## Supplementary Data

**Table 1:** Baseline Clinical Variables Used for Cluster Analysis

| | |
|---|---|
| **Patient Characteristics** | Age, Sex, Race, Weight, BMI, Systolic BP, Diastolic BP, Smoking Status, Alcohol Use, NYHA class, CCS angina class, LV Ejection Fraction, Number of Recent HF Hospitalizations, Resting Heart Rate |
| **Past Medical History** | Ischemic Heart Disease, Angina, Atrial Fibrillation/Flutter, Hypertension, Hyperlipidemia, PVD, Prior MI, Prior Stroke, Diabetes, COPD, Prior CABG, Prior Valve Surgery, Prior PCI, Pacemaker, ICD, Biventricular Pacemaker |
| **Laboratory Values** | Sodium, Creatinine, BUN |
| **Quality of Life Assessments** | KCCQ overall summary score, KCCQ symptom stability score, KCCQ total symptom score, Beck Depression score |
| **Exercise Variables** | 6MWD, Cardiopulmonary Exercise Testing Findings: ECG Ventricular Conduction, Peak HR, Peak $VO_2$, Peak Respiratory Exchange Ratio, $VeVCO_2$ Slope, Heart rate at end of test, CPX duration |

BMI indicates Body Mass Index; BP, blood pressure; NYHA, New York Heart Association; LV, left ventricle; HF, heart failure; PVD, peripheral vascular disease; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CCS, Canadian cardiovascular society; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; BUN, blood urea nitrogen; 6MWD, 6 minute walk distance; ECG, electrocardiogram; CPX, cardiopulmonary exercise duration.

**Table 2.** Baseline Characteristics of HF-ACTION Patients According to Inclusion in Cluster Analysis

| Characteristic | Total (N=2331) | Included (N=1619) | Excluded (N=712) | *P* |
|---|---|---|---|---|
| Age, years | 59 (51-68) | 59 (51-68) | 60 (51-68) | 012 |
| Female Sex, % | 28 | 27 | 31 | 0.11 |
| Race | | | | |
| Black, % | 33 | 34 | 29 | 0.06 |
| White, % | 62 | 61 | 65 | |
| Other, % | 5 | 5 | 6 | |
| BMI, $kg/m^2$ | 30 (26-35) | 30 (26-35) | 30 (26-35) | 0.51 |
| Systolic BP, mmHg | 111 (100-126) | 112 (100-126) | 110 (100-126) | 0.42 |
| Diastolic BP, mmHg | 70 (60-78) | 70 (62-80) | 70 (60-78) | 0.44 |
| Heart Rate at Rest, bpm | 70 (63-77) | 70 (63-76) | 70 (63-79) | 0.12 |
| Smoking Status | | | | |
| Never | 37 | 38 | 36 | 0.16 |
| Current | 17 | 16 | 19 | |
| Past | 46 | 46 | 45 | |
| Alcohol Use | 43 | 44 | 41 | |
| **Patient Status** | | | | 0.23 |
| HF Hospitalizations prior 6 months | | | | 0.95 |
| None, % | 74 | 73 | 74 | |
| 1, % | 20 | 20 | 19 | |
| 2, % | 4 | 4 | 4 | |
| ≥ 3, % | 2 | 2 | 2 | |
| Ischemic Etiology, % | 51 | 51 | 52 | 0.90 |
| LVEF, % | 25 (20-30) | 25 (20-30) | 25 (20-30) | 0.47 |
| NYHA Class | | | | 0.006 |
| NYHA II, % | 63 | 66 | 59 | |
| NYHA III, % | 36 | 34 | 40 | |
| NYHA IV, % | 1 | 1 | 1 | |
| **Patient History** | | | | |
| Hypertension | 60 | 62 | 56 | 0.01 |
| Diabetes | 32 | 33 | 31 | 0.36 |
| Atrial Fibrillation or Flutter | 21 | 21 | 21 | 0.92 |
| Hyperlipidemia | 66 | 66 | 65 | 0.61 |
| Myocardial Infarction | 42 | 42 | 42 | 0.78 |
| Stroke | 10 | 11 | 10 | 0.48 |
| PVD | 7 | 7 | 7 | 0.94 |
| COPD | 11 | 11 | 11 | 0.93 |
| Prior Valve Surgery | 6 | 5 | 6 | 0.61 |
| Prior PCI | 23 | 23 | 24 | 0.38 |

| | | | | |
|---|---|---|---|---|
| Prior CABG | 26 | 26 | 24 | 0.15 |
| **Patient Labs** | | | | |
| Sodium, mmol/L | 139 (137-141) | 139 (137-141) | 139 (137-141) | 0.53 |
| Potassium, mmol/L | 3.7 (0.0-4.3) | 3.7 (0.0-4.4) | 3.6 (0.0-4.3) | 0.73 |
| Glucose, mmol/L | 5.8 (5.1-7.2) | 5.7 (5.1-7.2) | 5.9 (5.1-7.4) | 0.19 |
| Creatinine, mg/dL | 1.2 (1.0-1.5) | 1.2 (1.0-1.5) | 1.2 (1.0-1.5) | 0.60 |
| Blood Urea Nitrogen, mg/dL | 20 (15-28) | 20 (15-27) | 22 (16-30) | 0.01 |
| **Patient Meds** | | | | |
| ACE-I or ARB | 94 | 94 | 95 | 0.62 |
| Beta Blocker | 95 | 95 | 94 | 0.12 |
| Loop Diuretic | 78 | 79 | 76 | 0.08 |
| Digoxin | 45 | 47 | 40 | <0.001 |
| **Patient Implant/Rhythm** | | | | |
| Implantable Cardioverter Defibrillator | 40 | 42 | 37 | 0.05 |
| Biventricular Pacemaker | 18 | 19 | 17 | 0.24 |
| Pacemaker | 18 | 17 | 19 | 0.51 |
| **Patient Exercise** | | | | |
| Peak Oxygen Consumption, mL/kg/min | 14.4 (11.5-17.7) | 14.5 (11.7-17.7) | 14.2 (11.1-17.7) | 0.03 |
| VeVCO2 Slope | 33 (28-39) | 32 (28-38) | 33 (28-39) | 0.07 |
| 6 Minute Walk Distance, m | 371 (299-435) | 375 (305-438) | 359 (274-428) | <0.001 |
| **Patient Quality of Life** | | | | |
| KCCQ Overall Summary Score | 68 (51-83) | 69 (52-83) | 67 (50-82) | 0.09 |
| Beck Depression Score | 8 (4-15) | 8 (5-15) | 8 (4-15) | 0.70 |
| **Patient Biomarkers** | | | | |
| NT-proBNP, pg/mL | 815 (341-1805) | 796 (337-1854) | 844 (351-1742) | 0.61 |
| Galectin-3, ng/mL | 14.0 (11.0-18.6) | 14.1 (11.0-18.7) | 13.7 (11.0-18.4) | 0.61 |
| ST2, ng/mL | 23.7 (18.6-31.8) | 23.8 (18.4-31.7) | 23.7 (18.8-32.3) | 0.47 |

BMI indicates Body Mass Index; BP, blood pressure; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; HF, heart failure; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CCS, Canadian Cardiovascular Society; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NT-proBNP, amino terminal proB-type natriuretic peptide.

**Statistical Methods**

The primary focus of this study was to identify clusters patients with different chronic systolic HF phenotypes. The process is outlined as follows.

***Variable Dimension Reduction***

Forty-five baseline variables representing patient characteristics, medical history, labs, quality of life scores, and exercise capabilities were identified for this aim. Given this large set of variables, we sought to reduce the dimension of our covariate list through variable clustering. A procedure (SAS PROC VARCLUS) was run separately for continuous and binary variables resulting in 6 clusters of continuous variables and 7 clusters of categorical variables. In brief, the SAS procedure PROC VARCLUS is an iterative process that divides a large set of variables into several disjoint clusters. At each iteration the procedure takes a given set of variables, identifies the first two principal components of those variables, and assigns each variable to the component with which it has strongest correlation. As a result, variables are aggregated into several non-overlapping clusters. For each variable cluster, a summary score, as a linear combination of variables within the cluster, can be derived for each patient. The coefficients of the variable cluster summary score are identified by the first principal component of the variable cluster.

Variable clustering was done separately for continuous and categorical variables. The underlying theory of principal components includes an assumption of multivariate normality. However, this assumption is relaxed when principal components are used as a descriptive technique (1). Here, we make no inference on the identified principal components and instead, only use them to categorize variables. Furthermore, for data in which all variables are binary, PCA does provide a plausible low-dimensional representation (2). Thus, we opt to separately analyze continuous variables and binary variables in an attempt to best identify a lower-dimension of variables that adequately describe the data.

Stopping rules for determining the appropriate number of continuous and categorical clusters were as follows. At each stage, a cluster is broken and variables reassigned. We evaluate (a)

total proportion of variation in the variables explained by the variable clusters, (b) the second eigenvalue of each cluster, (c) the change in the proportion of variation explained by the new clustering compared to the prior iteration, (d) the change in the highest second eigenvalue from one iteration to the next, and (e) potentially using clinical input to see if the clustered variables make intuitive sense (blinded to the consequences on later steps in the process). For example, increasing the number of continuous variable clusters up to 4 yielded a relative increase in variation explained >10% compared to each prior iteration, whereas more than 4 continuous variable clusters yielded less increase.

***Patient Clustering***

Given 13 scores for each patient after the variable reduction process, we next sought to identify clusters of similar patients. We standardized the 13 scores to have mean zero and a standard deviation of 1. After standardizing scores, using Ward's minimum variance method of clustering (implemented with SAS procedure PROC CLUSTER) we identified 4 patient clusters (3,4).

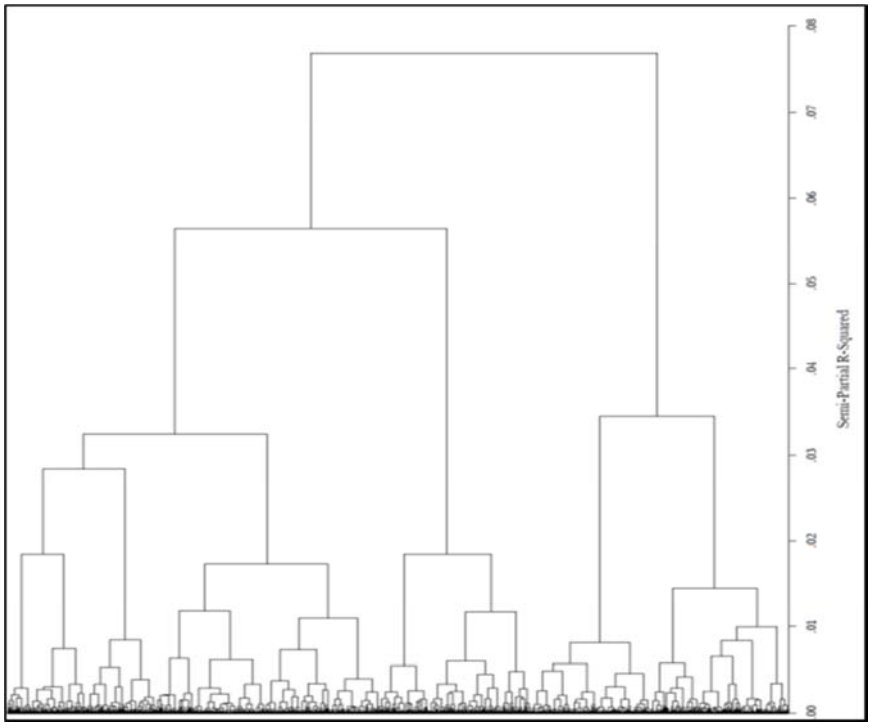
In brief, this is an agglomerative hierarchical clustering approach where we start with each patient as his/her own singleton cluster and we iteratively merge clusters together. When two clusters have been merged, they remain so for the remainder of the algorithm process.

For Ward's minimum variance method, at each stage we define the distance between two clusters *K* and *L* as

$$D_{K,L} = \frac{\sum_j \left(x_{K,j} - x_{L,j}\right)^2}{\frac{1}{n_K} + \frac{1}{n_L}}$$

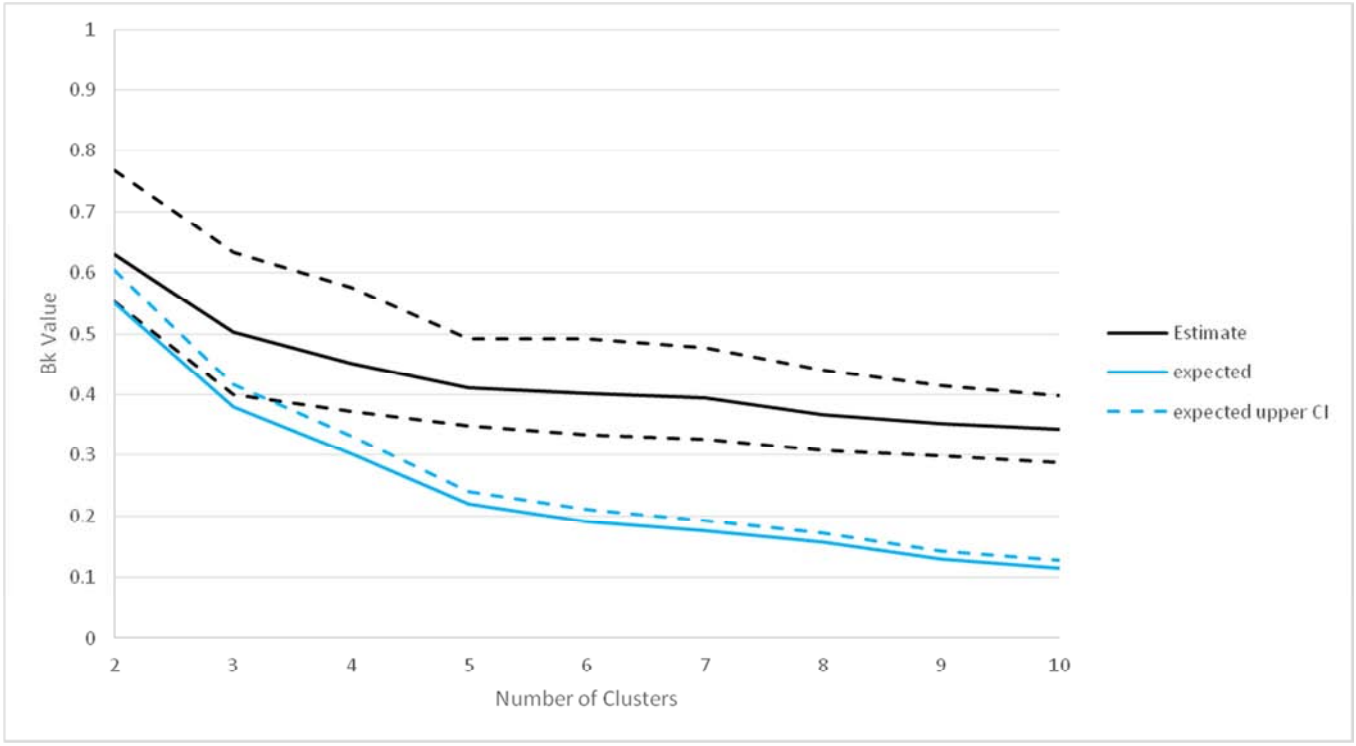
where *j* indexes the cluster's 13 variable scores. That is, $x_{K,j}$ is the value of the *j*th standardized variable score for cluster *K* and $n_K$ is the number of original patients in cluster *K* at that stage. Put another way, at any stage the distance between two clusters is defined as a function of the sum of squared differences in standardized scores. The distance is calculated between every possible combination of two clusters.

The two clusters with the smallest distance are merged and new scores (say, merging *K* and *L* forms a new cluster called *M*) $x_{M,j}$ are an average of scores from patients in the new cluster. Given N total patients in the sample, the process is iterative for N-1 steps until all patients have been merged into a single cluster. Ties in distance at any stage are broken arbitrarily, but in practice ties only occur at early stages. At each iteration, a cubic-clustering criterion, pseudo *F* statistic, and pseudo $t^2$ statistic are calculated (4). We also calculate the semi-partial $R^2$ at each iteration which roughly measures loss of homogeneity within clusters caused by their merger. Thus, small values of the semi-partial $R^2$ indicate that two similar clusters have been merged whereas large values indicate the merger of two heterogeneous clusters. A dendrogram (tree diagram) is provided according to the semi-partial $R^2$ describing the clustering process in this analysis. The decision to use 4 patient clusters was based on an a priori criteria of at least 200 patients per cluster to promote stability of effect estimates, but blinded to outcomes and response to exercise therapy. To assess the stability of the identified clusters, we used a bootstrap resampling method and applied the original clustering algorithm to create various numbers of clusters (K=2,3… 10) in 1000 permutated datasets. We then compared the bootstrap clustering to the original data clustering using the $B_K$ statistic, as proposed in Fowlkes and Mallows "A method for comparing two hierarchical clustering", to assess whether our clusters were more similar than what would be expected with random allocation alone (7). The $B_K$ statistic is a representation of the similarity between clusters, with a higher value indicating greater similarity. The overall $B_K$ estimate is the



average over the 1000 bootstrap samples and decreases with increasing number of clusters. The observed $B_K$ from the bootstrap samples for all K was significantly larger than the expected value had there been no correlation between each bootstrap clustering and the original clustering, and, as expected, we observed a decrease in average $B_K$ across K=2,3….10. We found that the observed $B_K$ was significantly larger than the expected $B_K$ in 999 of the 1000 bootstrap samples. Furthermore, we observed a relatively large decrease in $B_K$ when moving from 4 to 5 clusters, indicating that there is a substantial gain in similarity when using the threshold of 4 clusters (Figure). Therefore, the $B_K$ statistic indicates that our clustering method is better than random allocation for all K and supports the use of 4 clusters for this analysis.

**Figure :**




***Evaluation***

Baseline patient characteristics, labs, and medications are described according to the 4 identified clusters. Continuous variables are described as median and $25^{th}$ - $75^{th}$ percentiles; categorical

variables are described as percentage. Characteristics are compared across clusters using a Kruskal-Wallis test for continuous variables and Pearson chi-square test for categorical variables.

***Outcomes and Response to Exercise Therapy***

As an exploratory illustration, we assessed the association between cluster membership and clinical outcomes using Cox proportional hazards regression. The primary endpoint was the composite all-cause mortality or hospitalization. Secondary endpoints included all-cause mortality, cardiovascular (CV) mortality or CV hospitalization, and CV mortality or HF hospitalization. Proportional hazards assumptions were assessed for cluster; no significant violations were detected. Kaplan-Meier estimated mortality and rehospitalization rates were plotted.

Using interaction terms in a Cox regression model, we also assessed whether cluster membership is associated with a differential response to randomized exercise therapy for each of these outcomes. Finally, we assessed the interaction between treatment and cluster with the endpoint of change in Peak $VO_2$ from baseline to 3 months. Among patients in this analysis known to be alive at 3 months, approximately 15.2% were missing a 3 month measurement. Prior exploratory analyses suggested this missingness could be related to various patient characteristics such that some patient subgroups are more likely to return for follow up than others. To account for this potential bias, we assessed the relationship between cluster membership and change in Peak $VO_2$ using linear regression with inverse probability weighting. First, logistic regression assessed the each individual's probability of missing a 3 month value conditional on a large set of baseline patient variables. Then, in the linear model for change in peak $VO_2$, patients with an observation were weighted by the inverse of their probability to be observed. In this way, some patients are given more weight than others if they are likely to represent not just themselves but also other individuals who were similar but did not have follow up recorded. The linear regression assumption of homoscedasticity was assessed and change in peak $VO_2$ was assessed for normality; no violations were suggested.

Results are reported for clinical outcomes as hazard ratios (HR) and 95% confidence intervals (CI) for each cluster in comparison to a reference cluster and an overall p-value is provided to assess the relationship between cluster and outcome. In models with interactions, an interaction p-value is provided. We also provide the estimated HR and 95%CI for exercise therapy versus usual care within cluster subgroups. Finally, results for change in peak $VO_2$ are reported for the interaction p-value. The estimated exercise therapy effect (and 95%CI) is presented for cluster subgroups. For all analyses, $P<0.05$ was considered significant.

**References:**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