype 2		Phenotype 3		Phenotype 4	
	Event number	Incidence (per 100 py)	Event number	Incidence (per 100 py)	Event number	Incidence (per 100 py)	Event number	Incidence (per 100 py)
ACEi/ARB (-)	49/192	14.1	17/62	17.6	55/118	35.0	33/135	14.5
ACEi/ARB (+)	63/247	13.1	35/92	24.9	54/129	25.4	40/125	17.3
Beta blockers (-)	44/207	11.2	19/56	19.4	50/113	30.5	29/115	13.1
Beta blockers (+)	68/232	15.6	33/98	23.8	59/134	28.7	44/145	18.5
MRA (-)	65/249	13.4	43/112	26.1	62/153	26.8	44/153	15.2
MRA (+)	47/190	13.7	9/42	12.4	47/94	34.1	29/107	17.1
Statins (-)	82/309	14.1	31/86	21.7	78/165	31.6	41/168	13.4
Statins (+)	30/130	12.1	21/68	22.3	31/82	25.2	32/92	21.0

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid-receptor antagonist; py, person-year.

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