Circulation: Heart Failure

ORIGINAL ARTICLE

Data-Driven Approach to Identify Subgroups of Heart Failure With Reduced Ejection Fraction Patients With Different Prognoses and Aldosterone Antagonist Response Patterns

See Editorial by Chirinos and Lanfear

BACKGROUND: Patients with heart failure with reduced ejection fraction have a poor prognosis. The identification of subgroups with different outcomes and treatment response patterns may help to tailor strategies to each individual patient. We present an exploratory study of patients enrolled in the EMPHASIS-HF trial (Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms) using latent class analysis with validation using the EPHESUS trial (Eplerenone, a Selective Aldosterone Blocker, in Patients With Left Ventricular Dysfunction After Myocardial Infarction) to identify subgroups of patients with different prognosis and response to eplerenone therapy.

METHODS AND RESULTS: Latent class analysis identifies mutually exclusive groups of individuals maximizing within-group similarities and between-group differences. In the EMPHASIS-HF trial, 2279 heart failure with reduced ejection fraction patients were randomized to eplerenone or placebo and were characterized according to 18 clinical features. Subgroup definitions were applied to 6472 patients enrolled in the EPHESUS trial to validate observations. Event-free survival and effect of eplerenone on the composite of cardiovascular death and heart failure hospitalization were determined for each subgroup. Four subgroups were identified with significant differences in event-free survival (P=0.002). The subgroup C had the worst event-free survival in both studies and was characterized by older age, lower body mass index, worse renal function, higher baseline potassium levels, high prevalence of anemia, diabetes mellitus, previous revascularization and higher rates of eplerenone discontinuation, and hyperkalemia during follow-up. Two subgroups (B and C) showed a poorer response to eplerenone in both studies and these groups shared common features such as lower body mass index and high prevalence of anemia. Clinical profiles, prognosis, and treatment response patterns of the 4 subgroups applied in EPHESUS trial presented similarities to those observed in EMPHASIS.

CONCLUSIONS: Using a data-driven approach, we identified heart failure with reduced ejection fraction subgroups with significantly different prognoses and potentially different responses to eplerenone. However, these data should be regarded as hypothesis-generating and prospective validation is warranted, to assess the potential clinical implications of these subgroups.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00232180.

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WHAT IS NEW?

- The present study provides a latent class analysis of heart failure patients with systolic dysfunction (and with or without myocardial infarction) undergoing eplerenone treatment to create unsupervised mutually exclusive subgroups of patients with different prognoses and potentially different responses to treatment.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The latent class assignment can be easily used in routine clinical practice (with our available online calculator) to allocate each individual patient to one of the identified clusters and respective prognostic implications.
- In this regard, patients in cluster A and D likely have pronounced event-rate reduction, low risk for adverse events, and drug discontinuation.
- Cluster B have less pronounced event-rate reduction but also low risk for adverse events and drug discontinuation.
- Cluster C have less pronounced event-rate reduction and high risk for adverse events and drug discontinuation.

In the last 30 years, several drugs and devices have reduced morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF).[1,2] Among these drugs are the mineralocorticoid receptor antagonists (MRAs),[3–5] which are currently recommended as class IA indication for patients with HFrEF.[1,2] Despite these recommendations, MRA still largely underused.[6,7] Fear of hyperkalemia and renal function deterioration may be largely responsible for MRA underprescription.[8–14] The need of close monitoring of potassium and renal function[9] and a lack of education/promotion about these drugs and their indications may also contribute for their underprescription.[10–16] Identifying subgroups of patients with different prognosis and MRA response patterns (eg, subpopulations more prone to side effects such as hyperkalemia, drug discontinuation, and lower treatment benefit) may help clinicians in tailoring individualized strategies.[17] A previously published review article summarizes the reports that have identified subgroups of patients with different MRA response patterns.[18]

Latent class analysis (LCA) identifies mutually exclusive groups of individuals maximizing the within-group similarities and between-group differences and has been used for identification, characterization, and validation of HF subtypes.[19] Contrary to other phenomapping methods that use continuous variables for their computation,[20–22] LCA is suitable for analysis of categorical variables that are often present in clinical practice (eg, gender and comorbidities). Given its characteristics, LCA has been used to develop diagnostic criteria for complex diseases and to identify subgroups of diseases, risk stratification, and determining the likelihood of treatment response.[23,24]

In this retrospective, exploratory analysis, LCA was applied to clinical profiles of patients enrolled in the EMPHASIS-HF trial (Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms) to identify prevalent subgroups of patients with different treatment response and outcomes and externally validated in the EPHESUS trial (Eplerenone, a Selective Aldosterone Blocker, in Patients With Left Ventricular Dysfunction After Myocardial Infarction) population.

METHODS

The data, analytic methods, and study materials can be made available (on request) to other researchers for purposes of reproducing the results or replicating the procedure.

EMPHASIS-HF Trial Design

The design of EMPHASIS-HF has been described previously.[5] In short, EMPHASIS-HF was a randomized, double-blind trial that enrolled 2737 patients with New York Heart Association class II HF and an EF ≤35% to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes (cardiovascular mortality [CVM]) or hospitalization for heart failure (HFH). The median follow-up period was 21 months. The primary outcome occurred in 18.3% of patients in the eplerenone group as compared with 25.9% in the placebo group (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.54–0.74; $P<0.001$). In total, 2279 patients were included in LCA.

Subgroup Identification Using LCA

Patients were characterized according to 18 clinical features: age, gender, systolic blood pressure, heart rate, body mass index (BMI), left ventricular ejection fraction, estimated glomerular filtration rate (eGFR), hemoglobin, potassium (K^+), sodium (Na^+), hypertension, diabetes mellitus, smoking status, chronic obstructive pulmonary disease, atrial fibrillation, previous stroke, angina pectoris, and previous coronary revascularization. We selected these variables based on their availability in both cohorts and their potential prognostic value. Age, gender, systolic blood pressure, heart rate, BMI, eGFR, diabetes mellitus, hemoglobin, and coronary revascularization have been found to be independent outcome and treatment response predictors in EMPHASIS-HF.[25] Potassium levels may influence outcomes and MRA treatment response.[11,26] Sodium levels, smoking status, left ventricular ejection fraction, chronic obstructive pulmonary disease, atrial fibrillation, stroke history, and angina have all been identified as important prognostic factors in HF.[1,2]

We categorized continuous values based on their distribution across tertiles, clinical judgment, and international consensus. Age, systolic blood pressure, and heart rate

were categorized in tertiles with approximation for integer numbers. BMI was categorized according to World Health Organization classifications of normal weight, overweight, and obese. Left ventricular ejection fraction was dichotomized by the median value. Anemia was classified according to international consensus definition.[27] The eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration equation,[28] and eGFR was categorized using standard definitions for chronic kidney disease stages 1–5.[29] Hypertension, diabetes mellitus, smoking status, chronic obstructive pulmonary disease, stroke, angina, and percutaneous coronary intervention/coronary artery bypass grafting are categorical variables per se.

LCA was performed using the poLCA library in the R statistical package (version 2.15.0; R Foundation for Statistical Computing, Vienna, Austria). Latent class definitions were derived using maximum likelihood estimation to identify the most common patterns of the 18 variables for a range of 2 to 10 subgroups. The optimal number of subgroups for the EMPHASIS-HF was determined using the first minima of the Bayesian information criterion and χ^2 statistic with a condition to the percentage of patients in each cluster to be at least 10% of the total. Based on these criteria, the optimal number of clusters was 4. Probabilities of membership in each subgroup for every LCA variable were used to determine the most likely subgroup for each patient. Derivation of the latent class model and Bayesian determination of an individual patient's subgroup is detailed in the Data Supplement.

Subgroup Comparison and Outcome Associations

As above stated, 4 LCA groups (clusters) were identified (ie, clusters A, B, C, and D). In descriptive analyses, the categorical variables are expressed as frequencies and proportions (%) and compared using the χ^2 statistic.

Univariable time-to-event comparisons were performed using the log-rank test and survival was estimated with the Kaplan-Meier method. Cox proportional hazard regression models were used to assess long-term survival by LCA subgroups both in univariable and multivariable analysis. Cox proportional hazards assumption was assessed using log-log plots by LCA categories and Schoenfeld residuals test with a *P* value=0.12, meaning that no statistically significant proportional hazards violation was detected. LCA subgroups were treated as categorical covariates, and interactions between treatment allocation and outcomes were evaluated for each subgroup.

The % of missing values did not exceed 6% for the LCA computation variables and patients with missing values were excluded from the present analysis as LCA cannot be performed with missing data. As data were randomly missing and at low proportion for each individual variable, no imputation was performed as bias are negligible using complete-case analysis.[30]

A *P* value <0.05 was considered as statistically significant.

External Validation (EPHESUS Trial)

The design of EPHESUS trial has been described previously.[4] In short, the EPHESUS trial was a randomized, double-blind trial that enrolled 6632 patients with acute myocardial infarction (MI) complicated by left ventricular dysfunction (EF ≤35%) and heart failure to receive eplerenone (up to 50 mg daily) or placebo, in addition to recommended therapy. The primary end points were death from any cause and death from cardiovascular causes or HFH, acute MI, stroke, or ventricular arrhythmia. For consistency with the EMPHASIS-HF trial, we also assessed the composite outcome of death from cardiovascular causes or HFH. The median follow-up period was 16 months. Eplerenone reduced the rates of death from any cause (all-cause mortality) as well as the rates of death from cardiovascular causes or HFH, acute MI, stroke, or ventricular arrhythmia compared with placebo (HR, 0.85; 95% CI, 0.75–0.96; *P*=0.008; and HR, 0.87; 95% CI, 0.79–0.95; *P*=0.002; respectively). In total, 6472 patients had sufficient data to be included in LCA.

The same LCA definitions found in the EMPHASIS-HF trial were applied to the EPHESUS population using the same Bayesian calculator.

These studies were approved by the respective institutional review committees and all subjects gave informed consent to participate.

All statistical analyses were performed using the R software (The R Foundation for Statistical Computing).

RESULTS

Subgroup Characteristics

Patients in subgroup A were more often hypertensive and diabetic. Subgroup B had the highest proportion of patients with BMI<25 kg/m^2, and high proportion of patients with anemia and K^+<4.0 mmol/L. Subgroup C also had high proportion of patients with BMI<25 kg/m^2, and the highest proportion of patients with anemia, age>75 years, eGFR<45 mL/min per 1.73 m^2, previous revascularization and baseline K^+>4.5 mmol/L. Subgroup D patients were more often male and had similar proportion of patients with K^+>4.5 mmol/L as the subgroup C (Table 1; Figure 1).

Similar findings were observed in the EPHESUS population (Table I in the Data Supplement).

Outcomes

Patients included in the subgroup C had worse prognosis (compared with the remaining subgroups). The proportion of patients with the primary outcome of CVM or HFH was 29% in subgroup C (incidence-rate=20.5 [17.5–24.0] per 100 person-years), 22% in subgroup B (incidence-rate=14.1 [11.7–17.0] per 100 person-years), 19% in subgroup A (incidence-rate=10.7 [9.0–12.8] per 100 person-years), and 18% in subgroup D (incidence-rate=10.4 [8.6–12.6] per 100 person-years) (Table 1).

Setting subgroup A as the referent variable, the HR and respective 95% CI for CVM or HFH adjusted on treatment allocation were higher for subgroup C (HR, 1.87; 95% CI, 1.47–2.37; *P*<0.001), followed by subgroup B but not reaching statistical significance (HR, 1.27; 95% CI, 0.98–1.64; *P*=0.07), and were neutral for subgroup D (HR, 0.96; 95% CI, 0.74–1.25; *P*=0.77).

Table 1. Baseline Characteristics, Outcomes, and Risk Score of the EMPHASIS Population According to Clusters

Variables	Global (n=2279)	A (n=656)	B (n=512)	C (n=520)	D (n=591)	*P* Value
LCA variables						
Age ≤65	841 (36.9%)	175 (26.7%)	264 (51.6%)	41 (7.9%)	361 (61.1%)	<0.0001
66–75 y	973 (42.7%)	319 (48.6%)	207 (40.4%)	236 (45.4%)	211 (35.7%)	
>75 y	465 (20.4%)	162 (24.7%)	41 (8.0%)	243 (46.7%)	19 (3.2%)	
Male	1765 (77.4%)	349 (53.2%)	338 (66.0%)	495 (95.2%)	583 (98.6%)	<0.0001
SBP ≤120	1060 (46.5%)	156 (23.8%)	349 (68.2%)	330 (63.5%)	225 (38.1%)	<0.0001
121–130 mm Hg	544 (23.9%)	202 (30.8%)	91 (17.8%)	95 (18.3%)	156 (26.4%)	
>130 mm Hg	675 (29.6%)	298 (45.4%)	72 (14.1%)	95 (18.3%)	210 (35.5%)	
HR ≤65	746 (32.7%)	202 (30.8%)	104 (20.3%)	243 (46.7%)	197 (33.3%)	<0.0001
66–75 bpm	774 (34.0%)	205 (31.2%)	203 (39.6%)	178 (34.2%)	188 (31.8%)	
>75 bpm	759 (33.3%)	249 (38.0%)	205 (40.0%)	99 (19.0%)	206 (34.9%)	
BMI ≤25	677 (29.7%)	98 (14.9%)	306 (59.8%)	220 (42.3%)	53 (9.0%)	<0.0001
26–30 kg/m^2	982 (43.1%)	280 (42.7%)	136 (26.6%)	240 (46.2%)	326 (55.2%)	
>30 kg/m^2	620 (27.2%)	278 (42.4%)	70 (13.7%)	60 (11.5%)	212 (35.9%)	
LVEF ≥25%	1351 (59.3%)	465 (70.9%)	203 (39.6%)	306 (58.8%)	377 (63.8%)	<0.0001
eGFR ≤45	231 (10.1%)	69 (10.5%)	43 (8.4%)	115 (22.1%)	4 (0.7%)	<0.0001
46–60 mL/min per 1.73 m^2	522 (22.9%)	162 (24.7%)	94 (18.4%)	196 (37.7%)	70 (11.8%)	
>60 mL/min per 1.73 m^2	1526 (67.0%)	425 (64.8%)	375 (73.2%)	209 (40.2%)	517 (87.5%)	
Anemia*	578 (25.4%)	147 (22.4%)	137 (26.8%)	254 (48.8%)	40 (6.8%)	<0.0001
K^+ ≤4.0	560 (24.6%)	147 (22.4%)	183 (35.7%)	109 (21.0%)	121 (20.5%)	<0.0001
4.1–4.5 mmol/L	957 (42.0%)	288 (43.9%)	221 (43.2%)	210 (40.4%)	238 (40.3%)	
>4.5 mmol/L	762 (33.4%)	221 (33.7%)	108 (21.1%)	201 (38.7%)	232 (39.3%)	
Na^+ ≤135	213 (9.3%)	52 (7.9%)	103 (20.1%)	31 (6.0%)	27 (4.6%)	<0.0001
136–145 mmol/L	1917 (84.1%)	540 (82.3%)	395 (77.1%)	466 (89.6%)	516 (87.3%)	
>145 mmol/L	149 (6.5%)	64 (9.8%)	14 (2.7%)	23 (4.4%)	48 (8.1%)	
Hypertension	1538 (67.5%)	644 (98.2%)	123 (24.0%)	344 (66.2%)	427 (72.3%)	<0.0001
Diabetes mellitus	723 (31.7%)	246 (37.5%)	118 (23.0%)	166 (31.9%)	193 (32.7%)	<0.0001
Never smoker	1031 (45.2%)	599 (91.3%)	264 (51.6%)	133 (25.6%)	35 (5.9%)	<0.0001
Past smoker	1003 (44.0%)	53 (8.1%)	165 (32.2%)	356 (68.5%)	429 (72.6%)	
Current smoker	245 (10.8%)	4 (0.6%)	83 (16.2%)	31 (6.0%)	127 (21.5%)	
COPD	319 (14.0%)	42 (6.4%)	65 (12.7%)	80 (15.4%)	132 (22.3%)	<0.0001
AFib	717 (31.5%)	232 (35.4%)	118 (23.0%)	179 (34.4%)	188 (31.8%)	<0.0001
Stroke	221 (9.7%)	93 (14.2%)	31 (6.1%)	72 (13.8%)	25 (4.2%)	<0.0001
Angina pectoris	1045 (45.9%)	394 (60.1%)	39 (7.6%)	323 (62.1%)	289 (48.9%)	<0.0001
PCI or CABG	739 (32.4%)	137 (20.9%)	30 (5.9%)	365 (70.2%)	207 (35.0%)	<0.0001
Non-LCA variables						
ACE inhibitors/ARBs	2128 (93.4%)	613 (93.4%)	468 (91.4%)	484 (93.1%)	563 (95.3%)	0.082
β-blockers	1989 (87.7%)	561 (86.4%)	429 (84.3%)	471 (90.9%)	528 (89.3%)	0.005
Digoxin	637 (28.1%)	178 (27.4%)	187 (36.7%)	105 (20.3%)	167 (28.3%)	<0.0001
Loop diuretics	1721 (75.9%)	455 (70.1%)	430 (84.5%)	418 (80.7%)	418 (70.7%)	<0.0001
Antiplatelets	1524 (67.2%)	458 (70.6%)	272 (53.4%)	391 (75.5%)	403 (68.2%)	<0.0001
Eplerenone randomization	1144 (50.2%)	321 (48.9%)	252 (49.2%)	277 (53.3%)	294 (49.7%)	0.45
CVD or HFH	491 (21.5%)	125 (19.1%)	110 (21.5%)	152 (29.2%)	104 (17.6%)	<0.0001
Death	319 (14.0%)	72 (11.0%)	79 (15.4%)	106 (20.4%)	62 (10.5%)	<0.0001
Permanent study drug discontinuation†	319 (14.0%)	78 (11.9%)	47 (9.2%)	106 (20.4%)	88 (14.9%)	<0.0001

(*Continued*)

Table 1. Continued

Variables	Global (n=2279)	A (n=656)	B (n=512)	C (n=520)	D (n=591)	*P* Value
K^+>5.5 mmol/L during follow-up†	138 (12.3%)	37 (11.8%)	19 (7.7%)	41 (15.1%)	41 (14.1%)	0.049
WRF during follow-up‡	36 (3.7%)	13 (4.6%)	4 (1.9%)	12 (5.4%)	7 (2.7%)	0.18
EMPHASIS risk score						<0.0001
Low (0–4)	1098 (49.5%)	375 (59.5%)	284 (56.8%)	37 (7.4%)	402 (68.5%)	
Medium (5–6)	734 (33.1%)	191 (30.3%)	166 (33.2%)	214 (42.8%)	163 (27.8%)	
High (7–12)	385 (17.4%)	64 (10.2%)	50 (10.0%)	249 (49.8%)	22 (3.7%)	

WRF defined as a ≥50% drop in eGFR (using baseline eGFR as reference) during follow-up. ACE indicates angiotensin-converting enzyme; AFib, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular death; eGFR, estimated glomerular filtration rate; EMPHASIS-HF, Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms; Hb, hemoglobin; HFH, heart failure hospitalization; HR, heart rate; LCA, latent class analysis; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; and WRF, worsening renal function.

*Anemia was defined as Hb <12 g/L for women and <13 g/L for men.

†Defined as treatment discontinuation at least 1 mo before the end of follow-up.

‡In patients who underwent eplerenone allocation and excluding baseline value.

Similar pattern was observed for all-cause mortality: HR, 2.31; 95% CI, 1.71–3.12; *P*<0.001 for subgroup C and HR, 1.63; 95% CI, 1.18–2.24; *P*=0.003 for subgroup B (Table 2; Figures 2 and 3).

In the EPHESUS trial, the subgroup C also presented worse prognosis than the subgroup A (HR, 1.17; 95% CI, 1.01–1.35; *P*=0.033 for CVM or HFH), however, differently from EMPHASIS, the subgroup B and D presented better prognoses (HR, 0.81; 95% CI, 0.70–0.94; *P*=0.005 for subgroup B and HR, 0.57; 95% CI, 0.50–0.66; *P*<0.0001 for subgroup D) than subgroup A (Table II and Figures I and II in the Data Supplement).

Permanent Drug Discontinuation and Side Effects

The proportion of patients who permanently discontinued eplerenone while alive was higher in subgroup C (20%), followed in descending order by subgroups D (15%), A (12%), and B (9%). The proportion of patients with hyperkalemia (defined as K^+>5.5 mmol/L in the during follow-up) was also higher in subgroup C (15%) followed in descending order by subgroups D (14%), A (12%), and B (8%) (Table 1).

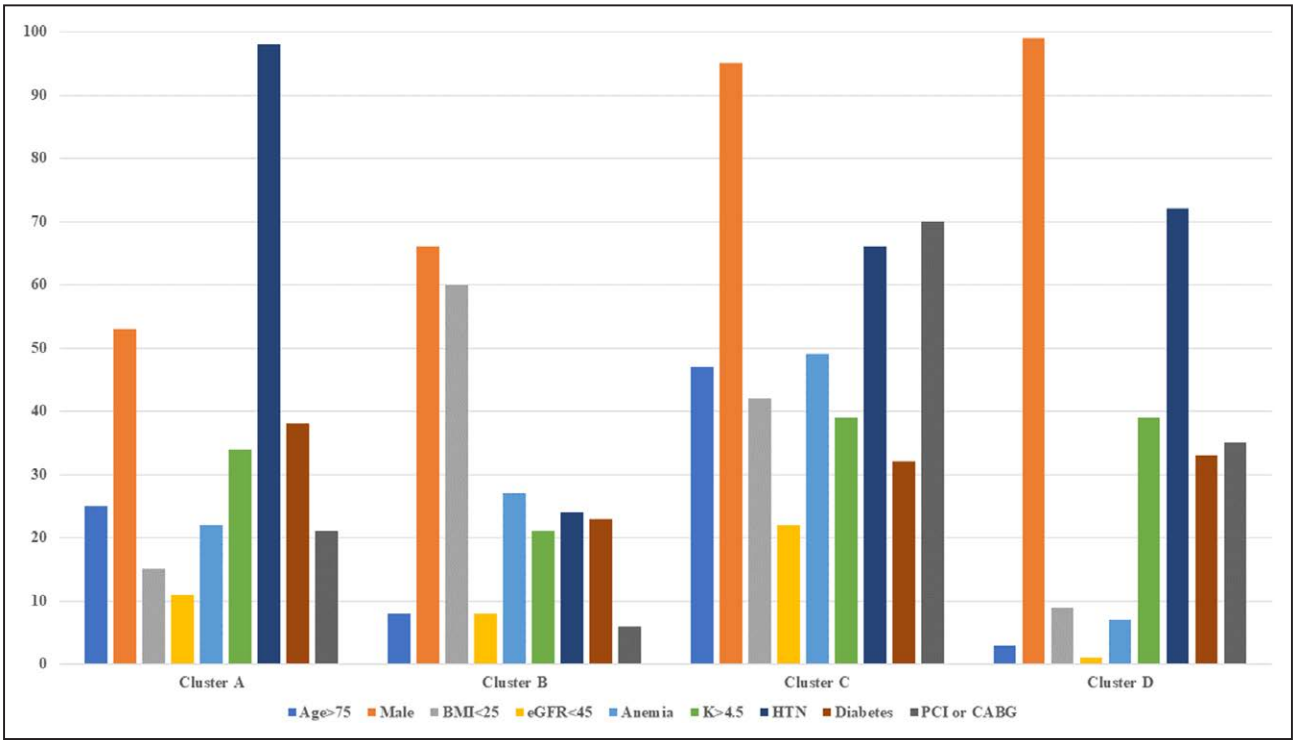

Figure 1. Main clinical characteristics in each cluster (%).
BMI indicates body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HTN, hypertension; K, potassium; PCI, percutaneous coronary intervention.

Table 2. EMPHASIS: Clusters and Respective Prognostic Associations

	HR (95% CI) for CVM or HFH	*P* Value	HR (95% CI) for ACM	*P* Value
Cluster	…	0.002	…	0.003
A	reference	…	reference	…
B	1.27 (0.98–1.64)	0.068	1.63 (1.18–2.24)	0.003
C	1.87 (1.47–2.37)	<0.0001	2.31 (1.71–3.12)	<0.0001
D	0.96 (0.74–1.25)	0.77	1.02 (0.73–1.43)	0.91

Models adjusted on treatment allocation as dummy variable. Cluster, subgroups identified by latent class analysis (see Methods section for details). ACM indicates all-cause mortality; CI, confidence interval; CVM, cardiovascular mortality; EMPHASIS-HF, Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms; HFH, heart failure hospitalization; and HR, hazard ratio.

The subgroup C also had higher proportion of permanent drug discontinuation and hyperkalemia in the EPHESUS trial (Table I in the Data Supplement).

The proportion of patients with worsening renal function defined as a 50% drop in eGFR during follow-up did not differ between subgroups in the EMPHASIS-HF trial (Table 1).

In the EPHESUS trial population, subgroups A (7%) and B (6%) had higher proportion of worsening renal function compared with groups C (5%) and D (4%) (Table I in the Data Supplement).

EMPHASIS-HF Risk Score Distribution

The EMPHASIS-HF risk score[25] was proportionally higher in subgroup C with 50% of patients classified as high risk (score points from 7–12), followed by the subgroups A (10%), B (10%), and D (4%) (Table 1).

Treatment Effect

The primary outcome event-rate reduction attributed to eplerenone treatment might have been higher in subgroups A and D (HR, 0.5; 95% CI, 0.3–0.7; $P \leq 0.001$ in both groups) compared with subgroups B and C where the eplerenone effect was less marked (HR, 0.85; 95% CI, 0.58–1.24; $P=0.39$ in subgroup B and HR, 0.77; 95% CI, 0.56–1.06; $P=0.11$ in subgroup C); P for interaction=0.076. Similar findings were observed for the outcome of all-cause mortality (Table 3; Figure 4).

In the EPHESUS trial, only subgroup D presented a marked eplerenone effect (HR [95%CI] for CVM or HFH =0.63 [0.50-0.78], $P<0.001$) while eplerenone effect was neutral in the other subgroups ($P>0.1$ for all; P for interaction =0.027; Table III in the Data Supplement).

Subgroup Membership and Analyses

The partial probabilities of being allocated to 1 of these 4 subgroups are presented in Table IV in the Data Supplement. Cluster assignment performed well with ≈90% of patients being assigned to a cluster with >50% probability, ≈60% of patients with >70% probability, and ≈30% with >90% probability in both cohorts (Table V in the Data Supplement). The indicators for the selection of the optimal number of clusters in the LCA model is represented in Figure III in the Data Supplement.

A sensitivity analysis including only the subset of patients with >50% and >70% of maximum cluster probability (n=2058; 90.3% of the total study population and n=1472; 65% of the total study population, respectively), showed similar (despite less precise) prognostic associations without tendency for treatment effect differences (likely because of the loss of statistical power; Tables VI and VII in the Data Supplement).

A calculator for application in routine clinical practice, that is, allocation of any real-world HFrEF MRA-treated patient to 1 of these 4 subgroups is available as online calculator in the Data Supplement.

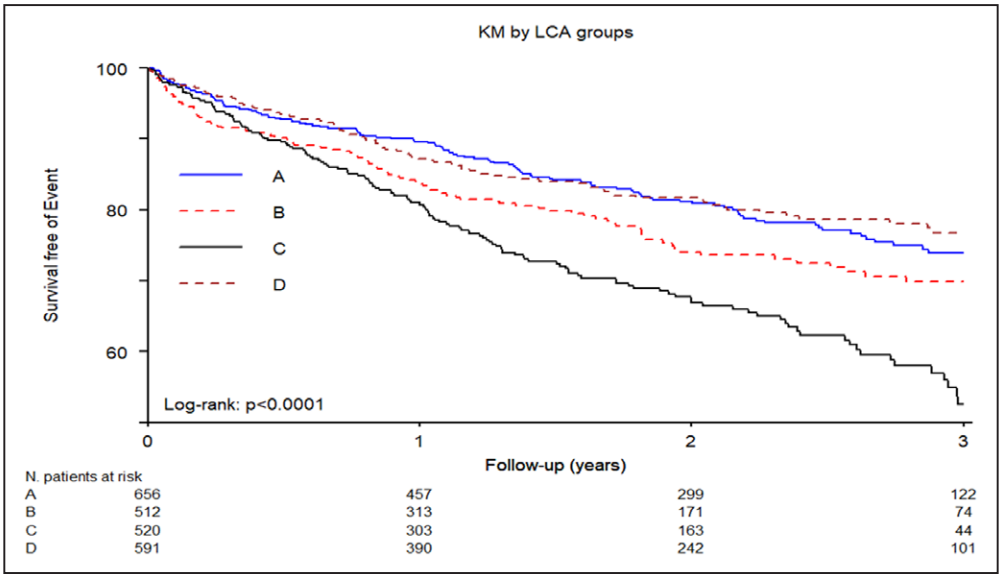

Figure 2. EMPHASIS: Kaplan–Meier (KM) curve for the primary outcome of cardiovascular death or heart failure hospitalization.
EMPHASIS-HF indicates Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms; and LCA, latent class analysis.

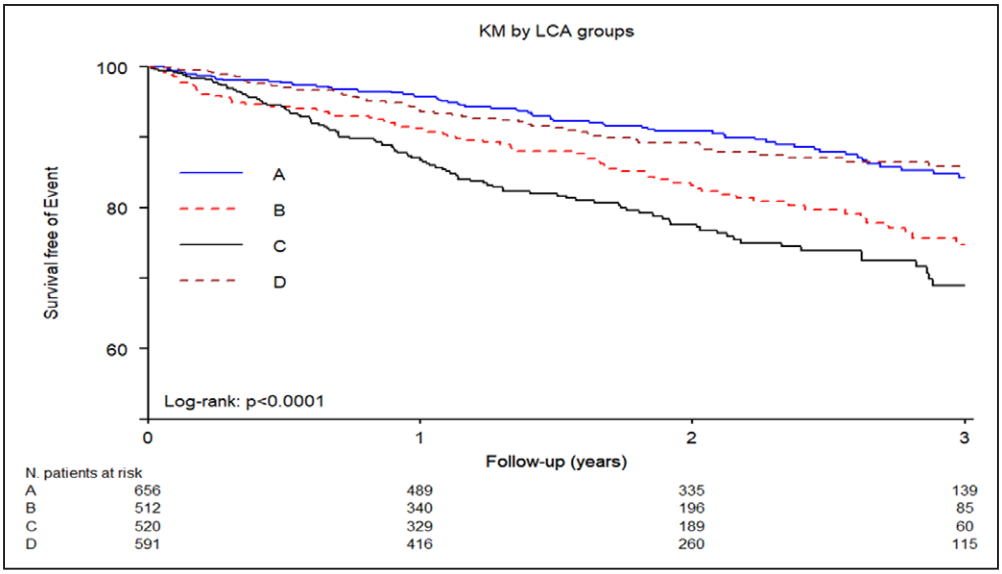

Figure 3. EMPHASIS: Kaplan-Meier (KM) curve for the secondary outcome of death.
EMPHASIS-HF indicates Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms; and LCA, latent class analysis.

DISCUSSION

Based on a data-driven approach using categorical variables easily available in routine clinical practice, our study identified subgroups of HFrEF patients with different clinical characteristics, prognoses, and response to eplerenone treatment. Patients in the subgroup C were older, had often BMI<25 kg/m^2, anemia, eGFR<45 mL/min per 1.73 m^2, previous revascularization and baseline K^+>4.5 mmol/L. Patients in subgroup B also presented high proportion of anemia and BMI<25 kg/m^2 but had lower proportion of patients with eGFR<45 mL/min per 1.73 m^2, previous revascularization and baseline K^+>4.5 mmol/L. Patients in the subgroups A and D were younger, had better renal function, less anemia, and higher BMI. The subgroup C presented the worst prognosis, higher rates of eplerenone discontinuation, and hyperkalemia during follow-up. The eplerenone effect might have been less marked in the subgroups B and C. These findings may help in risk stratification and in tailoring MRA therapy in patients with systolic dysfunction.

Patients with HF often represent a clinical challenge because of their complex comorbidity interplay.[31] Otherwise straightforward decisions, such as initiate an MRA in HFrEF, may encounter several roadblocks, such as impaired renal function, predisposition to develop hyperkalemia, willingness of both the doctor and patient to perform additional laboratory controls and adverse-event surveillance.[17,32] Some patients may be more prone to develop hyperkalemia or renal dysfunction while treated with MRAs, whereas others may benefit less because of characteristics inherent to each patient or because of competing risks (ie, age and comorbidities) that may overshadow the potential MRA benefit.[18] Each individual patient has unique characteristics and treatment decisions depend not only on available evidence but also on the art of all health professionals. During routine clinical practice, the complexity of clinical patterns within each individual patient can make difficult, if not impossible, to predict the treatment response and side-effect pattern after initiating an MRA even for an experienced clinician. However, the majority of clinical research reports look at only one

Table 3. EMPHASIS: Treatment Effect by Cluster Subgroup

Eplerenone Effect on Each Cluster	Eplerenone vs Placebo: HR (95% CI) for CVM or HFH	*P* Value	Eplerenone vs Placebo: HR (95% CI) for ACM	*P* Value
Four Clusters				
A	0.49 (0.34–0.71)	0.0002	0.56 (0.35–0.91)	0.018
B	0.85 (0.58–1.24)	0.39	0.94 (0.60–1.46)	0.77
C	0.77 (0.56–1.06)	0.11	0.94 (0.65–1.38)	0.76
D	0.50 (0.33–0.75)	0.001	0.61 (0.37–1.01)	0.053
Interaction	…	0.076	…	0.22

Cluster, subgroups identified by latent class analysis (see the methods section for details). ACM indicates all-cause mortality; CVM, cardiovascular mortality; EMPHASIS-HF, Eplerenone in Patients With Systolic Heart Failure and Mild Symptoms; HFH, heart failure hospitalization; and HR, hazard ratio.

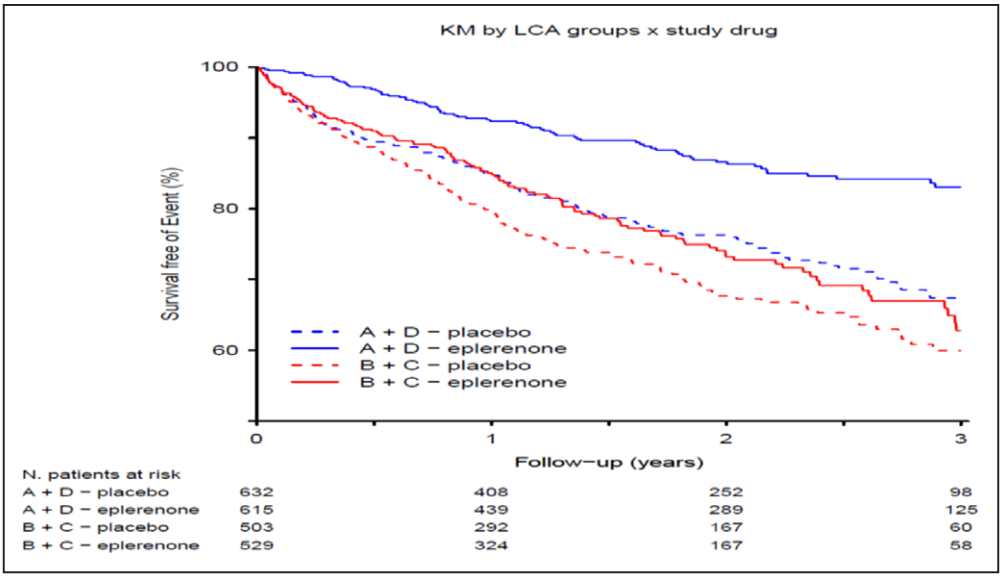

Figure 4. Treatment effect according to clusters for the primary outcome of cardiovascular death or heart failure hospitalization.
LCA indicates latent class analysis; and KM, Kaplan-Meier.

variable at a time (eg, heart rate, blood pressure, sodium, or potassium) trying to find associations between that variable and patients' outcome.[33–35] Likewise, for risk prediction, the model is built based on the variables with stronger association to the studied outcome.[25] On the contrary, the strategy presented here using a data-driven approach to identify prevalent constellations of clinical characteristics to identify mutually exclusive patients' subgroups without any a priori hypothesis, may provide a more close approximation from what is observed in routine clinical practice.[23] In real-life one looks at all the clinical features of the patient independently of their prognostic associations, and as in real-life a considerable overlap in patients' clinical features exists, and this was also reflected in the present analysis, that is, the 4 identified LCA subgroups share many clinical characteristics. The data-driven allocation of each individual patient to 1 of the 4 subgroups allowed the identification of subpopulations with higher event rates, more side effects and possibly lower MRA efficacy, suggesting that LCA may be an integrative, unbiased tool for identifying HFrEF subpopulations with different prognoses and MRA response patterns, leading to novel hypothesis for the evolution of precision medicine in HF and tailored MRA therapy.

Patients in subgroup C had clearly more comorbid conditions (eg, age >75 years, renal impairment, anemia, coronary artery disease, lower BMI, hyperkalemia, diabetes mellitus) that have been associated with worse prognosis in HF, hence is not surprising that patients included in this subgroup had highest event rates.[36–39] Accordingly, individuals in the subgroup C were also more frequently classified as high risk based on the EMPHASIS-HF risk score.[25] However, the concordance between subjects allocated to subgroup C and individuals at high risk based on the EMPHASIS-HF risk score was moderate with 50% of patients within subgroup C being also at high risk based on the score. The other subgroups had low proportion (≤10%) of individuals classified as high risk based on the score. Patients in subgroup B shared with those of subgroup C high proportion of individuals with BMI ≤25 kg/m^2 (60% versus 42%) and, to a lesser extent, anemia (27% versus 49%), but were markedly different about age, renal function, baseline potassium levels, proportion of diabetic, and patients with coronary artery disease (overall better risk profile). Patients in subgroup A were often hypertensive and had anemia proportionally similar to those in subgroup B (22% versus 27%). Patients in subgroup D had similar proportion of baseline K^+>4.5 to those of subgroup C (39% in both).

Patients in subgroup C were those with worse prognosis both in EMPHASIS and EPHESUS trials. Patients in subgroups B and C seemed to obtain a smaller (and A and D a larger) benefit from eplerenone in EMPHASIS-HF. Although the *P* value for interaction was not conventionally statistically significant (*P*=0.076), some authorities argue that a *P* for interaction <0.1 may still indicate a real subgroup-by-treatment interaction.[40] In EPHESUS, only subgroup D presented a pronounced treatment effect but without significant interaction (*P* for interaction=0.22). These findings may allow to provide insight and generate hypothesis on why these patients had worse prognosis and might have responded differently to treatment, allowing the study of potential tailored approaches.

Obesity has been described as protective factor in HFrEF—the so-called obesity paradox.[38] Moreover, among the patients included in the EMPHASIS-HF trial, those with abdominal obesity might have had a better

treatment response.[41,42] These reports support our findings from subgroups B and C that incorporated patients with lower BMI and had worse prognosis and hypothetically lower treatment effect. Another important aspect in the subgroup C was the high proportion of patients with anemia. Anemia is a well-documented detrimental prognostic factor in HF.[37,43–46] Whether anemia itself may influence eplerenone effect has not been documented to date. Nonetheless, patients with anemia have worse HF symptoms, are more often hospitalized and may be more prone to fatal events.[37,43–46] Thus, anemia may be a competing risk for eplerenone efficacy and should warrant a detailed workup as it may be a potential target for treatment and therapy.[46] A low hemoglobin concentration may also be associated with hemodilution and increased congestion. Patients in subgroup C also had high rates of eplerenone discontinuation—1 in each 5 patients from this subgroup permanently discontinued the study drug during follow-up while alive. This may be partly explained by higher rates (15%) of hyperkalemia and lower eGFR in this subgroup. These findings suggest that patients in subgroup C have more adverse clinical characteristics, a higher eplerenone discontinuation rate, a worse prognosis, and, possibly, a lower therapeutic response. These findings suggest that patients with the characteristics of those comprising subgroup C may benefit from closer monitoring, adjustments of treatment dose and may also be a group in which potassium binders might be useful.[47,48]

The partial replication of these findings in an independent cohort of patients with systolic dysfunction and HF after a MI reinforces the external validity of our findings. Patients allocated to subgroup C in the EPHESUS trial also had worse clinical characteristics, prognosis, potentially lower response to eplerenone treatment, higher rates of hyperkalemia, and permanent drug discontinuation.

Clinical and Research Implications

Probabilities of subgroup membership for each clinical variable can be used to classify any HFrEF patient receiving MRA treatment according to the subgroups presented here in a simple and readily accessible fashion; see the online calculator in the Data Supplement. Clinicians may use this tool to assess patients' prognosis and potential treatment response. However, one should notice that all HFrEF patients should receive an MRA unless contraindicated. Notwithstanding, this tool may help identify a subgroup likely to need closer surveillance and tailored treatment options (eg, lower MRA doses, MRA class switch, potassium binders, adjustment of other drugs that may increase serum potassium, and reduce eGFR). Patients with subgroup C characteristics may require particularly close surveillance and specific strategies to decrease discontinuation of eplerenone.

Limitations

Several limitations should be acknowledged in the present article. First, this is a nonprespecified retrospective analysis, hence causality cannot be inferred and these findings should be regarded as hypothesis-generating. Second, EMPHASIS and EPHESUS represent different populations (chronic HFrEF and MI with systolic dysfunction and HF, respectively) with different entry criteria and prognosis. For example, EPHESUS patients may have been submitted to a great number of medications after MI, and those who underwent revascularization may have been exposed to contrast agents that may have had influence on hemoglobin levels, renal function, and hyperkalemia rated reported herein. However, EPHESUS was the only available MRA data set with the required information to replicate these clinical variables (the RALES [Randomized Aldactone Evaluation Study] population[3] was potentially more similar to that represented in EMPHASIS-HF, however, the RALES data set has high proportion of missing values in key variables such as hemoglobin and height to compute BMI is completely absent in the data set). We acknowledge these population differences as a major limitation in our study. Third, the coefficients derived in this analysis assume that the population of interest is similar to EMPHASIS-HF. Profiles of subgroups created in independent populations using these coefficients may differ from those observed in EMPHASIS-HF. For example, in a subanalysis of the BEST trial (Beta-Blocker Evaluation of Survival), the authors incorporated different latent class variables and the former clusters differed from those found herein.[24] Fourth, subgroups identified by LCA represent statistical associations of variables and not necessarily pathophysiologic associations. Incorporating additional clinical, biomarker, and echocardiographic data will likely provide different phenotype definitions. Fifth, the variables included in the LCA were selected based on their availability in both data sets and routine clinical practice. We acknowledge that potentially relevant variables (such as natriuretic peptides) were missing (>80%) in the data sets. The addition of such variables could improve cluster separation. Furthermore, a need for harmonization in the variables to use in future cluster analysis should be discussed, to avoid discrepancies in the subgroup selection in different populations. Last, many clustering methods have been used[19–22] in different patient populations, using different variables, treatments and consequently finding different subgroups. Discussing the nuances of these methods is beyond the scope of this article. However, we feel that using categorical variables available in routine clinical practice (as require for LCA computation) may be more clinically relevant than using continuous scaled variables used for other clustering methods (eg, hierarchical clustering), as categorical variables are used for gender and most comorbidities and most continuous variables (such

as age, BMI, or eGFR) may be categorized based on clinical criteria/international recommendations making their clinical assessment easy for the clinician.

Conclusions

Using a data-driven approach, we identified HFrEF subgroups with significantly different prognoses, adverse-event profiles, and responses to eplerenone. The assignment of each individual patient to 1 of these 4 clusters may be performed in routine practice using our online calculator. However, these data should be regarded as hypothesis-generating and prospective validation is warranted to assess the potential clinical implications of these subgroups.

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Data-Driven Approach to Identify Subgroups of Heart Failure With Reduced Ejection Fraction Patients With Different Prognoses and Aldosterone Antagonist Response Patterns

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SUPPLEMENTAL MATERIAL

Supplemental Table 1. Baseline characteristics of the EPHESUS population according to "clusters"

Variables	Global (n=6472)	A (n=1589)	B (n=1572)	C (n=1166)	D (n=2145)	p-value
LCA variables						
Age ≤65	3408 (52.7 %)	507 (31.9 %)	954 (60.7 %)	207 (17.8 %)	1740 (81.1 %)	<0.0001
66-75	1962 (30.3 %)	669 (42.1 %)	446 (28.4 %)	476 (40.8 %)	371 (17.3 %)	
>75 yr	1102 (17.0 %)	413 (26.0 %)	172 (10.9 %)	483 (41.4 %)	34 (1.6 %)	
Male	4598 (71.0 %)	491 (30.9 %)	1003 (63.8 %)	1019 (87.4 %)	2085 (97.2 %)	<0.0001
SBP ≤120	4164 (64.3 %)	666 (41.9 %)	1318 (83.8 %)	856 (73.4 %)	1324 (61.7 %)	<0.0001
121-130	1131 (17.5 %)	392 (24.7 %)	147 (9.4 %)	153 (13.1 %)	439 (20.5 %)	
>130 mmHg	1177 (18.2 %)	531 (33.4 %)	107 (6.8 %)	157 (13.5 %)	382 (17.8 %)	
HR ≤65	1442 (22.3 %)	288 (18.1 %)	221 (14.1 %)	408 (35.0 %)	525 (24.5 %)	<0.0001
66-75	2135 (33.0 %)	547 (34.4 %)	493 (31.4 %)	395 (33.9 %)	700 (32.6 %)	
>75 bpm	2895 (44.7 %)	754 (47.5 %)	858 (54.6 %)	363 (31.1 %)	920 (42.9 %)	
BMI ≤25	2023 (31.3 %)	323 (20.3 %)	921 (58.6 %)	497 (42.6 %)	282 (13.1 %)	<0.0001
26-30	2906 (44.9 %)	668 (42.0 %)	458 (29.1 %)	564 (48.4 %)	1216 (56.7 %)	
>30 Kg/m^2	1543 (23.8 %)	598 (37.6 %)	193 (12.3 %)	105 (9.0 %)	647 (30.2 %)	
LVEF ≥25%	5530 (85.4 %)	1452 (91.4 %)	1223 (77.8 %)	946 (81.1 %)	1909 (89.0 %)	<0.0001
eGFR ≤45	902 (13.9 %)	361 (22.7 %)	150 (9.5 %)	376 (32.2 %)	15 (0.7 %)	<0.0001
46-60	1493 (23.1 %)	497 (31.3 %)	312 (19.8 %)	433 (37.1 %)	251 (11.7 %)	
>60 ml/min/1.73m^2	4077 (63.0 %)	731 (46.0 %)	1110 (70.6 %)	357 (30.6 %)	1879 (87.6 %)	
Hb <12/13 g/dL	2133 (33.0 %)	492 (31.0 %)	617 (39.2 %)	714 (61.2 %)	310 (14.5 %)	<0.0001
K^+ ≤4.0	1948 (30.1 %)	490 (30.8 %)	574 (36.5 %)	301 (25.8 %)	583 (27.2 %)	<0.0001
4.1-4.5	2652 (41.0 %)	606 (38.1 %)	664 (42.2 %)	490 (42.0 %)	892 (41.6 %)	
>4.5 mmol/L	1872 (28.9 %)	493 (31.0 %)	334 (21.2 %)	375 (32.2 %)	670 (31.2 %)	
Na^+ ≤135	946 (14.6 %)	195 (12.3 %)	384 (24.4 %)	147 (12.6 %)	220 (10.3 %)	<0.0001
136-145	5117 (79.1 %)	1225 (77.1 %)	1132 (72.0 %)	974 (83.5 %)	1786 (83.3 %)	
>145 mmol/L	409 (6.3 %)	169 (10.6 %)	56 (3.6 %)	45 (3.9 %)	139 (6.5 %)	
Hypertension	3906 (60.4 %)	1538 (96.8 %)	336 (21.4 %)	691 (59.3 %)	1341 (62.5 %)	<0.0001
Diabetes mellitus	2078 (32.1 %)	702 (44.2 %)	394 (25.1 %)	348 (29.8 %)	634 (29.6 %)	<0.0001
Never smoker	2523 (39.0 %)	1453 (91.4 %)	587 (37.3 %)	344 (29.5 %)	139 (6.5 %)	<0.0001
Past smoker	2004 (31.0 %)	71 (4.5 %)	499 (31.7 %)	348 (29.8 %)	1086 (50.6 %)	
Current smoker	1945 (30.1 %)	65 (4.1 %)	486 (30.9 %)	474 (40.7 %)	920 (42.9 %)	
COPD	604 (9.3 %)	81 (5.1 %)	134 (8.5 %)	161 (13.8 %)	228 (10.6 %)	<0.0001
AFib	849 (13.1 %)	288 (18.1 %)	147 (9.4 %)	213 (18.3 %)	201 (9.4 %)	<0.0001
Stroke	569 (8.8 %)	201 (12.6 %)	99 (6.3 %)	167 (14.3 %)	102 (4.8 %)	<0.0001
Angina pectoris	2672 (41.3 %)	911 (57.3 %)	226 (14.4 %)	654 (56.1 %)	881 (41.1 %)	<0.0001
PCI or CABG	2934 (45.3 %)	443 (27.9 %)	504 (32.1 %)	725 (62.2 %)	1262 (58.8 %)	<0.0001
Non-LCA variables						
ACEi/ARBs	5612 (86.7 %)	1399 (88.0 %)	1308 (83.2 %)	1019 (87.4 %)	1886 (87.9 %)	<0.0001
Beta-Blockers	4848 (74.9 %)	1160 (73.0 %)	1129 (71.8 %)	838 (71.9 %)	1721 (80.2 %)	<0.0001
Digoxin	970 (15.0 %)	241 (15.2 %)	263 (16.7 %)	220 (18.9 %)	246 (11.5 %)	<0.0001
Loop Diuretics	3552 (54.9 %)	959 (60.4 %)	892 (56.7 %)	749 (64.2 %)	952 (44.4 %)	<0.0001
Anti-Platelets	1861 (28.8 %)	289 (18.2 %)	393 (25.0 %)	402 (34.5 %)	777 (36.2 %)	<0.0001
Eplerenone rando.	3243 (50.1 %)	794 (50.0 %)	797 (50.7 %)	603 (51.7 %)	1049 (48.9 %)	0.44

CVD or HFH	1392 (21.5 %)	402 (25.3 %)	325 (20.7 %)	334 (28.6 %)	331 (15.4 %)	<0.0001
Death	989 (15.3 %)	277 (17.4 %)	260 (16.5 %)	239 (20.5 %)	213 (9.9 %)	<0.0001
Permanent study drug discontinuation*	892 (13.8 %)	209 (13.2 %)	209 (13.3 %)	209 (17.9 %)	265 (12.4 %)	<0.0001
K^+>5.5 mmol/L during follow-up**	506 (15.8 %)	144 (18.3 %)	100 (12.8 %)	129 (21.6 %)	133 (12.0 %)	<0.0001
WRF during follow-up**	159 (5.2 %)	49 (6.5 %)	48 (6.4 %)	26 (4.6 %)	36 (3.6%)	0.013

*defined as treatment discontinuation at least 1 month before the end of follow-up
**in patients who underwent eplerenone allocation and excluding baseline value
WRF defined as a ≥50% drop in eGFR (using baseline eGFR as reference) during follow-up
Legend: SBP, systolic blood pressure; HR, heart rate; BMI, body mass index; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; COPD, chronic obstructive pulmonary disease; AFib, atrial fibrillation; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CVD, cardiovascular death; HFH, heart failure hospitalization.

Supplemental Table 2. EPHESUS “clusters” and respective prognostic associations

	HR (95%CI) for CVM or HFH	p-value	HR (95%CI) for ACM	p-value
Cluster	-	0.008	-	0.009
A	reference	-	reference	-
B	0.81 (0.70-0.94)	0.005	0.95 (0.80-1.13)	0.55
C	1.17 (1.01-1.35)	0.033	1.20 (1.01-1.42)	0.041
D	0.57 (0.50-0.66)	<0.0001	0.54 (0.45-0.65)	<0.0001

Models adjusted on treatment allocation as “dummy variable”.

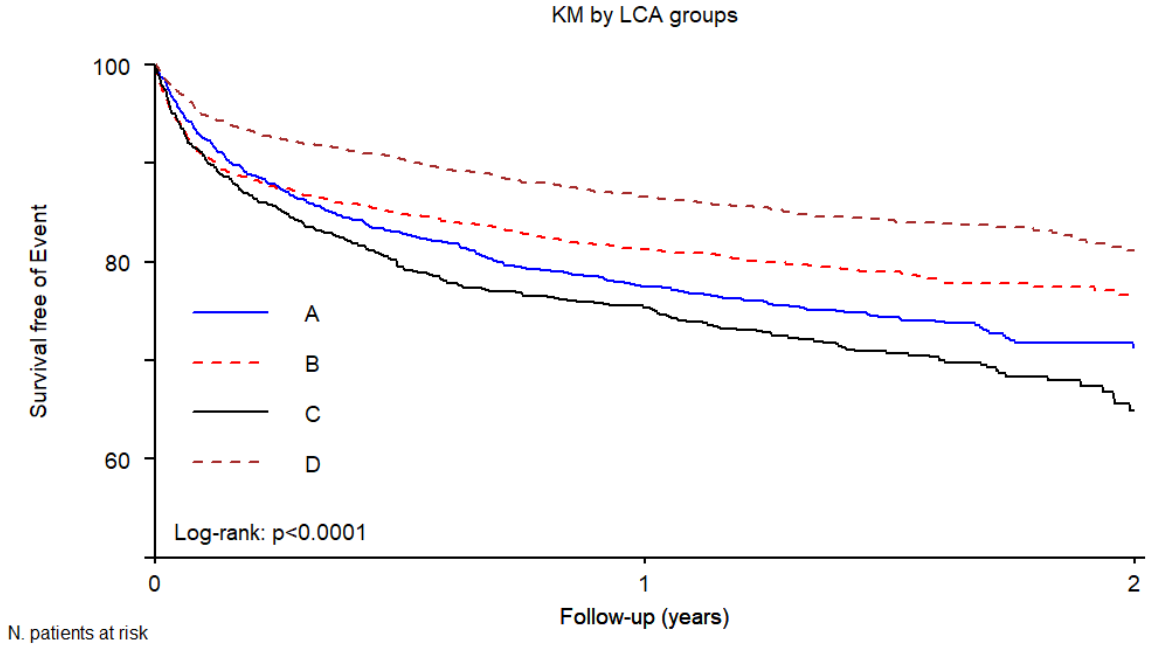
Legend: HR, hazard ratio; CVM, cardiovascular mortality; HFH, heart failure hospitalization; ACM, all-cause mortality; Cluster, subgroups identified by latent class analysis (please see the methods section for details).

Supplemental Table 3. EPHESUS: treatment effect by “cluster” subgroup

Eplerenone effect on each cluster	Eplerenone vs. Placebo: HR (95%CI) for CVM or HFH	P-value	Eplerenone vs. Placebo: HR (95%CI) for ACM	p-value
4-clusters				
A	0.86 (0.71-1.05)	0.13	0.77 (0.61-0.98)	0.033
B	0.99 (0.79-1.23)	0.90	1.06 (0.83-1.35)	0.66
C	0.90 (0.73-1.11)	0.33	0.89 (0.69-1.15)	0.37
D	0.63 (0.50-0.78)	<0.0001	0.65 (0.50-0.86)	0.002
Interaction	-	0.027	-	0.062

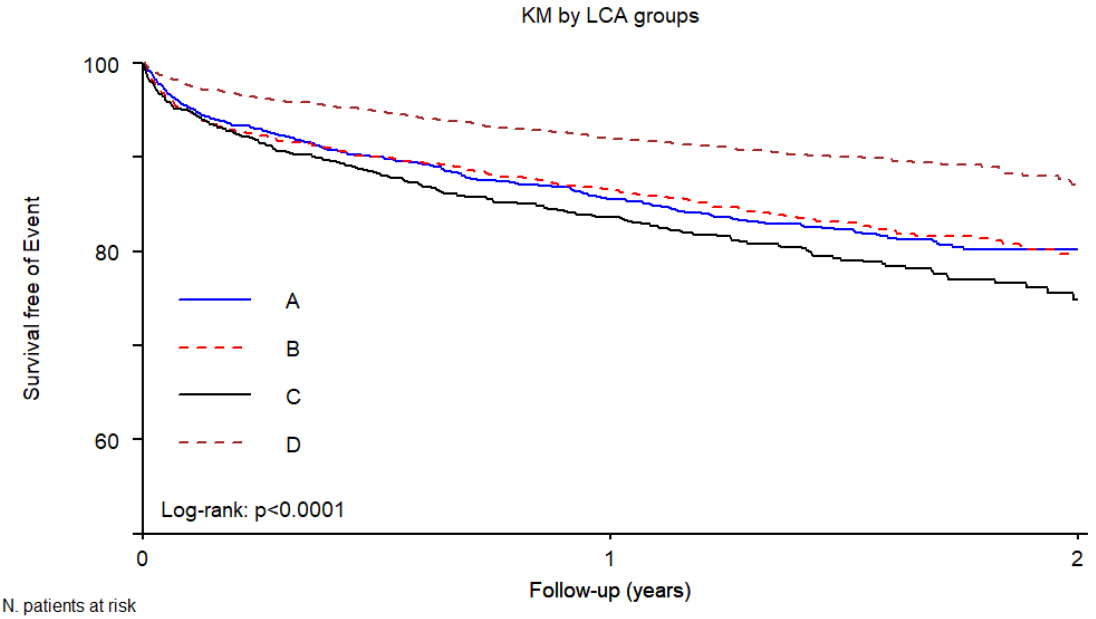
Legend: HR, hazard ratio; CVM, cardiovascular mortality; HFH, heart failure hospitalization; ACM, all-cause mortality; Cluster, subgroups identified by latent class analysis (please see the methods section for details).

Supplemental Figure 1. EPHESUS: KM curve for the primary outcome of CVD or HFH



N. patients at risk			
A	1589	1008	130
B	1572	1053	156
C	1166	714	91
D	2145	1570	208

Supplemental Figure 2. EPHESUS: KM curve for the outcome of death



N. patients at risk			
A	1589	1128	147
B	1572	1146	164
C	1166	819	109
D	2145	1685	240

Supplemental Table 4. EMPHASIS-HF: partial probabilities of group membership

Subgroup membership probabilities	A	B	C	D
LCA variables and respective coding rank				
Age ≤65 (=1)	0.2613451	0.51300065	0.1199357	0.58360749
66-75 (=2)	0.4821775	0.39568206	0.4573407	0.36909334
>75 yr (=3)	0.2564774	0.09131728	0.4227236	0.04729917
Male (=2)	0.5416788	0.6634589	0.92524485	0.97274864
SBP ≤120 (=1)	0.2475716	0.6730646	0.6008262	0.3864782
121-130 (=2)	0.3060049	0.1734854	0.1918381	0.2682449
>130 mmHg (=3)	0.4464235	0.1534500	0.2073357	0.3452768
HR ≤65 (=1)	0.3103507	0.2176058	0.4457511	0.3312980
66-75 (=2)	0.3170126	0.3842764	0.3424503	0.3218881
>75 bpm (=3)	0.3726368	0.3981179	0.2117986	0.3468139
BMI ≤25 (=1)	0.1535111	0.5561475	0.4001056	0.1277802
26-30 (=2)	0.4304856	0.2851777	0.4660217	0.5248322
>30 Kg/m^2 (=3)	0.4160033	0.1586747	0.1338727	0.3473876
LVEF ≥25% (=2)	0.7131139	0.4207964	0.5810081	0.627651
eGFR ≤45 (=1)	0.1099545	0.08985947	0.2040777	0.008569909
46-60 (=2)	0.2535555	0.18619746	0.3536022	0.126905865
>60 ml/min/1.73m^2 (=3)	0.6364900	0.72394307	0.4423201	0.864524226
Hb <12/13 g/dL (=2)	0.233694	0.2758026	0.4375189	0.08707852
K^+ ≤4.0 (=1)	0.2336549	0.3470771	0.2036496	0.2092371
4.1-4.5 (=2)	0.4210071	0.4395151	0.4082729	0.4125486
>4.5 mmol/L (=3)	0.3453379	0.2134078	0.3880775	0.3782143
Na^+ ≤135 (=1)	0.07982246	0.18286860	0.06288182	0.05840385
136-145 (=2)	0.81652969	0.78832449	0.88928120	0.86817247
>145 mmol/L (=3)	0.10364784	0.02880691	0.04783698	0.07342369
Hypertension (=2)	0.95782212	0.291259	0.6677948	0.7198585
Diabetes mellitus (=2)	0.3704646	0.2414213	0.3200791	0.325074
Never smoker (=1)	0.85020850	0.5025730	0.29594510	0.1413273
Past smoker (=2)	0.13663803	0.3358644	0.63947979	0.6611485
Current smoker (=3)	0.01315347	0.1615626	0.06457511	0.1975241
COPD (=2)	0.06937354	0.1322352	0.1555271	0.2053263
AFib (=2)	0.3519607	0.2441655	0.3444749	0.3095015
Stroke (=2)	0.1375413	0.06803143	0.1323315	0.04773665
Angina pectoris (=2)	0.5964257	0.1104264	0.59113	0.495141
PCI or CABG (=2)	0.2172403	0.08130754	0.6400417	0.3557468

Calculator Example:

The likelihood membership of an individual in each of the 4 subgroups is then calculated in a Bayesian fashion:

Using a hypothetical patient:
Age = 65 → Age rank = 1 → Subgroup A likelihood = 0.261
Gender = Male → Gender rank = 2 → Subgroup A likelihood = 0.542
SBP = 125 → SBP rank = 2 → Subgroup A likelihood = 0.306
HR = 80 → HR rank = 3 → Subgroup A likelihood = 0.373
BMI = 30 → BMI rank = 2 → Subgroup A likelihood = 0.430
LVEF = 35 → LVEF rank = 2 → Subgroup A likelihood = 0.713
eGFR = 30 → eGFR rank =1 → Subgroup A likelihood = 0.110
Hb = 10 → Anemia rank = 2 → Subgroup A likelihood = 0.234
K^+ = 5 → K^+ rank = 3 → Subgroup A likelihood = 0.345
Na^+ = 140 → Na^+ rank = 2 → Subgroup A likelihood = 0.817
Hypertension = Yes → Hypertension rank = 2 → Subgroup A likelihood = 0.958
Diabetes = No → Diabetes rank = 1 → Subgroup A likelihood = 1-0.370 = 0.630
Smoker = Past → Smoker rank = 2 → Subgroup A likelihood = 0.137
COPD = No → COPD rank = 1 → Subgroup A likelihood = 1-0.069 = 0.931
AFib = Yes → AFib rank = 2 → Subgroup A likelihood = 0.352
Stroke = No → Stroke rank = 1 → Subgroup A likelihood = 1-0.138 = 0.862
Angina pectoris = Yes → Angina rank = 2 → Subgroup A likelihood = 0.596
PCI/CABG = Yes → PCI/CABG rank = 2 → Subgroup A likelihood = 0.217

Likelihood of being Subgroup A =
0.261*0.542*0.306*0.373*0.430*0.713*0.110*0.234*0.345*0.817*0.958*0.630*0.137*0.931*0.352*0.862*0.596*0.217 = 1.084951e-07
Likelihood of being Subgroup B (same variable order) =
0.513*0.663*0.173*0.398*0.285*0.421*0.090*0.275*0.213*0.788*0.291*0.759*0.336*0.868*0.244*0.932*0.110*0.081 = 1.52351e-09
Likelihood of being Subgroup C (same variable order) =
0.120*0.925*0.192*0.212*0.466*0.581*0.204*0.437*0.388*0.889*0.668*0.680*0.639*0.844*0.344*0.868*0.591*0.640 = 1.040738e-06
Likelihood of being Subgroup D (same variable order) =
0.583*0.973*0.268*0.347*0.525*0.628*0.009*0.087*0.378*0.868*0.720*0.675*0.661*0.795*0.310*0.952*0.495*0.356 = 5.93467e-08

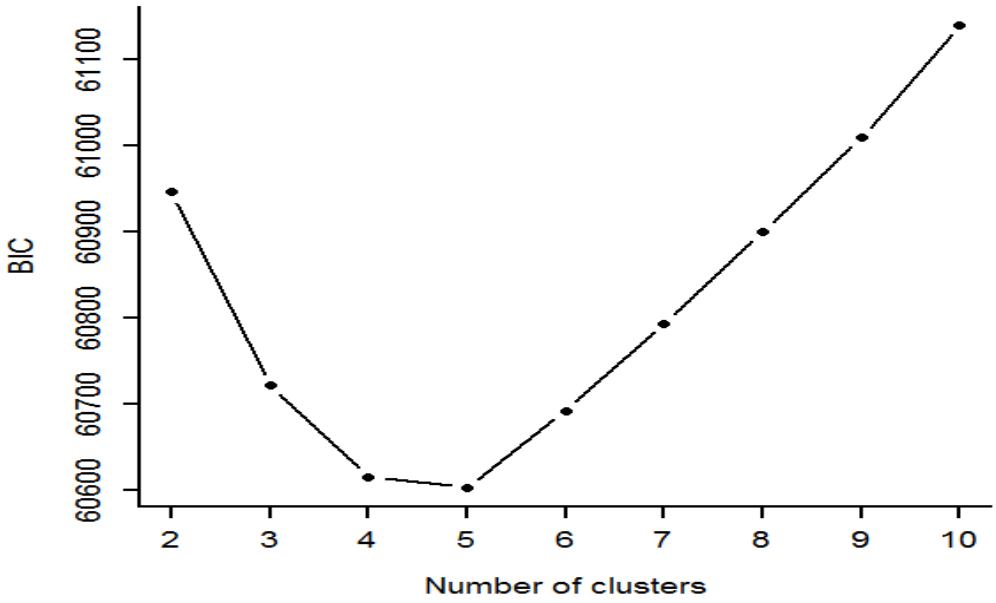
Sum of partial probabilities:
1.084951e-07 + 1.52351e-09 + 1.040738e-06 + 5.93467e-08 = 1.210103e-06

Final probability of subgroup membership:
Subgroup A: 1.084951e-07/1.210103e-06 = 0.089
Subgroup B: 1.52351e-09/1.210103e-06 = 0.001
Subgroup C: 1.040738e-06/1.210103e-06 = **0.860 → Classified as Subgroup C**
Subgroup D: 5.93467e-08/1.210103e-06= 0.049

Supplemental Table 5. Maximum cluster probability

EMPHASIS-HF					
	Overall (n=2279)	**Cluster A (n=656)**	**Cluster B (n=512)**	**Cluster C (n=520)**	**Cluster D (n=591)**
Maximum cluster probability	79.1 (62.2-92.5)	80.1 (62.3-93.4)	80.1 (62.7-95.3)	79.3 (60.9-92.5)	77.4 (62.9-90.0)
Maximum cluster probability >90%	708 (31.1%)	218 (33.2%)	185 (36.1%)	158 (30.4%)	147 (24.9%)
Maximum cluster probability >70%	1472 (64.6%)	435 (66.3%)	327 (63.9%)	321 (61.7%)	389 (65.8%)
Maximum cluster probability >50%	2058 (90.3%)	600 (91.5%)	468 (91.4%)	470 (90.4%)	520 (88.0%)
EPHESUS					
	Overall (n=6472)	**Cluster A (n=1589)**	**Cluster B (n=1572)**	**Cluster C (n=1166)**	**Cluster D (n=2145)**
Maximum cluster probability	76.5 (59.0-90.7)	82.9 (64.1-95.6)	73.6 (57.6-89.4)	69.1 (54.3-85.7)	77.4 (60.5-89.7)
Maximum cluster probability >90%	1724 (26.6%)	629 (39.6%)	374 (23.8%)	197 (16.9%)	524 (24.4%)
Maximum cluster probability >70%	3864 (59.7%)	1088 (68.5%)	875 (55.7%)	563 (48.3%)	1338 (62.4%)
Maximum cluster probability >50%	5716 (88.3%)	1453 (91.4%)	1357 (86.3%)	976 (83.7%)	1930 (90.0%)

Supplemental Figure 3. Indicators for the number of clusters in LCA model



The "elbow" of the BIC is on 4 or 5 clusters, and several other methods pointed to 4/5 clusters as the optimal number of clusters (see table).

Number of clusters	Degree of freedom	G^2	AIC	CAIC	BIC	BIC_{adj}
2	53	25356.98	60642.12	60998.89	60945.89	60777.50
3	80	24923.38	60262.53	60801.05	60721.05	60466.87
4	107	24608.56	60001.70	60721.97	60614.97	60275.01
5	134	24387.14	59834.28	60736.30	60602.30	60176.56
6	161	24267.34	59768.49	60852.26	60691.26	60179.73
7	188	24160.61	59715.76	60981.28	60793.28	60195.97
8	215	24058.06	59667.20	61114.47	60899.47	60216.38
9	242	23959.21	59622.35	61251.37	61009.37	60240.49
10	269	23881.13	59598.27	61409.05	61140.05	60285.39

We set a condition to the percentage of patients in each cluster to be at least 10% of the total of patients providing an optimal number of clusters =4 (if we had chosen 5 clusters, one of these would *have only 7% of patients).*

Supplemental Table 6. EMPHASIS: “clusters” and respective prognostic associations in subgroup of patients with maximum cluster probability >50% or >70%

			CVM or HFH		ACM	
			HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
In subgroup of patients with maximum cluster probability > 50% (n=2058)	Cluster		-	<0.0001	-	<0.0001
		A	reference	-	reference	-
		B	1.36 (1.04 - 1.78)	0.023	1.79 (1.28 - 2.50)	0.0007
		C	2.01 (1.57 - 2.57)	<0.0001	2.49 (1.81 - 3.42)	<0.0001
		D	0.99 (0.75 - 1.31)	0.94	1.08 (0.75 - 1.56)	0.66
In subgroup of patients with maximum cluster probability > 70% (n=1472)	Cluster		-	<0.0001	-	<0.0001
		A	reference	-	reference	-
		B	1.63 (1.19 - 2.22)	0.002	2.31 (1.54 - 3.47)	<0.0001
		C	2.07 (1.53 - 2.79)	<0.0001	3.04 (2.06 - 4.49)	<0.0001
		D	1.01 (0.73 - 1.40)	0.94	1.28 (0.83 - 1.98)	0.27

Models adjusted on treatment allocation as “dummy variable”.

Legend: HR, hazard ratio; CVM, cardiovascular mortality; HFH, heart failure hospitalization; ACM, all-cause mortality; Cluster, subgroups identified by latent class analysis (please see the methods section for details).

Supplemental Table 7. EMPHASIS: treatment effect by "cluster" subgroup in subgroup of patients with maximum cluster probability >50% or >70%

		CVM or HFH		ACM	
		HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
In subgroup of patients with maximum cluster probability > 50% (n=2058)	Eplerenone effect in cluster				
	A	0.46 (0.31 - 0.68)	0.0001	0.57 (0.34 - 0.95)	0.031
	B	0.81 (0.55 - 1.19)	0.27	0.98 (0.62 - 1.54)	0.93
	C	0.72 (0.52 - 1.00)	0.053	0.87 (0.58 - 1.29)	0.49
	D	0.50 (0.33 - 0.77)	0.002	0.68 (0.39 - 1.16)	0.16
		p-value for interaction = 0.13		p-value for interaction = 0.40	
In subgroup of patients with maximum cluster probability > 70% (n=1472)	Eplerenone effect in cluster				
	A	0.47 (0.29 - 0.75)	0.001	0.56 (0.30 - 1.07)	0.080
	B	0.76 (0.49 - 1.19)	0.23	0.78 (0.46 - 1.33)	0.36
	C	0.51 (0.33 - 0.77)	0.001	0.61 (0.38 - 0.99)	0.046
	D	0.50 (0.30 - 0.83)	0.007	0.62 (0.33 - 1.16)	0.14
		p-value for interaction = 0.42		p-value for interaction = 0.87	

Legend: HR, hazard ratio; CVM, cardiovascular mortality; HFH, heart failure hospitalization; ACM, all-cause mortality; Cluster, subgroups identified by latent class analysis (please see the methods section for details).