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ORIGINAL INVESTIGATIONS

Clinical Implications of Chronic Heart Failure Phenotypes Defined by Cluster Analysis

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ABSTRACT

BACKGROUND Classification of chronic heart failure (HF) is on the basis of criteria that may not adequately capture disease heterogeneity. Improved phenotyping may help inform research and therapeutic strategies.

OBJECTIVES This study used cluster analysis to explore clinical phenotypes in chronic HF patients.

METHODS A cluster analysis was performed on 45 baseline clinical variables from 1,619 participants in the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study, which evaluated exercise training versus usual care in chronic systolic HF. An association between identified clusters and clinical outcomes was assessed using Cox proportional hazards modeling. Differential associations between clinical outcomes and exercise testing were examined using interaction testing.

RESULTS Four clusters were identified (ranging from 248 to 773 patients in each), in which patients varied considerably among measures of age, sex, race, symptoms, comorbidities, HF etiology, socioeconomic status, quality of life, cardiopulmonary exercise testing parameters, and biomarker levels. Differential associations were observed for hospitalization and mortality risks between and within clusters. Compared with cluster 1, risk of all-cause mortality and/or all-cause hospitalization ranged from 0.65 (95% confidence interval [95% CI]: 0.54 to 0.78) for cluster 4 to 1.02 (95% CI: 0.87 to 1.19) for cluster 3. However, for all-cause mortality, cluster 3 had a disproportionately lower risk of 0.61 (95% CI: 0.44 to 0.86). Evidence suggested differential effects of exercise treatment on changes in peak oxygen consumption and clinical outcomes between clusters (p for interaction <0.04).

CONCLUSIONS Cluster analysis of clinical variables identified 4 distinct phenotypes of chronic HF. Our findings underscore the high degree of disease heterogeneity that exists within chronic HF patients and the need for improved phenotyping of the syndrome. (Exercise Training Program to Improve Clinical Outcomes in Individuals With Congestive Heart Failure; NCT00047437) (J Am Coll Cardiol 2014;64:1765–74) © 2014 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

AF = atrial fibrillation

COPD = chronic obstructive pulmonary disease

CPET = cardiopulmonary exercise testing

CRT = cardiac resynchronization therapy

CV = cardiovascular

HF = heart failure

ICD = implantable cardioverter-defibrillators

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

NYHA = New York Heart Association

QOL = quality of life

VO_2 = oxygen consumption

Chronic heart failure (HF) is a syndrome rather than a specific disease, with several subtypes that may respond uniquely to therapeutic interventions (1). However, despite advances in our understanding of HF pathogenesis, its classification continues to rely on imprecise measures that may lead to overlapping diagnostic labels and misclassification (2,3). For example, chronic HF is still clinically defined along subjective measures of functional status (New York Heart Association [NYHA] functional class), arbitrary left ventricular ejection fraction (LVEF) cutpoints (HF with preserved vs. reduced EF), or stages (A to D), despite the increasing recognition that these constructs provide inadequate phenotyping of the syndrome (4–6).

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Inadequately classifying patients within a disease state like HF may produce several potentially important consequences. Because therapeutic interventions are frequently based on targeting certain patient subgroups, it may lead to ineffective or inappropriate treatments. In fact, the shortcomings in contemporary HF classification have been posited as a possible explanation for why we have seen such little progress in developing new treatments for this disorder (7,8). Improving the "taxonomy" of clinical classification may therefore offer important clinical benefits. Although molecular phenotyping can theoretically provide more rational disease descriptions, an essential first step is to identify disease subtypes on the basis of key clinical variables, such that downstream biological measurements can be appropriately anchored in patient-level data. To address these issues, the National Research Council has released a report that calls for a new taxonomy of disease on the basis of both clinical and molecular measures that will provide a more accurate classification of disease, with the ultimate goal of enhancing diagnosis and treatment (9).

A widely used exploratory and hypothesis-generating approach in biological studies, called clustering, can play a role in identifying subtypes in complex diseases. This approach has been extensively used in analyzing molecular data across disease states, but it has seldom been used to examine clinical variables. However, several reports have suggested that clustering can lead to improved characterization of the disease phenotype (10,11). Accordingly, we applied cluster analysis to examine the presence of clinically important patient subgroups within a well-characterized cohort of chronic systolic HF patients who were randomized to exercise training versus usual care. We also examined patterns of adverse clinical outcomes among derived patient clusters and interaction with randomized treatment assignment.

METHODS

STUDY POPULATION. Details of the design, rationale, and primary results of the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study have been published elsewhere (12,13). Briefly, HF-ACTION (NCT00047437) was a randomized clinical trial that evaluated the effect of exercise training versus usual care on long-term morbidity and mortality in 2,331 patients with chronic HF due to LV systolic dysfunction (NYHA functional classes II to IV, LVEF ≤35%). Patients were randomized to either usual HF care or a structured, group-based, supervised exercise program. All patients, regardless of treatment group, received detailed self-management educational materials that included information on medications, fluid management, symptom exacerbation, sodium intake, and amount of activity recommended by American College of Cardiology/American Heart Association guidelines (14). Patients were followed for a median of 2.6 years.

ASSESSMENT OF CLINICAL VARIABLES AND BIOMARKERS. At the baseline clinic visit before randomization, demographic characteristics, socioeconomic status, medical history, current medications, a physical examination, and the most recent laboratory tests were obtained. Participants reported race and ethnicity at the time of study enrollment using categories defined by the National Institutes of Health. All patients underwent baseline and 3-month cardiopulmonary exercise testing (CPET), during which key exercise parameters were ascertained. In addition, a standard 6-min walk test (6MWD) was performed in each patient during the baseline visit. Transthoracic echocardiography (TTE) was performed at baseline, and key measures were acquired by the

and Novartis. All other authors have reported that they have no relationships relevant to this paper to disclose.
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core laboratory, including LVEF and mitral regurgitation assessment. Health status measures were ascertained using several validated psychometric instruments at baseline to measure health-related quality of life (QOL), pain, depression, and social support, including the Kansas City Cardiomyopathy Questionnaire, and the Multidimensional Scale of Perceived Social Support (15). Baseline biomarker levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), ST2, and galectin-3 were evaluated in a subset of patients who agreed to participate in the biomarker substudy, using previously described methodologies (16,17).

CLINICAL ENDPOINTS. The primary endpoint of HF-ACTION was a composite of all-cause mortality and all-cause hospitalization over a median follow-up of 2.6 years. Additional endpoints of interest included the change from baseline in peak oxygen consumption (VO_2) per unit of time at 3 months, all-cause mortality, a composite endpoint of cardiovascular (CV) mortality or CV hospitalization, and the composite endpoint of CV mortality or HF hospitalization. An independent clinical events committee adjudicated all deaths and all first hospitalizations.

STATISTICAL ANALYSIS. Cluster analysis defines the distances between subjects on the basis of the combined values of their measured characteristics. Using a matrix of distance measurements, cluster analysis finds groups of subjects who are more similar to each other than in those in other groups (Online Figure 1). It can be used to describe disease phenotypes without the need for historical or arbitrary a priori assumptions about classification.

Details of the statistical analysis performed are included in the Online Appendix. Briefly, we selected 45 candidate variables measured at baseline that represented key characteristics of patients with HF, including demographic characteristics, medical history, laboratory values, QOL scores, and exercise capabilities (Online Table 1). As is necessary for cluster analysis, patients with missing data for any variables were excluded, resulting in an analytical population of 1,619 of 2,331 patients (70% of the baseline study population). We performed a cluster analysis on these variables and obtained 4 distinct clusters of chronic HF patients (Online Figure 2). The association between cluster membership and clinical outcomes was assessed using Cox proportional hazards regression. We assessed proportional hazards assumptions graphically by evaluating the standardized score process and the supremum test, and found no violations (18). Using interaction terms in a Cox regression model, we also assessed whether cluster membership was associated with a differential response to randomized exercise therapy for each outcome.

All analyses were performed with SAS version 9.2 (SAS Institute, Cary, North Carolina) and R 2.15.3 (R Development Core Team, Vienna, Austria). A p value ≤ 0.05 was considered statistically significant for all analyses. All of the authors had full access to the data and take full responsibility for data integrity.

RESULTS

Complete baseline data for the pre-specified 45 clinical variables of interest were available for 1,619 of the 2,331 patients who participated in the HF-ACTION trial; these patients were included in the study. The cluster analysis identified 4 patient clusters. Clinical variables according to cluster are shown in **Table 1**, and socioeconomic variables in **Table 2**. **Table 3** contains objective measures of HF according to patient cluster. Baseline characteristics of the overall population and the subgroup used for the analysis were broadly similar, and are shown in Online Table 2. Key characteristics of each patient cluster were as follows.

CLUSTER 1 (n = 773). This was the largest cluster with >2 times more patients than the other clusters. Patients tended to be older Caucasian men (age >60 years) with a history of tobacco use, high rates of ischemic cardiomyopathy (68%), and advanced NYHA functional class (39% with class III or IV). Despite having the second highest rates of coronary artery bypass graft surgery and percutaneous coronary intervention, they had the second lowest rates of angina symptoms (11.3%), with only 1% with Canadian Cardiovascular Society angina classes 2 to 4. They had the highest rates of common comorbidities, such as atrial fibrillation (AF), renal insufficiency, and chronic obstructive pulmonary disease (COPD), as well as use of implantable cardioverter-defibrillators (ICDs) and coronary resynchronization therapy (CRT). Cluster 1 patients were most likely to be married, least likely to be divorced, had the second highest rates of college graduation and income, and were most likely to either be employed or retired (63%). They had objective evidence of the most advanced disease—lowest median peak VO_2 levels (13.5 ml/kg/min), highest ventilation versus carbon dioxide production slope (34), and lowest 6MWD (351 m)—but they had the second lowest rates of previous HF hospitalization and the second highest QOL scores. They also had the highest median levels of all of the 3 HF biomarkers studied: NT-proBNP (1,079 pg/ml), galectin-3 (15.4 ng/ml), and ST2 (26.2 ng/ml).

CLUSTER 2 (n = 287). These patients were, on average, the youngest (median age 49 years). They were the most likely to be African American (69%) and had the second highest percent of women

TABLE 1 Baseline Clinical Characteristics According to Patient Clusters

	Cluster 1 (n = 773)	Cluster 2 (n = 287)	Cluster 3 (n = 313)	Cluster 4 (n = 246)	p Value*
Age, yrs	63 (56–72)	49 (40–56)	60 (53–68)	55 (46–64)	<0.001
Female	21.0	38.0	25.0	39.0	<0.001
Black	28.0	69.0	28.0	20.0	<0.001
White	67.0	27.0	67.0	77.0	<0.001
BMI, kg/m^2	30 (26–34)	34 (27–41)	29 (27–33)	28 (25–33)	<0.001
Systolic BP, mm Hg	112 (102–126)	117 (108–130)	114 (102–130)	104 (94–114)	<0.001
Diastolic BP, mm Hg	70 (62–78)	76 (68–84)	70 (60–80)	64 (60–72)	<0.001
Ischemic cardiomyopathy	68.0	10.0	80.0	9.0	<0.001
Previous heart failure hospitalizations					
None	76.8	56.1	74.4	81.3	<0.001
1	17.9	33.4	19.2	14.6	
2	3.5	7.7	3.2	2.4	
≥3	1.8	2.8	3.2	1.6	
Symptoms					
NYHA functional classes III–IV	39.0	27.0	43.0	21.0	<0.001
History of angina	11.0	14.0	97.0	7.0	<0.001
CCS angina class					
0	95.0	90.0	29.0	98.0	<0.001
1	4.0	8.0	28.0	2.0	
2–4	1.0	2.0	43.0	0.0	
Medical and surgical history					
History of MI	55.2	6.6	70.9	6.1	<0.001
Hypertension	71.2	64.5	74.1	12.6	<0.001
Diabetes	41.9	21.6	41.2	5.7	<0.001
Atrial fibrillation/flutter	31.8	6.6	14.7	11.8	<0.001
Hyperlipidemia	76.8	40.8	83.7	38.6	<0.001
Stroke	12.0	12.5	9.9	4.1	0.003
PVD	9.7	4.2	6.7	0.8	<0.001
COPD	12.7	13.2	8.9	4.5	0.001
Previous valve surgery	8.0	1.0	3.2	4.9	<0.001
Previous PCI	27.8	3.1	42.8	2.8	<0.001
Previous CABG	37.1	1.7	42.2	1.6	<0.001
Laboratories					
Sodium, mmol/l	139 (137–141)	139 (138–141)	139 (137–141)	139 (137–140)	0.033
Creatinine, mg/dl	1.3 (1.1–1.6)	1.1 (0.9–1.3)	1.2 (1.0–1.4)	1.1 (0.9–1.2)	<0.001
Blood urea nitrogen, mg/dl	23 (17–32)	16 (12–20)	20 (15–26)	18 (14–24)	<0.001
Medications and devices					
ACE-I or ARB	93.4	94.8	93.3	97.2	0.140
Beta-blocker	95.0	95.8	95.2	93.9	0.787
Loop diuretic agent	81.0	81.9	78.0	69.5	<0.001
Digoxin	49.5	43.2	43.5	49.6	0.118
ICD	53.3	15.7	39.6	37.4	<0.001
CRT	25.2	4.5	14.7	19.1	<0.001
Resting ECG conduction					
Normal	31.8	73.9	46.6	37.0	
LBBB	14.9	8.7	16.3	26.4	
RBBB	4.8	2.8	4.2	1.6	<0.001
IVCD	14.9	10.8	13.7	14.2	
Paced	33.6	3.8	19.2	20.7	

Values are median (interquartile range), or %. *p Values for the comparisons of variables across clusters.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; HF = heart failure; ICD = implantable cardioverter-defibrillator; IVCD = intraventricular conduction delay; LBBB = left bundle branch block; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; RBBB = right bundle branch block.

(38.3% vs. 39% in cluster 4). Median body mass index was the highest (34 kg/m^2), and HF etiology was overwhelmingly (>90%) due to nonischemic causes despite high rates of risk factors for atherosclerotic heart disease. Patients in this cluster had the highest rates of previous cerebrovascular accident and COPD, but they also had low rates of other comorbidities, such as AF and peripheral vascular disease. They had the lowest rates of ICD and CRT use (15.7% and 4.5%, respectively), which was less than one-half of that in the next lowest group (37.4% and 19.1%, respectively, in cluster 4). Cluster 2 patients were the least likely to be married or employed, and had the lowest levels of education and income. They exhibited objective evidence of less advanced HF; after cluster 4, they had the second highest median peak VO_2 levels (15.0 ml/kg/min) and 6MWD (351 m). They also had the lowest median levels of NT-proBNP (418 pg/ml) and galectin-3 (11.9 ng/ml), and ST2 levels were similar to cluster 4 (21.2 ng/ml vs. 21.1 ng/ml). Despite this, cluster 2 patients had the highest rates of previous hospitalization and the second lowest QOL scores.

CLUSTER 3 (n = 313). In terms of age, sex, and racial makeup, these patients were similar to the overall HF-ACTION study (means age 60 years, 64% Caucasian, and 75% male). HF was primarily due to ischemic cardiomyopathy (80%). The unique characteristic in these patients appeared to be their high burden of angina symptoms (97%; 43% in Canadian Cardiovascular Society class III or IV vs. <2% for all other clusters), and consistent with this, they had the highest rates of prior percutaneous coronary intervention and coronary artery bypass graft surgery. After cluster 1 patients, they had the second highest rates of ICD and CRT use. Cluster 3 patients had the second lowest rates of education, employment, and income. They displayed objective evidence of advanced HF, and had the second lowest median peak VO_2 levels (14.7 ml/kg/min) and 6MWD (376 m). Consistent with this, they had the second highest levels of all 3 prognostic biomarkers (after cluster 1): NT-proBNP (775 pg/ml), galectin-3 (14.5 ng/ml), and ST2 (23.5 ng/ml). They had the second highest rates of previous hospitalizations, and the lowest QOL scores.

CLUSTER 4 (n = 246). This cluster included the highest percent of Caucasians (77%) and women (39%), with a median age of 55 years. The majority had HF due to nonischemic causes (>90%), and they had considerably lower rates of risk factors and comorbidities than all other patients (except for AF, which was only lower in cluster 2). Cluster 4 patients were the least likely to have been smokers; they had the highest levels of educational attainment and income, and were the most likely to be employed. These patients had objective evidence of the mildest degree of HF with the highest median peak VO_2 levels (17.5 ml/kg/min) and 6MWD (427 m). They also had the second lowest median levels of NT-proBNP and galectin-3 (after cluster 2). These patients had the lowest rates of previous hospitalization and the highest QOL scores. At baseline, 37.4% had an ICD, and they had the second highest usage of CRT devices (19.1%).

TABLE 2 Baseline Psychosocial Characteristics According to Patient Clusters

	Cluster 1 (n = 773)	Cluster 2 (n = 287)	Cluster 3 (n = 313)	Cluster 4 (n = 246)	p Value*
Marital status					
Married	64	38	63	60	
Divorced	13	16	14	14	<0.001†
Single (never married)	7	25	8	13	
Other	16	21	15	13	
Smoking status					
Never	31	44	32	59	<0.001
Current	14	28	13	9	
Past	54	28	55	35	
Alcohol use	43	43	46	43	0.864
Highest level of education					
Less than high school	11	12	14	5	
High school	28	32	29	25	0.004†
Associate degree	9	11	10	10	
College	19	9	12	22	
Graduate school	9	5	6	16	
Other	24	31	29	22	
Employment status					
Employed full time	16	23	14	27	
Employed part time	6	5	6	5	
Disabled	27	44	38	28	<0.001†
Unemployed	4	13	4	7	
Retired	47	11	34	28	
Other	0	4	4	5	
Income					
<$15,000	17	27	24	13	
$15,000-$24,999	16	18	17	17	
$25,000-$34,999	13	14	16	12	
$35,000-$49,999	16	13	15	11	<0.001†
$50,000-$74,999	15	10	14	19	
$75,000-$99,999	8	4	6	8	
>$100,000	6	3	4	12	
Quality of life					
KCCQ Score	72 (54–85)	63 (43–80)	60 (47–76)	76 (60–86)	<0.001
BDI-II Score	8 (4–13)	10 (5–19)	10 (6–16)	7 (4–13)	<0.001
Euro thermometer	70 (60–80)	66 (50–80)	65 (50–80)	70 (60–80)	<0.001

Values are % or median (interquartile range). *p Values for comparisons across clusters. †p Values for the dichotomized comparison of each variable as follows: income: <$25,000 versus ≥$25,000; education: <high school versus ≥high school; marital status: positive current or previous partner (married, living with partner, widowed) versus no partner (single, divorced, separated); employment status: employed, volunteer, student, homemaker, or retired versus unemployed or disabled.

BDI-II = Beck Depression Inventory-II; KCCQ = Kansas City Cardiomyopathy Questionnaire.

CLINICAL OUTCOMES. Figure 1 shows the risk of primary and secondary clinical outcomes of the HF-ACTION study for each cluster, with cluster 1 (highest risk) as the comparator group. Compared with

TABLE 3 Objective Predictors of Heart Failure Prognosis According to Patient Clusters

Patient Biomarkers	Cluster 1 (n = 773)	Cluster 2 (n = 287)	Cluster 3 (n = 313)	Cluster 4 (n = 246)	p Value
LVEF, %	25 (20-30)	25 (20-30)	25 (20-30)	24 (19-30)	0.606
Peak VO_2, ml/kg/min	13.5 (11.0-16.5)	15.0 (12.1-18.0)	14.7 (12.0-17.9)	17.5 (14.2-20.7)	<0.001
$VEVCO_2$ slope	34 (30-40)	30 (26-34)	33 (29-39)	31 (27-35)	<0.001
6MWD, m	351 (290-416)	394 (320-439)	376 (305-441)	427 (363-476)	<0.001
NT-proBNP, pg/ml (n = 1,011)	1,079 (461-2,517)	418 (194-978)	775 (359-1,663)	558 (206-1,606)	<0.001
Galectin-3, ng/ml (n = 664)	15.4 (11.9-21.0)	11.9 (9.8-14.9)	14.5 (10.8-20.1)	12.3 (10.2-16.7)	<0.001
ST2, ng/ml (n = 677)	26.2 (20.5-35.1)	21.2 (15.7-28.3)	23.5 (19.0-30.5)	21.1 (16.3-26.7)	<0.001

Values are median (interquartile range).

6MWD = 6-min walking distance; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; $VEVCO_2$ = minute ventilation – carbon dioxide production relationship; VO_2 = oxygen consumption per unit of time.

cluster 1, risk of the composite endpoint of all-cause mortality and/or all-cause hospitalization ranged from 0.65 (95% confidence interval [95% CI]: 0.54 to 0.78) for cluster 4 to an equivalent 1.02 (95% CI: 0.87 to 1.19) for cluster 3. When considering all-cause mortality, cluster 3 patients demonstrated an almost 40% lower risk of mortality (0.61 [95% CI: 0.44 to 0.86]), but risk of other outcomes was similar, suggesting a higher risk of hospitalization. Cluster 4 patients had the best risk profile, with 35% to 55% lower risk for adverse outcomes compared with cluster 1.

Figure 2 shows Kaplan-Meier curves, according to patient cluster, for the primary endpoint of all-cause death or all-cause hospitalization, and the secondary endpoint of all-cause mortality. As shown, patients in clusters 1 and 3 were at the highest risk for the primary outcome; patients in cluster 4 were at the lowest risk. When considering all-cause death, cluster 1 patients had the highest mortality rates, suggesting that cluster 3 patients had high rates of hospitalization.

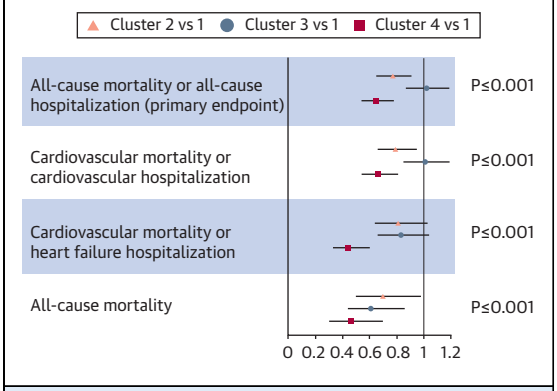


FIGURE 1 Risk of Clinical Events Compared With Cluster 1 (Highest Risk)*

***Symbols** represent hazard ratios and 95% confidence intervals.

INTERACTION WITH EXERCISE TRAINING INTERVENTION. Benefits from exercise training, the randomized intervention tested in HF-ACTION, varied across patient clusters (Central Illustration). We found evidence of significant improvements in 3-month peak VO_2 levels with exercise training in cluster 2 and 3 patients (1.33 [95% CI: 0.67 to 1.98] ml/min and 0.87 [95% CI: 0.24 to 1.51] ml/min, respectively; p for interaction = 0.04). Significant differences were also seen in the impact of exercise training on 2 clinical outcomes (CV death and/or CV hospitalization; p for interaction = 0.0396, and CV death and/or HF hospitalization; p for interaction = 0.0316). Clusters 1 and 2 appeared to have 12% to 30% risk reduction from exercise training, whereas cluster 4 had an indication for increased harm (50% to 62%); however, the confidence intervals were wide and included 1 in all cases, except for the endpoint of CV death and/or CV hospitalization.

DISCUSSION

We applied a novel approach to a robust database from a recent, large, randomized, controlled trial of exercise training to identify 4 clinically relevant phenotypes of chronic systolic HF. Patients within each cluster varied considerably among the measures of age, sex, race, symptoms, comorbidities, HF etiology, socioeconomic status, QOL, CPET parameters, and biomarker levels. We noted differential associations with risk of hospitalization and mortality between and within clusters, as well as varied responses to exercise therapy (Central Illustration). These findings underscore the significant heterogeneity that exists within chronic HF patients and the need for improved syndrome phenotyping.

To our knowledge, this is the first application of cluster analysis to identify distinct clinical phenotypes in a large cohort of patients with chronic HF,

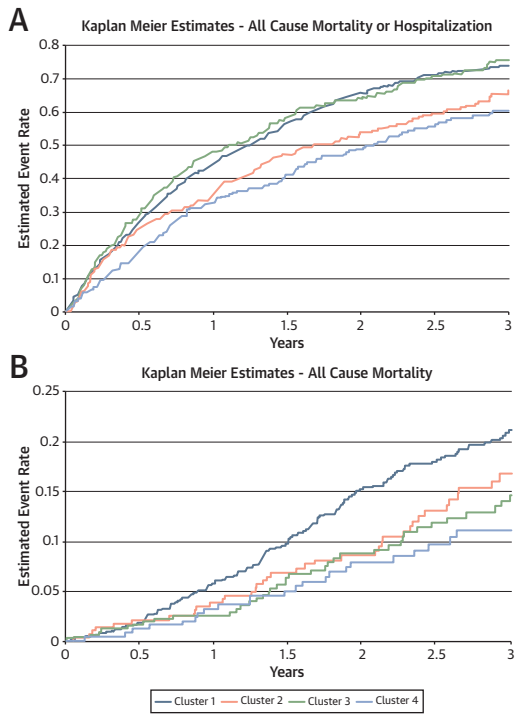
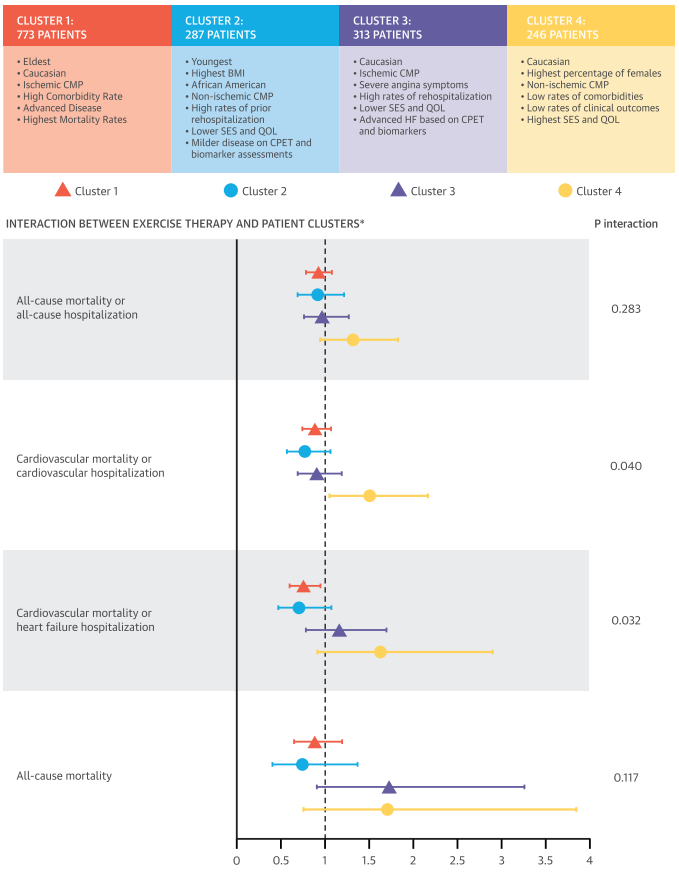


FIGURE 2 Time to All-Cause Mortality/All-Cause Hospitalization and to All-Cause Mortality

Kaplan-Meier curves, according to patient cluster, that depict **(A)** the primary endpoint of death or hospitalization (from any cause), and **(B)** the secondary endpoint of death from any cause.



CENTRAL ILLUSTRATION Consort Diagram Showing Cluster Methodology Applied to the HF-ACTION Study and the 4 Distinct Clusters That Emerge

Interaction between exercise therapy and patient clusters extracted from the study. **Symbols** represent hazard ratios (HR) and 95% confidence intervals, with HR <1.00 denoting benefit from exercise, and HR >1.00 denoting harm. BMI = body mass index; CMP = cardiomyopathy; CPET = cardiopulmonary exercise testing; HF = heart failure; QOL = quality of life; SES = socioeconomic status.

a syndrome believed to comprise multiple disease subtypes (3). Several previous studies have used this method to identify clinically relevant patient subgroups within similarly complex, yet disparate syndromes, such as COPD, Parkinson's disease, and human encephalitis, leading to new insights about disease pathophysiology (19–22). In general, the impact of these studies was limited by their small size, low number of available clinical variables, a well-phenotyped population, and lack of outcome data. The HF-ACTION database was ideal to overcome these limitations.

The findings presented here are important for several reasons, especially when considering that measurement of the LVEF—the methodology most commonly used to describe HF—was 1 of only a handful of variables that was statistically identical across all 4 patient clusters; this emphasizes the need for improved descriptions of HF subtypes. We identified 2 clusters of patients with HF as a result of ischemic cardiomyopathy (clusters 1 and 3) that differed dramatically in frequency and intensity of angina symptoms (prevalence: 11% vs. 97%; Canadian Cardiology Society angina classes II to IV: 1% vs. 43%). Consequently, despite having objective measures of milder disease and far higher rates of revascularization procedures, patients in cluster 3 had greater risk of hospitalization and the poorest QOL. Previous studies have noted the persistence of anginal symptoms in HF patients despite revascularization, suggesting that pain mechanisms in this patient population might not entirely be ameliorated by restoring epicardial blood flow (23). Despite higher rates of rehospitalization, the mortality rates for cluster 3 patients were 40% lower than cluster 1 patients. This suggests that novel strategies to improve angina symptoms in this patient subtype might be clinically impactful (24).

We also identified a cluster of patients who tended to be young, obese African Americans with nonischemic cardiomyopathy. Despite objective evidence of milder disease on the basis of CPET parameters and HF biomarkers, these patients had high rates of hospitalization and low QOL scores, which confirmed previous pre-specified analyses in this patient population (25). These patients also exhibited the lowest rates of ICD use (15.7%), although almost all qualified on the basis of EF and NYHA criteria. Whether socioeconomic factors caused these differences is unknown, although racial and socioeconomic differences in medical device use have been noted previously (26). Furthermore, the etiology of HF in these patients was unclear; whether it resulted from hypertension or other known causes, or it represented a distinct pathophysiological entity, is an intriguing notion that requires further study (27).

Cluster 2 patients also possessed surprisingly low rates of conduction abnormalities and the lowest levels of biomarkers that elevate in response to myocardial stretch and fibrosis. This might explain the distinct natural history of HF previously noted in this patient population, and potentially, differential responses to therapeutics (28–30). Lastly, it appears that the highest rates of rehospitalization in these patients occurred despite objective measures of milder HF; this might suggest that therapies aimed at improving disease state alone would not decrease rehospitalization rates. Rather, a focused effort at understanding the global reasons for rehospitalization might result in more effective prevention strategies (31,32).

The fourth cluster mostly included Caucasian patients with the highest percent of women (39%) and the highest socioeconomic status, as well as the mildest form of HF from nonischemic cardiomyopathy. These patients had the lowest rates of comorbidities, objective measures that signified the most cardiopulmonary reserve, and highest QOL scores. Intriguingly, exercise therapy appeared to be associated with worse outcomes in these patients. Although highly speculative because of the sample size, this might suggest that universal recommendations for HF patients might not always be beneficial for lower risk patients.

Beyond what has been previously discussed, these data carry important implications for patient care. Although guidelines recommend treatment of all HF patients according to disease severity and using measures that might not capture disease heterogeneity, our findings imply that it may be important to tailor therapeutics according to disease subtype on the basis of a comprehensive evaluation of readily available clinical data. Patients who resemble those in cluster 1, for example, may benefit from management of their numerous comorbid conditions along with HF, whereas patients similar to those in cluster 3 could benefit from a focus on minimizing angina symptoms. Furthermore, the increased use of electronic medical records may soon allow us to use clustering algorithms on large amounts of clinical data to improve phenotyping of patients, present actionable information to medical practitioners, and ultimately improve quality of care (33).

Our findings also shed light on the shortcomings of clinical trials in patients with HF: a mechanistically sound therapeutic intervention might not show efficacy when tested on a disease state with large phenotypic variations in etiology, clinical features, and natural history (7,34). It has even been suggested that a percent of patients in large clinical trials of HF might not even have HF; this issue, therefore, might explain the high number of negative results reported in large trials of promising interventions for HF (35).

STUDY LIMITATIONS. Several limitations of this analysis require consideration. First and foremost, the present study was not meant to propose a new classification for chronic systolic HF, because the clusters are likely to vary according to patient characteristics and available data. These results serve to underscore the need for novel multidimensional HF classification approaches for improving patient care and trial quality. Furthermore, they are aimed to generate hypotheses for future studies that will integrate clinical and biological data in patients with the goal of improving HF phenotyping. Second, patients with incomplete datasets were excluded from cluster analyses, which necessitates complete data on individual patients. Third, the patient population represented those who participated in the HF-ACTION clinical trial and might not generalizable to the entire population of chronic HF patients. Fourth, the clustering algorithm yielded results on the basis of the available clinical variables, and the results might have differed with more complete and accurate data. Fifth, the choice of stopping the clustering algorithm at 4 clusters included investigator discretion and preference; a larger number of clusters might refine cluster descriptions, but smaller sizes might have limited our ability to explore relationships with clinical outcomes. In summary, we considered this analysis to be hypothesis-generating; further studies will be required to address these hypotheses.

CONCLUSIONS

We demonstrated that using a clustering algorithm on the baseline clinical data of chronic HF patients can

identify 4 phenotypically distinct and clinically meaningful groups. Patients within each cluster varied considerably among the measures of age, sex, race, symptoms, comorbidities, HF etiology, socioeconomic status, QOL, CPET parameters, and biomarker levels. We also demonstrated that patients in each cluster responded distinctively to randomized intervention assignment—in this case, exercise therapy. These findings highlight the significant heterogeneity that exists within chronic HF patients and the need for improved phenotyping of the syndrome to enhance therapeutic efficacy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There is considerable heterogeneity among patients with chronic HF related to etiology, clinical manifestations, and natural history; certain characteristics identified by cluster analysis are associated with differences in outcomes.

COMPETENCY IN PATIENT CARE: In managing patients with chronic HF, therapy should be individualized on the basis of recognition of heterogeneity in key clinical characteristics.

TRANSLATIONAL OUTLOOK: Clinical trials could evaluate responses to specific therapeutic interventions in subgroups of patients with chronic HF who are distinguished by cluster analysis.

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KEY WORDS mortality, prognosis, rehospitalization, socioeconomic

APPENDIX For supplemental figures and tables, please see the online version of this article.