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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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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2022-322181).

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Received 24 November 2022
Accepted 7 February 2023
Published Online First 23 February 2023

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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► http://dx.doi.org/10.1136/heartjnl-2023-322475

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To cite: Sotomi Y, Hikoso S, Nakatani D, *et al*. *Heart* 2023;**109**:1231–1240.

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.

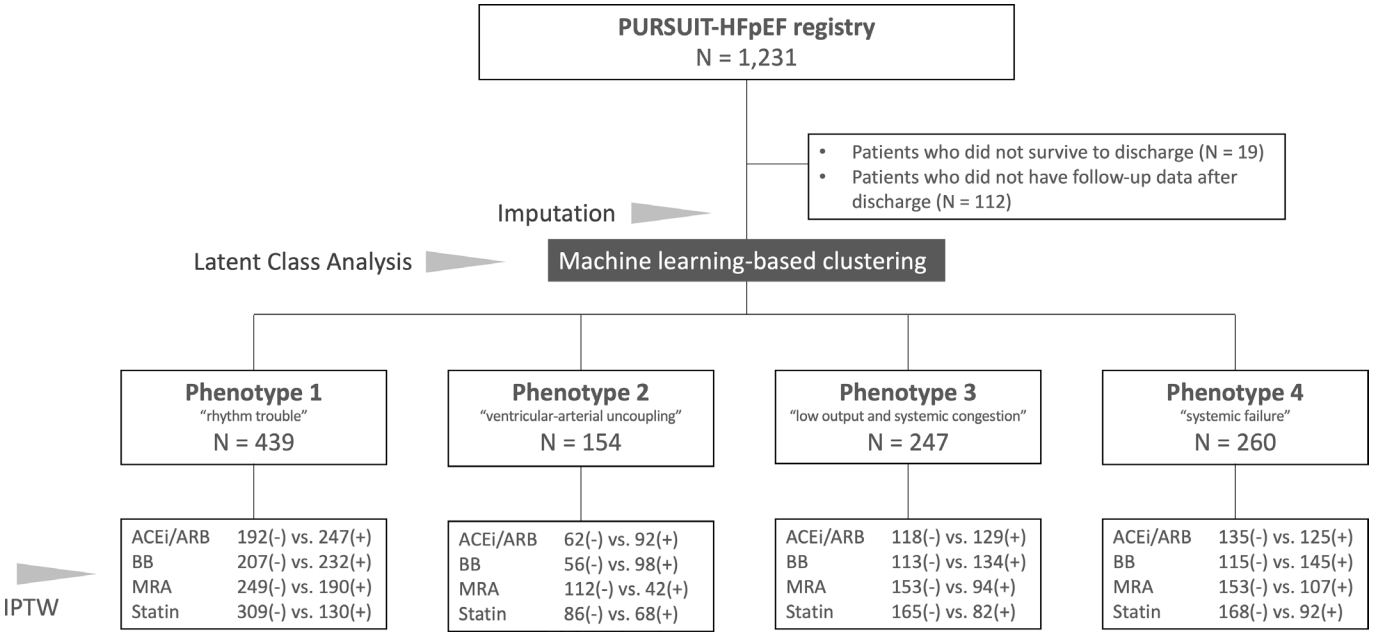

Figure 1 Analysis flowchart. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BB, beta blocker; MRA, mineralocorticoid-receptor antagonist; IPTW, inverse-probability-of-treatment weighting.

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

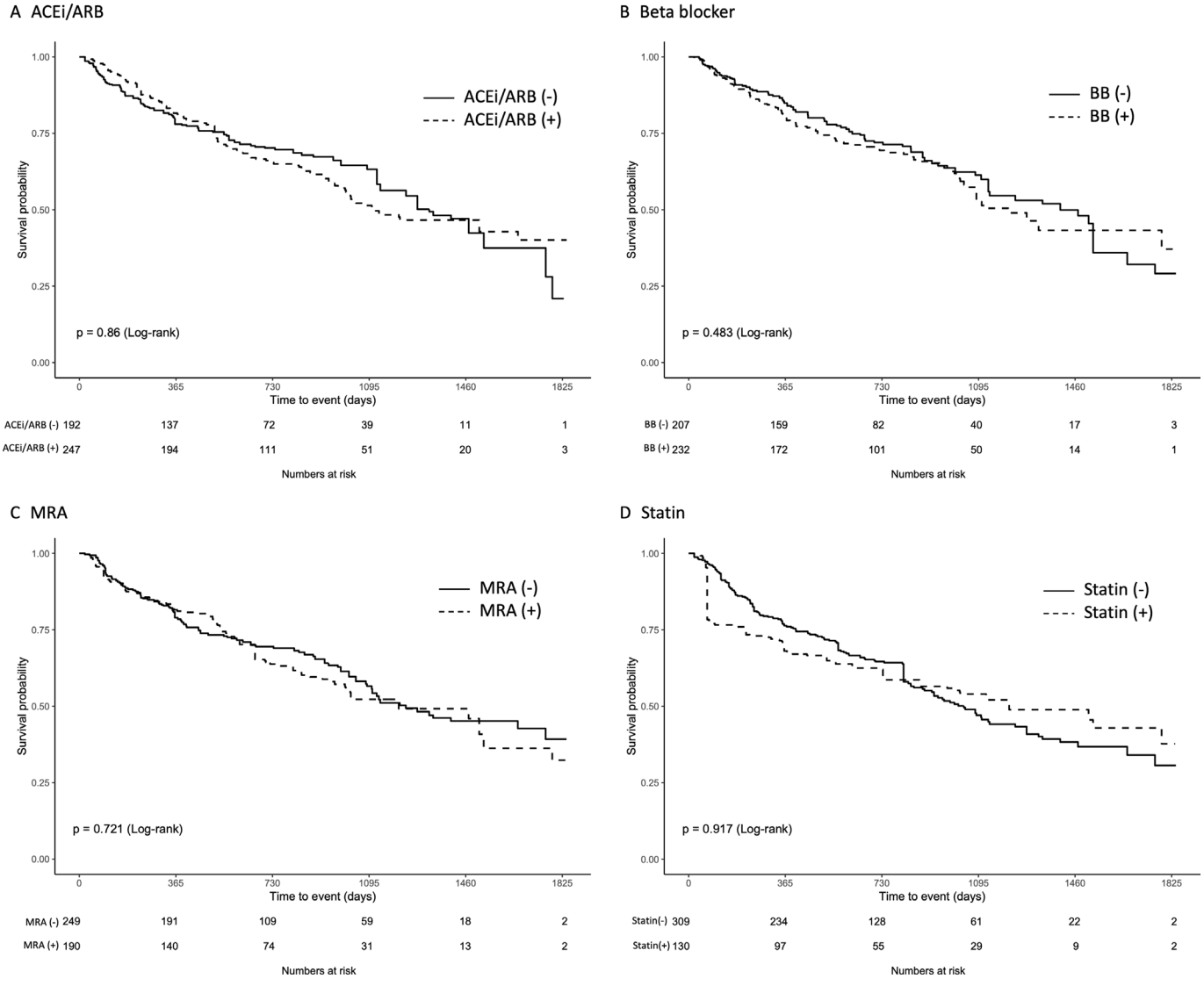

Figure 2 Weighted Kaplan-Meier curves for phenotype 1. Survival analysis for a composite of all-cause death and HF hospitalisation using the weighted Kaplan-Meier method for ACEi/ARB (A), BB (B), MRA (C) and statins (D) in phenotype 1. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II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

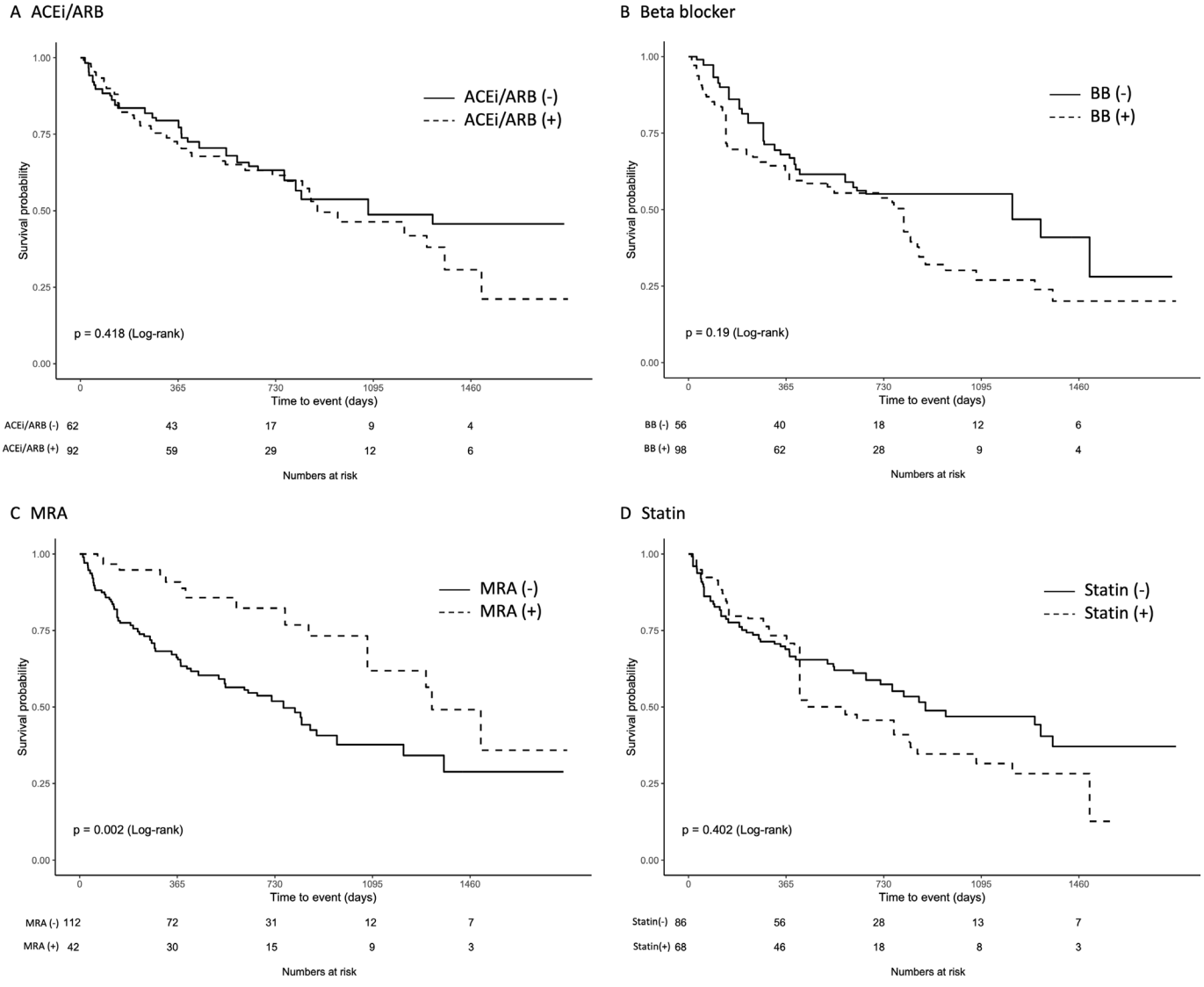

Figure 3 Weighted Kaplan-Meier curves for phenotype 2. Survival analysis for a composite of all-cause death and HF hospitalisation using the weighted Kaplan-Meier method for ACEi/ARB (A), BB (B), MRA (C) and statins (D) in phenotype 2. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II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

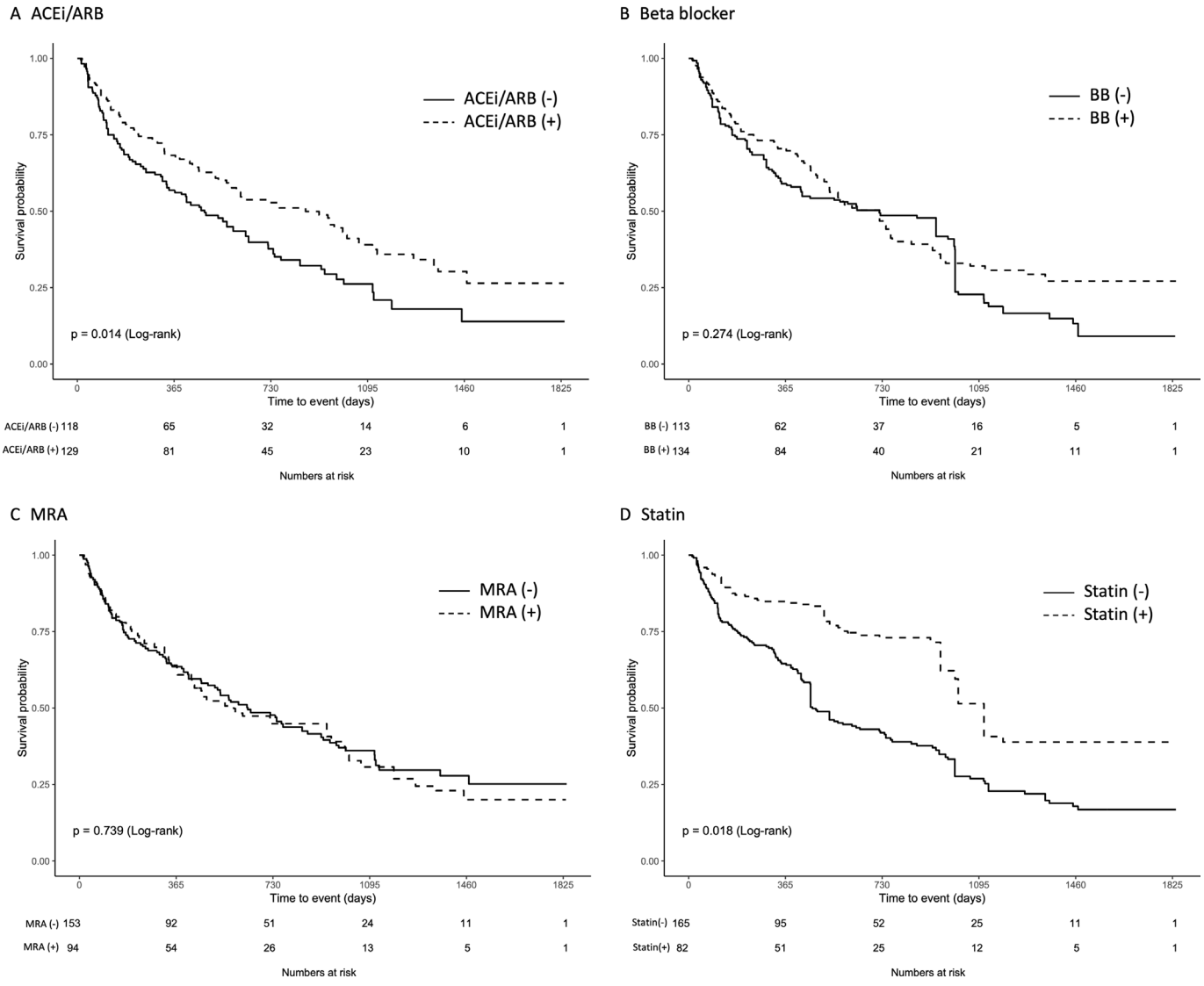

Figure 4 Weighted Kaplan-Meier curves for phenotype 3. Survival analysis for a composite of all-cause death and HF hospitalisation using the weighted Kaplan-Meier method for ACEi/ARB (A), BB (B), MRA (C) and statins (D) in phenotype 3. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II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

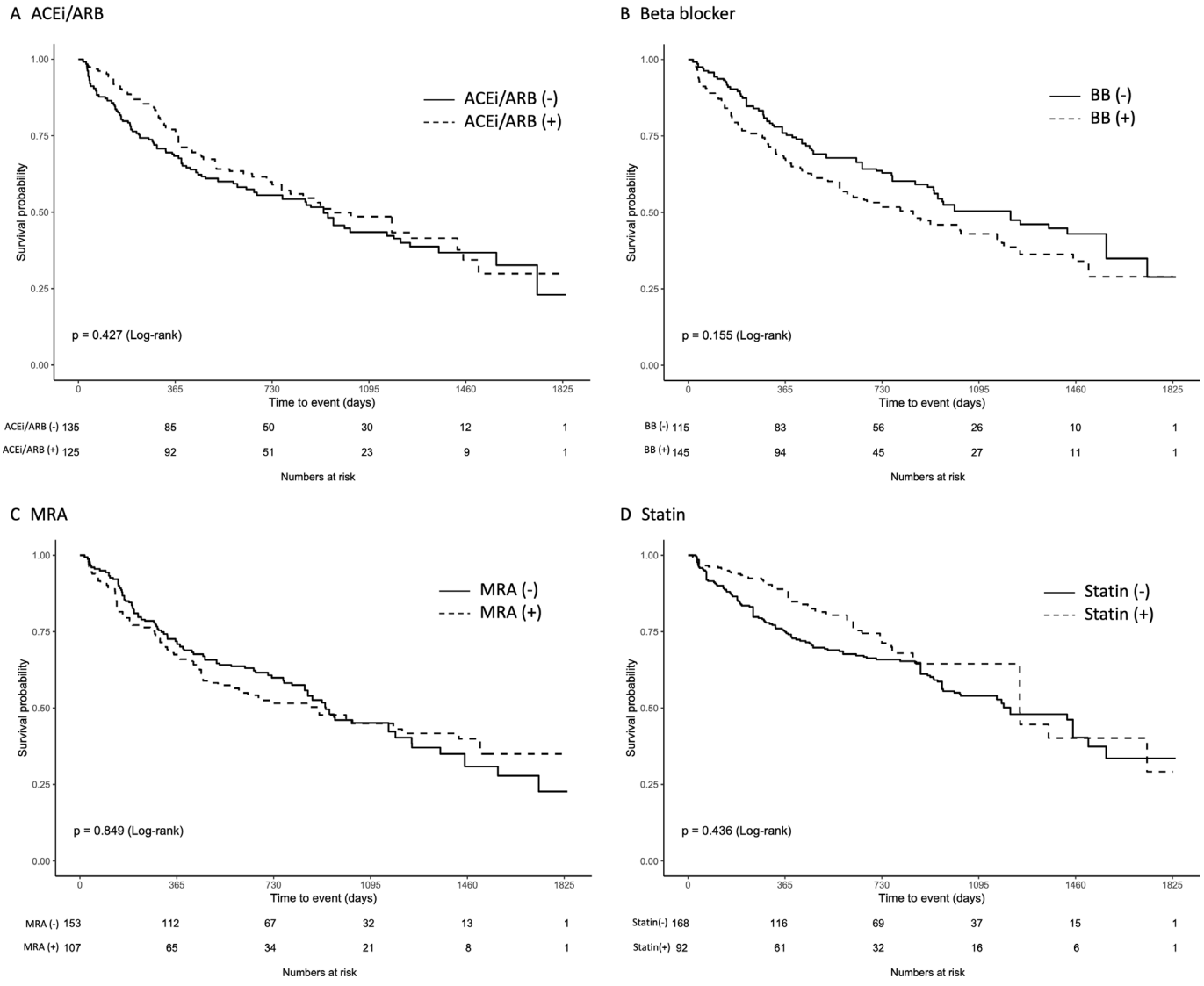

Figure 5 Weighted Kaplan Meier curves for phenotype 4. Survival analysis for a composite of all-cause death and HF hospitalisation using the weighted Kaplan-Meier method for ACEi/ARB (A), BB (B), MRA (C) and statin (D) in phenotype 4. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II 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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Acknowledgements The authors thank Sugako Mitsuoka, Nagisa Yoshioka, Satomi Kishimoto, Kyoko Tatsumi and Noriko Murakami for their excellent assistance in data collection, data management and secretarial work.

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Contributors Concept and design: YSo, SH and YSa. Data analysis and statistical analysis: YSo and SH. Manuscript draft: YSo, SH and YSa. Critical revision, editing and approval of the final manuscript: all authors. Guarantors: YSo, SH and YSa.

Funding This work was funded by Roche Diagnostics K.K. and Fuji Film Toyama Chemical Co. Ltd.

Competing interests SH has received grants from Roche Diagnostics, FUJIFILM Toyama Chemical and Actelion Pharmaceuticals; and personal fees from Daiichi Sankyo, Astellas Pharma, Bayer, Pfizer Pharmaceuticals, Boehringer Ingelheim Japan, Kowa Company and Ono Pharmaceutical. DN has received personal fees from Roche Diagnostics. TK has received honoraria from AstraZeneca. YS has received personal fees from Otsuka Pharmaceutical, Ono Pharmaceutical, Daiichi Sankyo, Mitsubishi Tanabe Pharma Corporation, AstraZeneca K.K. and Actelion Pharmaceuticals, and grants from Roche Diagnostic, FUJIFILM Toyama Chemical, Bristol-Myers Squibb, Co, Biosense Webster, Inc., Abbott Medical Japan, Otsuka Pharmaceutical, Daiichi Sankyo Company, Mitsubishi Tanabe Pharma Corporation, Astellas Pharma, Kowa Company, Boehringer Ingelheim Japan, and Biotronik. The other authors have nothing to disclose.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Kansai Rosai Hospital Institutional Review Board (approval ID: 16co10g), Kawachi General Hospital Ethics Committee (approval ID was not available, but approved on 26 Apr 2016), Osaka Rosai Hospital Ethics Committee (approval ID: 28-5), Higashiosaka City Medical Center Institutional Review Board (approval ID: 02-0313), Osaka Prefectural Hospital Organization Osaka General Medical Center Institutional Review Board(approval ID: 28-2002), Hyogo Prefectural Nishinomiya Hospital Ethics Committee (approval ID: H28-3), Ikeda Municipal Hospital Ethics Committee (approval ID: 3280), Kawanishi City Hospital Institutional Review Board (approval ID: 28001), Rinku General Medical Center Ethics Committee (approval ID: 27-40), Saiseikai Senri Hospital Ethics Committee (approval ID: 280304), Yao Municipal Hospital Institutional Review Board (approval ID: H28-6), Kawasaki Hospital Ethics Committee (approval ID was not available, but approved on 12 May 2016), Minoh City Hospital Ethics Committee (approval ID was not available, but approved on 24 May 2016), National Hospital Organization Osaka National Hospital Second Institutional Review Board (approval ID: 16024), Kano General Hospital Ethics Committee (approval ID was not available, but approved on 9 June 2016), Toyonaka Municipal Hospital Ethics Committee (approval ID: 2016-04-02), Kinan Hospital Ethics Committee 121, Japan Community Health Care Organization Osaka Hospital Ethics Committee (approval ID: 2016-2), Kobe Ekisaikai Hospital Ethics Committee (approval ID: 2016-3), Sakurabashi Watanabe Hospital Ethics Committee (approval ID: 16-15), Sumitomo Hospital Research Ethics Committee (approval ID: 28-01), Suita Municipal Hospital Institutional Review Board (approval ID: 2017-8), Kinki Central Hospital Ethics Committee (approval ID: 288), Osaka Police Hospital Institutional Review Board (approval ID: 593), Japan Community Health Care Organization Hoshigaoka Medical Center Institutional Review Board (approval ID: 1618), National Hospital Organization Osaka Minami Medical Center Institutional Review Board (approval ID: 28-3), Japan Community Health Care Organization Osaka Minato Central Hospital Ethics Committee (approval ID was not available, but approved on 10 June 2016), Amagasaki Chuo Hospital Ethics Committee (approval ID was not available, but approved on 1 Aug 2017), Otemae Hospital Institutional Review Board (approval ID: 2017-020), Osaka University Hospital Clinical Research Review Committee (approval ID: 15471), Osaka International Cancer Institute Institutional Review Board (No.20097). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. Our study data will not be made available to other researchers for purposes of reproducing the results because of institutional review board restrictions.

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