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Factors Related to Morbidity and Mortality in Patients with Chronic Heart Failure with Systolic Dysfunction: The HF-ACTION Predictive Risk Score Model

Christopher M. O'Connor, MD, **David J. Whellan, MD, MHS**, **Daniel Wojdyla, MSc**, **Eric Leifer, PhD**, **Robert M. Clare, MS**, **Stephen J. Ellis, PhD**, **Lawrence J. Fine, MD, DrPH**, **Jerome L. Fleg, MD**, **Faiez Zannad, MD**, **Steven J. Keteyian, PhD**, **Dalane W. Kitzman, MD**, **William E. Kraus, MD**, **David Rendall, PA-C**, **Ileana L. Piña, MD**, **Lawton S. Cooper, MD**, **Mona Fiuzat, PharmD**, and **Kerry L. Lee, PhD**

Duke Clinical Research Institute, Durham, NC (C.M.O., D.W., R.M.C., S.J.E., M.F., D.R., K.L.L.); Thomas Jefferson University, Philadelphia, PA (D.J.W.); National Heart, Lung and Blood Institute, Bethesda, MD (E.L., L.J.F., J.L.F., L.S.C.); Nancy University, Nancy, France (F.Z.); Henry Ford Hospital, Detroit, MI (S.J.K.); Department of Internal Medicine, Wake Forest University School of Medicine, Winston-Salem, NC (D.W.K.); Departments of Psychiatry and Behavioral Science and Medicine, Duke University School of Medicine, Durham, NC (W.E.K.); and Montefiore Medical Center, New York, NY (I.L.P.)

Abstract

Background—We aimed to develop a multivariable statistical model for risk stratification in patients with chronic heart failure (HF) with systolic dysfunction, using patient data that are routinely collected and easily obtained at the time of initial presentation.

Methods and Results—In a cohort of 2331 patients enrolled in the HF-ACTION study (New York Heart Association [NYHA] class II-IV, left ventricular ejection fraction [LVEF] ≤0.35, randomized to exercise training and usual care vs. usual care alone, median follow-up 2.5 years), we performed risk modeling using Cox proportional hazards models and analyzed the relationship between baseline clinical factors and the primary composite endpoint of death or all-cause hospitalization and the secondary endpoint of all-cause death alone. Prognostic relationships for continuous variables were examined using restricted cubic spline functions, and key predictors were identified using a backward variable selection process and bootstrapping methods. For ease of use in clinical practice, point-based risk scores were developed from the risk models. Exercise duration on the baseline cardiopulmonary exercise (CPX) test was the most important predictor of both the primary endpoint and all-cause death. Additional important predictors for the primary endpoint risk model (in descending strength) were Kansas City Cardiomyopathy Questionnaire (KCCQ) symptom stability score, higher blood urea nitrogen (BUN), and male sex (all P <0.0001). Important additional predictors for the mortality risk model were higher BUN, male sex, and lower body mass index (BMI) (all P <0.0001).

Correspondence to: Christopher M. O'Connor, MD DUMC Box 3356 Durham, NC 27710 Phone: 919-681-6195 Fax: 919-681-7755 Oconn002@mc.duke.edu.

Disclosures None.

Conclusions—Risk models using simple, readily obtainable clinical characteristics can provide important prognostic information in ambulatory patients with chronic HF with systolic dysfunction.

Clinical Trial Registration—URL: http:///www.clinicaltrials.gov. Unique identifier: NCT00047437.

Keywords

heart failure; systolic dysfunction; risk score; risk model; exercise capacity

Despite advances in the treatment of patients with chronic heart failure (HF) with systolic dysfunction, these patients remain at high risk for hospitalization and/or death.[1] This risk may be attributed to the aging of the population, progressive disease, increasing frequency of HF hospitalizations, and persistently high event rates following decompensated HF episodes, with up to 30% of patients experiencing a serious adverse cardiovascular event or death following an admission for HF.[2]

Timing for the introduction of second-line therapies, including aldosterone antagonists, resynchronization pacing, left ventricular assist devices (LVADs), or cardiac transplantation is often based on an assessment of patient risk. A risk assessment algorithm ideally should integrate all clinically relevant, validated, and appropriately weighted variables; further, these variables should be easy to obtain from a broad cohort of HF patients in typical clinical settings. Previous attempts to develop such risk models have achieved varying degrees of success.[3-11] Importantly, most (including The Seattle Heart Failure Model) were developed before modern evidence-based therapies and performance measures were broadly applied.[12]

The recently completed Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTION) trial[13] included 2331 well-characterized ambulatory HF patients. Study participants received guideline-based therapies and were systematically followed with standardized assessments of clinical outcomes that included the primary composite endpoint of death or hospitalization from any cause and the secondary endpoint of death alone. We used this robust database to develop a predictive risk model for these endpoints from easily obtainable clinical patient characteristics and laboratory data. We also developed a simple point-based risk score to facilitate ease of use in clinical practice for identifying patients with HF who are at higher risk for morbidity and mortality.

Methods

Patient Cohort

The HF-ACTION trial design and outcomes have been described.[13] Briefly, the study was a multicenter randomized controlled trial testing the long-term safety and efficacy of aerobic exercise training plus evidence-based medical therapy versus evidence-based medical therapy alone in medically stable outpatients with left ventricular systolic dysfunction (ejection fraction <35%) and New York Heart Association [NYHA] class II-IV HF. Adult subjects receiving angiotensin-converting enzyme (ACE)-inhibitor and beta-adrenergic blockade (unless there was documented rationale for variation) for ≥6 weeks were eligible. Exclusion criteria included inability to exercise, regular aerobic exercise (>once/week), and a major cardiovascular event in the previous 6 weeks. The primary endpoint was the composite of death or all-cause hospitalization. Death (all-cause) was a prespecified secondary endpoint. Patients were randomly assigned to usual care alone (optimal medical therapy and a recommendation for regular physical activity) or usual care plus a prescription

of 36 sessions of supervised aerobic exercise training at 60%–70% of heart rate reserve 3 times/week, followed by home-based training at the same intensity 5 times/week. Randomization was stratified by center and HF etiology. Participants were followed for a median of 2.5 years.

Data Considerations

Patient characteristics, laboratory values, health status, and physiologic parameters at rest and during exercise were collected on standardized forms at baseline and at several points throughout the study. Specific instructions and definitions for all variables were provided to assist sites with form completion.

Statistical Methods

Baseline characteristics were summarized by counts and percentages for categorical variables and by medians with interquartile ranges for continuous variables. For both the primary endpoint (all-cause death or hospitalization) and secondary endpoint (all-cause death), predictive models were developed using a set of 48 candidate variables for possible model inclusion (Supplemental Table 1). The candidate variables represented a broad range of baseline characteristics, including demographics, past medical history, laboratory values, baseline exercise test values, and quality of life indices (Kansas City Cardiomyopathy Questionnaire [KCCQ]); however, the candidate variables were restricted to intrinsic patient-level characteristics (e.g., excluding such things as geographic region and use of medications). The aim in developing these predictive models was to provide a useful tool for estimating as accurately as possible the risk of the given endpoint for individual patients.

Although the data were relatively complete for most of the candidate predictor variables, there were several variables with a small number (<5%) of missing values, and five variables with more missing data (mitral regurgitation [8%], creatinine [10%], sodium [11%], BUN [13%], and hemoglobin [24%]). To include variables with missing values in the analysis without deleting valuable patient information, the methods of multiple imputation were employed.[14] The SAS procedure PROC MI was used to create five complete data sets with imputed values to fill in the missing values among candidate predictors. With the five completed datasets, the SAS procedure PROC MIANALYZE was used in conjunction with SAS procedure PROC PHREG to develop the predictive risk models. The relationship of each continuous candidate predictor with the outcome of interest was checked for linearity of the log hazard ratio using restricted cubic spline functions. Where relationships were nonlinear, appropriate transformations using piecewise linear splines were used. Two hundred bootstrap samples were obtained from each imputed data set (giving a total of 1000 bootstrap samples). For each bootstrap sample, a backward selection algorithm was applied with the Cox proportional hazards regression model using a nominal 0.05 critical value for model inclusion. A candidate predictor was included in the model if it met the 0.05 significance level in 75% (for the primary endpoint) or 60% (for the mortality endpoint) of bootstrap samples. These cutoffs were chosen by examining the optimism-corrected c-indices of various possible cutoffs.[15] The predictor variable relationships with the respective clinical outcomes were descriptively characterized by averaging the Cox model parameter estimates and corresponding χ^2 statistics across the five imputation datasets. Model calibration for the predictive models was assessed by comparing 1-year predicted and observed event rates according to deciles of risk.

Risk scores based on assigning points to various risk factors were developed from the predictive models. For ease of clinical use, these risk scores used a subset of the variables included in the predictive models, termed the *simplified* predictive models. The subset in each case was obtained through a stepwise process, eliminating at each step the variable that

would reduce the c-index the least, and continuing until any further reduction would markedly reduce the c-index.

Results

From April 2003 through February 2007, 2331 patients were enrolled in HF-ACTION at 82 centers in the United States, Canada, and France. There were no major differences in baseline characteristics between treatment groups. Over a median follow-up of 2.5 years, a total of 1555 (67%) participants experienced the primary endpoint, and 387 (17%) experienced the mortality endpoint.

Table 1 shows clinical characteristics for participants with and without events. Median age was 59 years; 28% were women; 63% had NYHA class II HF, 36% class III, and 1% class IV. African Americans comprised 33% of participants. Median LVEF was 25%; β-blockade was used in 95% of patients, while ACE inhibitors were used in 74% of patients. Participants experiencing the primary composite endpoint or the secondary mortality endpoint had a higher median baseline age, a higher median LVEF, and a higher percentage of males and of non-white race. Participants experiencing either of these endpoints also had a higher percentage with severe mitral regurgitation, with abnormal ventricular conduction patterns on the resting electrocardiogram, with a history of diabetes mellitus, and with an ischemic etiology of HF.

Clinical Predictors of Events in HF-ACTION

The full predictive model for the primary endpoint (all-cause death or hospitalization) is presented in Supplemental Table 2. The key prognostic factors associated with increased risk of this outcome included measures of performance on the baseline cardiopulmonary exercise test (shorter exercise duration and lower peak VO_2), measures from the KCCQ, lower values of LVEF, higher values of BUN, the presence of ventricular conduction defects, severe mitral regurgitation, and selected demographics (male sex and non-white race).

The full predictive model for all-cause mortality is presented in Supplemental Table 3. Several factors from the primary endpoint model were also highly prognostic in the mortality model (decreased exercise duration, lower LVEF, severe mitral regurgitation, ventricular conduction defects, male sex, and elevated BUN). In addition, other significant factors included BMI, serum creatinine, diastolic blood pressure, and angina classification.

Additionally, the treatment group variable was incorporated into each of the full predictive models, and there was essentially no impact on the coefficients (including hazard ratios) of the other variables. The c-index was virtually unchanged, going from 0.6437 without treatment group to 0.6439 with treatment group in the model for the primary endpoint. Moreover, adding the treatment group variable did not change the c-index for the mortality model: c=0.7357 without treatment, c=0.7358 with treatment. The treatment group variable did not improve the predictive ability, nor did it change the estimate of the relationship between the other variables and the outcome variable in each model.

Clinical Predictors for Simple Risk Score Models

Tables 2 and 3 display variables most strongly associated with the primary composite endpoint and mortality endpoint, respectively, in the *simplified* predictive models. The strongest baseline predictor of both the primary and mortality endpoints was exercise duration on the cardiopulmonary exercise (CPX) test: for every additional minute of

exercise duration, there was an associated 8% reduction in risk for the primary endpoint and an 18% reduction in risk for mortality.

The second most important variable for the primary endpoint's predictive model was the KCCQ Symptom Stability score (in which participants classified their symptoms according to a 5-point Likert scale). This variable consisted of the response to the following question asked of the patient: "Compared with 2 weeks ago, have your symptoms of heart failure (shortness of breath, fatigue, or ankle swelling) changed?" When compared with the group who indicated "no change" or had no symptoms, a response of "much worse or slightly worse" was associated with a hazard ratio of 1.9 (95% CI, 1.6 to 2.3), while a response of "much better or slightly better" was associated with a hazard ratio of 1.3 (95% CI, 1.1 to 1.4). Higher blood urea nitrogen (BUN) and male sex were also strong predictors of the primary endpoint. The model's c-index was 0.63, suggesting a modest capacity of the model to determine which patients are at greatest risk for the primary composite endpoint.

For the mortality model, higher BUN, male sex, and lower body mass index (BMI) were important determinants of higher mortality in addition to baseline exercise duration. The model c-index was 0.73, suggesting moderately good capacity to discriminate patients at greater risk for death.

Risk Scores

The multivariable model for the primary endpoint was converted into a point-based additive risk score (Table 4) that included four clinical variables. Scores were assigned based on each variable's relative contribution to risk, with a maximum of 100 points possible; the mortality risk score was developed using the same methodology (Table 5). Scores were categorized into deciles and used to compare predicted vs. observed 1-year risk. As shown (Tables 6 and 7), the risk score allowed discrimination across a wide range of patients: from 21% risk for the primary endpoint among patients in the first decile (scores 0–38), to nearly 70% risk among patients in the tenth decile (scores 68–100) (Table 6). Risk of mortality alone ranged from 1% in the first decile to 14% in patients in the tenth decile (Table 7). The risk score of the primary endpoint had an optimism-corrected c-index of 0.63, the same as the c-index of the simplified predictive model (Table 2). The risk score for mortality had an optimism-corrected c-index of 0.70, slightly less than the c-index of 0.73 for the simplified predictive model for mortality (Table 3).

Discussion

This analysis from the HF-ACTION clinical trial database represents the first risk prediction model for patients with HF due to systolic dysfunction treated with a high degree of evidence-based therapy (95% beta-blockade, 74% use of an ACE inhibitor; 40% ICD; and 18% biventricular pacing). Our risk scores use clinical variables that are readily available for bedside use and encompass a wide range of risks, making this a valuable tool for clinical decision-making. Collectively, these clinical variables were able to discriminate moderately for the primary endpoint and reasonably well for the mortality endpoint.

Peak exercise capacity as measured by exercise duration during baseline CPX test was the most important predictor for both the primary endpoint and the secondary mortality endpoint in the simplified risk-score models developed in this cohort of outpatient ambulatory NYHA II–IV HF patients. Exercise duration is highly correlated with peak oxygen uptake (VO_2)[16] and integrates similar physiologic information; moreover, it offers the advantages of technical simplicity, wider availability, lower cost, and lower patient burden relative to peak VO_2.

Previous studies have demonstrated the prognostic value of exercise duration in patients with cardiovascular disease,[17,18] but information regarding this parameter in ambulatory HF patients is limited, although recent observational data support the prognostic utility of exercise duration in HF patients.[19] However, this utility depends upon the adoption of a standardized protocol for comparison among cohorts such as the Modified Naughton protocol used in the present study. Importantly, determination of exercise duration in this trial occurred with the simultaneous collection and analysis of expired air for determination of respiratory exchange ratio, a parameter used to avoid termination of an exercise test prior to attainment of peak effort. Finally, recent literature involving prognosis in HF patients suggests that ventilator efficiency (i.e., relationship between volume of air exhaled and volume of CO_2 exhaled [V_E/VCO_2 slope]) during exercise is a strong predictor of clinical events in these patients.[20-22] In our multivariable modeling, exercise duration during baseline CPX testing was a stronger predictor of outcomes than V_E/VCO_2 slope and a slightly stronger predictor than peak VO_2. For this reason, V_E/VCO_2 slope and peak VO_2 were not included in the final predictive models.

In the KCCQ, the single question "compared with 2 weeks ago, have your symptoms of heart failure changed?" had substantial prognostic value for the primary endpoint. To our knowledge, this is the first time that a KCCQ symptom domain was observed to carry prognostic information of this magnitude. Any change from stable (better or worse) was associated with an increased risk of cardiovascular events. Previous studies have correlated quality of life (QOL) with outcomes, including KCCQ.[23-25] The importance of this finding resides in the simplicity of the question, which can be incorporated into everyday practice, perhaps capturing a part of the medical history or a progressive change in symptoms. The observation that patients who had stable symptoms had better outcomes versus those with recent improvement reflects the benefit of a more consistent course over time.

Consistent with other studies, renal function was also an important predictor of outcomes.[26-29] BUN was a stronger predictor of outcome than creatinine, which accords with previous observations that included patients presenting with acute decompensated HF.[30,31] The greater prognostic power of BUN may be due to its incorporation of both pre-renal and renal function status, a factor incorporated into other predictive models.

Female sex was associated with lower risk of morbidity/mortality and mortality, as previously observed,[32] but findings have been inconsistent (Table 8). Although the mechanism of this sex differential in level of risk is likely complex, it may be related to degree of LV dysfunction and the presence or degree of coronary disease with subsequent amount of angina, diuretic dosing, renal dysfunction, and BMI.[33] In large cohorts, women with HF are also more likely to have a non-ischemic etiology, which may have a better prognosis. Further analyses by sex are warranted.

BMI was inversely related to all-cause mortality, but only for values <25 kg/m^2. This finding is consistent with the previous work of Anker et al. suggesting the benefit of higher BMI and detrimental effects of cachexia on mortality.[34] Treatment group (exercise vs. usual care) appears in none of the final models, as treatment group was not among the strong predictors of either of these endpoints.

Notably, our models were developed with a cohort of ambulatory patients with HF with systolic dysfunction, and further study is needed to determine the discriminatory capacity of these models in a patient cohort with severe HF. Gorodeski et al. recently applied the Seattle Heart Failure Model to patients with advanced HF undergoing evaluation for LVAD or cardiac transplantation.[35] The investigators demonstrated only a modest predictive accuracy (c-index 0.63–0.68) with substantial underestimation of risk. The addition of brain

natriuretic peptide (BNP), peak VO_2, and BUN improved the discrimination of the Seattle Heart Failure Model. This finding has implications for the applicability of our models, since BUN is included in the HF-ACTION models.

The development of risk models for ambulatory patients with HF with systolic dysfunction can be helpful for evaluating prognosis at the time of clinical evaluation, although many models have been too complex to be integrated into practice. By developing simple risk scores based on the most important prognostic factors, we have overcome this limitation. For example, a male patient with a BUN of 50 mg/dL able to tolerate exercise for only 8 minutes who reports feeling worse over the past month would have a high probability (almost 70%) of experiencing a hospitalization or death within the next year, and thus would likely require aggressive treatment and monitoring.

The HF-ACTION risk scores offer specific advantages over similar models and risk scores. First, the variables were obtained in an outpatient setting from evaluation of clinical characteristics, KCCQ questionnaires, routine laboratory tests, and exercise tests. Second, the risk scores were developed in the setting of evidence-based therapy (74% use of ACE inhibition, 95% use of beta blockade and 40% use of ICD therapy), making them applicable to a broad range of contemporary patients with HF. Third, the cohort studied represents a spectrum of ambulatory HF patients with reduced ejection fraction and NYHA Class II–IV symptoms. Finally, the scores incorporate information that, although readily available to HF specialists, has seen only modest prognostic application in patients with less severe HF. Unfortunately, few clinicians routinely use a health status instrument or exercise test data in everyday practice, despite the prognostic potential of these simple assessments.

Our analysis has several limitations. First, although our study cohort is broad, non-ambulatory patients and those with preserved systolic function were excluded. On the other hand, these risk scores are the first to include a large cohort of women and African American patients. The median age of 59 years, though typical of many clinical HF trials, is considerably younger than the average age of HF patients in the community.[36] Some variables (e.g., NT-proBNP) were not obtained in sufficient numbers of patients and were excluded from the analysis. Other potentially important variables were not collected at all (e.g., serum uric acid or lymphocyte count; allopurinol use). Exercise duration data measured during CPX testing included a small percentage of patients tested using a cycle ergometer protocol instead of the treadmill protocol used in the vast majority of patients. Without this mixture of modalities, the association of exercise duration with clinical outcomes might have been even stronger. Although the trial was international in scope, there was only a modest representation of patients from outside the U.S., thus limiting generalizability of these results to non-U.S. patients. Finally, although we employed internal validation that incorporated bootstrapping with optimism-corrected c-indexes, this model has not been externally validated in an independent cohort of HF patients because there are no known similar HF datasets that include peak VO_2, CPX duration, and KCCQ data. It should also be noted that the optimism-corrected c-indexes were not adjusted to reflect possible additional variability due to the variable selection process employed in developing the predictive models.

Ambulatory HF patients with systolic dysfunction (LVEF <0.35) have a high rate of morbidity and mortality despite widespread use of evidence-based therapies. In such patients, simple, easily-obtained clinical and laboratory characteristics are important determinants of all-cause hospitalization and/or all-cause death. The use of predictive risk scores to assess patient risk, both in clinical practice and clinical trials, may be a powerful tool for treatment decisions for HF patients with systolic dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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This is an analysis from the HF-ACTION trial of 2331 patients to understand the predictive variables of the primary endpoint of all-cause hospitalization and all-cause death, and all-cause death alone in a modern cohort of ambulatory, NYHA class II-IV heart failure patients. Our study revealed that despite a patient population with >90% use of ACE inhibitors and beta-blockers as background therapy, and >40% background device therapy, peak VO_2 remained the most predictive determinant of the primary endpoint. This finding is remarkable because this test, which has been shown to be highly predictive in the advanced NYHA Class IV heart failure population, now emerges as the most significant determinant of clinically important outcomes in patients with milder forms of heart failure. These finding imply that the use of cardiopulmonary exercise testing in mild to moderate heart failure may be useful in risk stratification of patients. In addition, we found that a simple question on the Kansas City Cardiomyopathy Questionnaire (KCCQ) regarding stability of symptoms in the previous 2 weeks was also highly predictive. Further, this finding could be easily incorporated into the history intake when evaluating patients. More traditional risk factors were also found to be determinants of clinical outcome, such as renal function and sex. In summary, this modern predictive model with a risk score can be easily implemented to provide risk stratification for patients with heart failure, and will help us better understand how heightened surveillance can be used to monitor high-risk patients.

Table 1

Baseline Characteristics by Event

Variable	With Primary Endpoint Event (n=1555)	Without Primary Endpoint Event (n=776)	With Mortality Endpoint Event (n=387)	Without Mortality Endpoint Event (n=1944)	Total (N=2331)
Age, y (n=2331)	60 (52-70)	58 (50-66)	64 (54-73)	59 (51-67)	59 (51-68)
Female sex, No. (%)	420 (27)	241 (31)	75 (19)	586 (30)	661 (28)
Race, No. (%)					
Black/African American	523 (34)	226 (30)	134 (35)	615 (32)	749 (33)
White	926 (60)	500 (66)	225 (59)	1201 (63)	1426 (62)
Other	84 (5.5)	37 (4.9)	23 (6.0)	98 (5.1)	121 (5.3)
Country, No. (%)					
Canada	114 (7.3)	74 (9.5)	33 (8.5)	155 (8.0)	188 (8.1)
France	28 (1.8)	47 (6.1)	3 (0.8)	72 (3.7)	75 (3.2)
USA	1413 (91)	655 (84)	351 (91)	1717 (88)	2068 (89)
BMI, kg/m^2 (n=2324)	30 (26-35)	30 (26-35)	29 (25-35)	30 (26-35)	30 (26-35)
NYHA Class, No. (%)					
II	907 (58)	570 (73)	187 (48)	1290 (66)	1477 (63)
III-IV	648 (42)	206 (27)	200 (52)	654 (34)	854 (37)
CCS angina class, No. (%)					
No angina	1274 (82)	676 (87)	327 (84)	1623 (84)	1950 (84)
I	144 (9.3)	56 (7.2)	37 (9.6)	163 (8.4)	200 (8.6)
II-IV	135 (8.7)	43 (5.6)	23 (5.9)	155 (8.0)	178 (7.6)
Ischemic HF etiology, No. (%)	834 (54)	363 (47)	227 (59)	970 (50)	1197 (51)
Blood pressure, mm HG					
SBP (n=2327)	110 (100-125)	112 (101-128)	110 (100-122)	112 (100-126)	111 (100-126)
DBP (n=2326)	70 (60-78)	70 (62-80)	68 (60-74)	70 (62-80)	70 (60-78)
LVEF, % (n=2327)	24 (19-30)	26 (21-32)	23 (18-29)	25 (21-30)	25 (20-30)
Mitral regurgitation, No. (%)					
None/non-severe *	1225 (86)	654 (92)	281 (81)	1598 (89)	1879 (88)
Severe †	201 (14)	55 (8)	65 (19)	191 (11)	256 (12)
Ventricular conduction prior to CPX, No. (%)					
Normal	578 (38)	401 (53)	127 (34)	852 (45)	979 (43)
LBBB	253 (17)	126 (17)	51 (14)	328 (17)	379 (17)
RBBB	71 (4.7)	14 (1.9)	23 (6.1)	62 (3.3)	85 (3.7)
IVCD	211 (14)	81 (11)	53 (14)	239 (13)	292 (13)
Paced	401 (26)	135 (18)	123 (33)	413 (22)	536 (24)
History of AF/flutter, No. (%)	373 (24)	115 (15)	125 (32)	363 (19)	488 (21)

Variable	With Primary Endpoint Event (n=1555)	Without Primary Endpoint Event (n=776)	With Mortality Endpoint Event (n=387)	Without Mortality Endpoint Event (n=1944)	Total (N=2331)
History of diabetes mellitus, No. (%)	537 (35)	211 (27)	147 (38)	601 (31)	748 (32)
Serum creatinine mg/dL (n=2091)	1.2 (1.0-1.5)	1.1 (0.9-1.3)	1.4 (1.1-1.8)	1.2 (1.0-1.4)	1.2 (1.0-1.5)
BUN, mg/dL (n=2028)	21 (16-31)	18 (14-24)	26 (18-37)	19 (15-26)	20 (15-28)
β blocker dose, mg/day carvedilol equivalent (n=2311)	25 (13-50)	50 (25-50)	25 (13-50)	38 (13-50)	25 (13-50)
Loop diuretic dose, mg/day furosemide equivalent (n=2298)	40 (20-80)	40 (0-60)	70 (40-100)	40 (10-80)	40 (20-80)
Peak VO_2, mL/kg/min (n=2275)	13.5 (10.8-16.5)	16.5 (13.4-19.4)	11.9 (9.5-14.7)	15.1 (12.1-18.1)	14.4 (11.5-17.7)
Weber class, No. (%)					
A (Peak VO_2 %gt; 20)	142 (9.3)	163 (22)	15 (4.0)	290 (15)	305 (13)
B (Peak VO_2 16.1-20)	286 (19)	245 (32)	48 (13)	483 (25)	531 (23)
C (Peak VO_2 10.1-16)	800 (53)	300 (40)	197 (52)	903 (48)	1100 (48)
D (Peak $VO_2 \leq 10$)	292 (19)	47 (6.2)	119 (31)	220 (12)	339 (15)
CPX duration, min (n=2309)	8.8 (6.3-11.2)	11.0 (8.4-13.7)	7.3 (5.1-9.7)	10.0 (7.4-12.4)	9.6 (6.9-12.0)
6MWD, m (n=2280)	356 (283-423)	400 (331-450)	320 (248-392)	380 (308-442)	371 (299-435)
Beck Depression Inventory II (n=2322)	9 (5-16)	7 (4-13)	9 (5-16)	8 (4-15)	8 (4-15)
KCCQ Overall Summary Score (n=2330)	66 (49-82)	72 (56-86)	63 (47-80)	69 (52-84)	68 (51-83)
KCCQ symptom stability, No. (%)					
Much worse/slightly worse	153 (10)	33 (4.3)	37 (9.6)	149 (7.7)	186 (8.0)
No change/no symptoms	1084 (70)	620 (80)	260 (68)	1444 (75)	1704 (74)
Much better/slightly better	308 (20)	119 (15)	87 (23)	340 (18)	427 (18)
KCCQ Total Symptom Score (n=2330)	75 (56-88)	81 (67-94)	72 (54-88)	77 (60-91)	77 (58-90)

All values given as median (IQR) unless otherwise noted.

*a combination of these original categories: None, Trivial, Mild, Mild to Moderate, and Moderate.

†a combination of the original categories Severe and Moderate to Severe.

AF, atrial fibrillation; BMI, body mass index; BUN, blood urea nitrogen ; CCS, Canadian Cardiovascular Society; CPX, cardiopulmonary exercise test; DBP, diastolic blood pressure; HF, heart failure; IVCD, intraventricular conduction delay; KCCQ, Kansas City Cardiomyopathy Questionnaire; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association (class); RBBB, right bundle branch block; SBP, systolic blood pressure; VO2, oxygen consumption; 6MWD; 6-minute walk distance.

Table 2

Simplified Predictive Model for Primary Composite Endpoint (Death/Hospitalization)

Parameter	Average χ^2	*P* value	HR (95% CI)
Exercise duration on CPX test (HR for 1-min increase)	153.0	<0.0001	0.92 (0.91-0.93)
KCCQ symptom stability			
Much worse/slightly worse	61.8	<0.0001	1.91 (1.62-2.27)
Much better/slightly better			1.26 (1.11-1.43)
BUN (HR for 10 mg/dL increase)	38.8	<0.0001	1.07 (1.05-1.09)
Sex: female	16.7	<0.0001	0.79 (0.70-0.88)

Model results are based on data sets containing imputed values of some covariates. BUN, blood urea nitrogen; CI, confidence interval; CPX, cardiopulmonary exercise test; HR, hazard ratio, KCCQ, Kansas City Cardiomyopathy Questionnaire.

Reference categories: KCCQ symptom stability=no change or no symptoms; sex=male

Table 3

Simplified Predictive Model for Mortality Endpoint

Parameter	Average χ^2	*P* value	HR (CI)
Exercise duration on CPX test (HR for 1-min increase)	151.7	<0.0001	0.82 (0.80-0.85)
BUN (HR for 10 mg/dL increase)	35.9	<0.0001	1.08 (1.05-1.11)
Sex: female	32.7	<0.0001	0.48 (0.37-0.61)
BMI (HR for 2 kg/m^2 increase, truncated above 25)	17.9	<0.0001	0.79 (0.70-0.88)

BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; CPX, cardiopulmonary exercise test; HR, hazard ratio.

Reference categories: Sex=male

Table 4

Simplified Risk Score Calculation: Primary Endpoint

Score element	Risk score points
CPX duration	65-(2.2×duration [min])
Symptom stability	
Much worse/slightly worse	15
Much better/slightly better	8
No change/no symptoms	0
Blood urea nitrogen	
0-19	0
20-39	3
40-59	7
60-79	10
80+	14
Male sex	6

CPX, cardiopulmonary exercise test

Table 5

Simplified Risk Score Calculation: Mortality Endpoint

Score element	Risk score points
CPX duration	69-(2.3×duration [min])
Body mass index	
<17.5	14
17.5 to <22.5	7
≥22.5	0
Blood urea nitrogen	
0-19	0
20-39	2
40-59	4
60-79	6
80+	8
Male sex	9

CPX, cardiopulmonary exercise test

Table 6

Estimated Probability of Event (Primary Endpoint) Based on Risk Score Calculation

Risk Score Decile	Patients	Observed %* of Patients with Event in 1st Year of Follow-up	Expected % of Patients with Event in 1st Year
1 (0-38)	234	18.7	21.4
2 (39-43)	233	26.3	28.5
3 (44-47)	233	30.2	32.7
4 (48-49)	234	33.6	35.9
5 (50-52)	232	42.1	39.1
6 (53-55)	233	39.2	42.3
7 (56-58)	233	46.3	46.1
8 (59-62)	233	51.7	50.5
9 (63-67)	233	64.0	56.4
10 (68-100)	233	67.1	68.0

* Kaplan-Meier estimate at 365 days

Table 7

Estimated Probability of Death Based on Risk Score Calculation

Risk Score Decile	Patients	Observed %* of Patients with Event in 1st Year of Follow-up	Expected % of Deaths in 1st Year
1 (0-41)	233	1.8	0.8
2 (42-46)	230	0.4	1.4
3 (47-50)	233	3.9	2.0
4 (51-52)	228	0.4	2.6
5 (53-55)	231	2.6	3.3
6 (56-57)	231	2.6	4.0
7 (58-60)	231	3.9	5.0
8 (61-63)	231	5.7	6.3
9 (64-68)	231	7.9	8.6
10 (69-100)	230	19.1	14.3

*Kaplan-Meier estimate at 365 days

Table 8

Model Comparisons

Trial	Predictors	Endpoints	C-Index
ESCAPE[7] (N=423)	Brain natriuretic peptide Cardiac arrest or mechanical ventilation Sodium level	6-month mortality	0.76
EFFECT[6] (N=2624)	Age Systolic blood pressure Respiratory rate Sodium level Blood urea nitrogen Comorbid conditions: cerebrovascular disease, dementia, COPD, hepatic cirrhosis, cancer	30-day mortality 1-year mortality	0.8 0.77
CHARM[3] (N=7599)	Age Ejection fraction Diabetes mellitus Body mass index Female sex New York Heart Association class III/IV Current smoker Bundle branch block Cardiomegaly Prior heart failure hospitalization Diastolic blood pressure Diagnosis of heart failure >2 years Previous myocardial infarction Dependent edema Heart rate Pulmonary crackles Pulmonary edema Mitral regurgitation Atrial fibrillation Rest dyspnea Candesartan	All-cause mortality (2 years)	0.75
CORONA[11] (N=3342)	NT-proBNP Age Diabetes mellitus Left ventricular ejection fraction Body mass index Coronary artery bypass grafting Female sex Atrial fibrillation New York Heart Association class Apo A-1 Serum creatinine Intermittent claudication Heart rate Myocardial infarction	All-cause mortality	0.72
Seattle HF Model (N=1125)[12]	Age Gender Ischemic etiology New York Heart Association class Ejection fraction Systolic blood pressure Potassium-sparing diuretic use Statin use Allopurinol use Hemoglobin % lymphocyte count Uric acid Sodium Cholesterol Diuretic dose/kg	Survival	0.73 (1-year ROC)
HF-ACTION (N=2331)[13]	Exercise duration on CPX test Blood urea nitrogen Female sex Body mass index	All-cause mortality (median follow-up 2.5 years)	0.73

Apo A-1, apolipoprotein A-1; COPD, chronic obstructive pulmonary disease; CPX, cardiopulmonary exercise test; NT-proBNP, N-terminal fragment pro-brain natriuretic peptide; ROC, receiver operating characteristic curve.