Factors Associated With Outcome in Heart Failure With Preserved Ejection Fraction

Findings From the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE)

Michel Komajda, MD; Peter E. Carson, MD; Scott Hetzel, MS; Robert McKelvie, MD; John McMurray, MD; Agata Ptaszynska, MD; Michael R. Zile, MD; David DeMets, PhD; Barry M. Massie, MD

Background—The determinants of prognosis in patients with heart failure and preserved ejection fraction (HF-PEF) are poorly documented.

Methods and Results—We evaluated data from 4128 patients in the I-PRESERVE trial (Irbesartan in Heart Failure with Preserved Ejection Fraction Study). Multivariable Cox regression models were developed using 58 baseline demographic, clinical, and biological variables to model the primary outcome of all-cause mortality or cardiovascular hospitalization (1505 events), all-cause mortality (881 events), and HF death or hospitalization (716 events). Log N-terminal pro–B-type natriuretic peptide, age, diabetes mellitus, and previous hospitalization for HF were the most powerful factors associated with the primary outcome and with the HF composite. For all-cause mortality, log N-terminal pro–B-type natriuretic peptide, age, diabetes mellitus, and left ventricular EF were the strongest independent factors. Other independent factors associated with poor outcome included quality of life, a history of chronic obstructive lung disease, log neutrophil count, heart rate, and estimated glomerular filtration rate. The models accurately stratified the actual 3-year rate of outcomes from 8.1% to 59.9% (primary outcome) 2.7% to 36.5% (all-cause mortality), and 2.1% to 38.9% (HF composite) for the lowest to highest septiles of predicted risks.

Conclusions—In a large sample of elderly patients with HF and preserved EF enrolled in I-Preserve, simple clinical, demographic, and biological variables were associated with outcome and identified subgroups at very high and very low risk of events.

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Key Words: heart failure ■ preserved ejection fraction ■ outcome ■ prognosis evaluation

Recent surveys suggest that up to half of the patients with heart failure have a preserved left ventricular ejection fraction (HF-PEF).[1–3] Patients with HF-PEF are more commonly older women and a greater proportion have hypertensive etiology.[4–8] Although some reports suggested that mortality in patients with HF-PEF was similar to that observed in HF with low EF, most studies show that survival is better in HF-PEF suggesting that a continuum of risk exists.[1,5] This condition is also associated with a high rate of rehospitalization.[1,5] In HF-PEF, identification of factors predicting mortality or morbidity in HF-PEF remains largely unexplored, in contrast to patients with HF and low EF. I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction Study) enrolled 4128 patients with HF-PEF. We used this large database to assess the factors associated with outcome in this condition and to quantify their individual power by the development of prognostic models.

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Methods

The I-PRESERVE design and results have been described and reported previously.[9,10] In brief, patients enrolled in the trial were at least 60 years of age and had HF symptoms and a left ventricular EF of at least 45%. In addition, we required patients who had been

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From the Pitie Salpetriere Hospital–University Pierre and Marie Curie Paris VI (M.K.), Paris, France; Georgetown University and Washington DC Veterans Affairs Medical Center (P.E.C.), Washington, DC; the Department of Biostatistics and Medical Informatics (S.H.), University of Wisconsin-Madison, Madison, Wis; Hamilton Health Sciences (R.M.), McMaster University, Hamilton, Ontario, Canada; British Heart Foundation Glasgow Cardiovascular Research Centre (J.M.), University of Glasgow, Glasgow, United Kingdom; Bristol-Myers Squibb (A.P.), Princeton, NJ; RHJ Department of Veterans Affairs Medical Center and Medical University of South Carolina (M.R.Z.), Charleston, SC; the Department of Biostatistics and Medical Informatics (D.D.), University of Wisconsin-Madison, Madison, Wis; and the University of California, San Francisco, and San Francisco Veterans Affairs Medical Center (B.M.M.), San Francisco, Calif.

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Correspondence to Michel Komajda, MD, CHU Pitié-Salpêtrière, Institut de Cardiologie, 47/83, Boulevard de l'Hôpital, 75013 Paris, France. E-mail michel.komajda@psl.aphp.fr

hospitalized for HF during the previous 6 months to have current New York Heart Association class II, III, or IV symptoms with corroborative evidence. If they had not been hospitalized, they were required to have ongoing class III or IV symptoms with corroborative evidence.

Exclusion criteria have been detailed previously. Patients were enrolled after informed consent was given at 293 sites in 25 countries.

End points used for the current analysis were (1) the primary composite end point of the trial: all-cause mortality and protocol-specified cardiovascular hospitalizations (HF, myocardial infarction, stroke, and ventricular or atrial arrhythmias); (2) all-cause mortality; and (3) the composite of HF death or hospitalization.

The Minnesota Living with Heart Failure score at baseline was used to assess quality of life (QOL).[11] The plasma level of N-terminal pro–B-type natriuretic peptide (NT-proBNP) was measured at random assignment and analyzed in a central laboratory (Esoterix, Belgium). Values (expressed in pg/mL) were log-transformed.

Statistical Methods

To develop the final predictive models, we started from the entire list of variables collected at the baseline visit in I-PRESERVE and a variable for irbesartan versus placebo, excluding nonrandomized medical therapy. With the remaining list of 58 variables, univariate Cox proportional hazards models were fit individually for each of the 3 outcomes mentioned above. Association of each variable to the outcomes was determined by comparing with an intercept only base model. Any variable that had a χ^2 probability value <0.01 in any of the models was considered as a candidate variable for the final models.

The database for analysis included patients with all 58 variables, which narrowed the study cohort from 4128 to 2563 patients. The baseline characteristics of the subjects with full data and subjects with missing data were examined for significant differences (Table 1). Based on Bonferroni-adjusted probability values, significant differences were noted. Further, examination of the outcomes between the 2 cohorts by log-rank tests showed that those that had missing data had a greater occurrence of primary events and all-cause mortality.

Because there were significant differences between those with full data and those with missing data and the number of subjects with missing data was large, we examined multiple methods of imputation and model building. The methods included (1) building and fitting the model based on the full data cohort, (2) building the model based on the full data cohort and fitting the model after imputation with mean or median was used to fill in the missing data, (3) same as 2 but with a regression based imputation after building the model, and (4) building and fitting the model after a regression based imputation[12] for the missing data. The major difference in method 4 compared with methods 1 to 3 was to impute first and then build the model based on all 4128 subjects. There were some differences in model variables between method 4 and methods 1 to 3. All variables in methods 1 to 3 entered into the method 4 model except for history of myocardial infarction. With increased sample size, because imputation occurred before model building, there was more power to fit more variables in the model. Additional variables that made it into the models based on imputed data were sex, systolic blood pressure, blood urea nitrogen, stroke or transient ischemic attack, pulmonary congestion, body mass index, and atrial fibrillation. Most of these entered after the variables from the methods 1 to 3 were already entered. Each method's model was fit, and Harrell C-statistic[13] for discrimination ability of models with censored data were calculated and compared. There was very little variation in the C-statistics for each model: Primary outcome ranged from 0.711 to 0.717; all-cause mortality, 0.733 to 0.745; and HF composite, 0.765 to 0.777. Because imputation by regression methods is more robust than by mean or median, model-building based on full data does not depend on imputation assumptions, and because the discrimination ability of the different models are similar, we present the model that is built based on the 2563 subjects with full data and then fit this model to the total cohort after regression based imputation to replace the missing baseline values (method 3).

Individually for each outcome, Cox proportional hazards models were developed using a forward-only stepwise process with $P<0.01$ as our threshold for entry into the model. Once the model was built, forward, then backward, processes were run to see whether the same models would be achieved, and they were the same. Final models included the union of the variables that were in at least 1 of the outcome's model. Statistical strength of each variable in the final models was quantified by the change in the log-likelihoods that occurred by fitting a model with each variable individually dropped from the full model. These quantities are χ^2 values, each with 1 degree of freedom.

β-Coefficients for each continuous variable and outcome were examined for linearity. This was done by splitting the variable into groups by septiles or by relevant steps and plotting the hazard ratios compared with a reference group on a log scale. Hazard ratios were examined for ease of clinical interpretation. Those variables that showed nonlinearity in the β-coefficients were log-transformed accordingly. For some variables in the model, linearity was seen only after certain cut points: QOL >50 on a 0 to 100 scale, EF $<60\%$, and estimated glomerular filtration rate (GFR) <90 mL/min/1.73 m^2 of body surface area using the Modification of Diet in Renal Disease (MDRD) formula.[14] Values in regions where there was no risk nor benefit were truncated to the cut-point, and these were then modeled as continuous variables beyond the cut-point. In the supplemental material, Figure A, B, C, and D show the log scale hazard ratio relationship for EF, log NT-proBNP, estimated GFR, and age as continuous variables for the 3 outcomes. Linearity was established through logarithmic transformations for NT-proBNP and neutrophil count. Binary and categorical variables were modeled with appropriate dummy variables.

Once models were finalized with the full data cohort, the effects of missing data were examined. The majority of missing data was due to QOL and NT-proBNP. Missing data accounted for 601 primary events (364 all-cause mortality and 271 composite HF events) to be left out of analysis. The effect of missing data on the model was examined by imputing the missing data using a nonlinear regression method and then fitting the model to the full cohort of patients. The differences in estimates for each model were marginal, and therefore we decided to include all events. We validated and presented the final models as based on the full cohort with imputed data.

Risk scores were determined for each patient from the final models and split into septiles of risk. A risk score is the linear combination of the values for each risk factor and their corresponding coefficient from the model. For ease in reporting, we multiplied the risk scores by a factor of 10. An Efron bootstrap with 200 resamples was used to examine the model calibration by predicted versus observed rates of event within 3 years by risk score septiles. Kaplan–Meier curves of the septile groups were used to show the ability to correctly separate populations of patients at risk. The models' discrimination abilities were assessed by Harrell C-statistic for models with censored data,[13] and internal validity was examined by average C-statistic from 200 Efron bootstrap resamples.[15]

Results

Table 1 compares the baseline characteristics of the total cohort, the model-building full data cohort, and the missing data cohort. Based on Bonferroni-adjusted (32 tests) probability values, statistically and clinically significant differences between the full data cohort and missing data cohort were seen for left ventricular hypertrophy, hypertension etiology, and anemia and history of hypertension, angina, percutaneous coronary intervention or coronary artery bypass grafting, and diabetes. Also, log-rank tests between the groups showed significantly higher occurrence of the primary outcome and all-cause mortality in those that needed imputed data. During follow-up of the total cohort, 1505 primary end points

Table 1. Clinical, Demographic, and Biological Baseline Characteristics and Rate of Events of the Overall I-PRESERVE Population, of the Cohort of Patients With Full Data, and of the Cohort of Patients With Missing Data

Characteristic	Full Cohort (n=4128)	Full Data Cohort (n=2563)	Missing Data Cohort (n=1656)	*P* Value
Demographic				
Age				
Mean, y	72±7	71±7	72±7	0.2412
≥75 y, n (%)	1413 (34)	844 (33)	569 (36)	0.8496
Female sex, n (%)	2491 (60)	1562 (61)	929 (59)	1
Race, n (%)				0.2782
White	3859 (93)	2421 (94)	1438 (92)	
Black	82 (2)	45 (2)	37 (2)	
Asian	34 (1)	15 (1)	19 (1)	
Other	152 (4)	81 (3)	71 (5)	
Clinical				
New York Heart Association class, n (%)				1
II	870 (21)	552 (22)	318 (20)	
III	3144 (76)	1944 (76)	1200 (77)	
IV	112 (3)	67 (3)	45 (3)	
Heart rate, beats/min	71±10	71±10	72±11	1
Blood pressure, mm Hg				
Systolic	136±15	136±15	136±15	1
Diastolic	79±9	79±9	78±9	0.0181
Body mass index	30±5	30±5	30±5	1
ECG findings, n (%)				
Left ventricular hypertrophy	1260 (31)	840 (33)	420 (27)	0.0021
Left bundle-branch block	336 (8)	210 (8)	126 (8)	1
Atrial fibrillation or flutter	697 (17)	425 (17)	272 (17)	1
EF	0.59±0.09	0.59±0.09	0.59±0.09	1
Cause of HF, n (%)				
Ischemia	1036 (25)	618 (24)	418 (27)	1
Hypertension	2622 (64)	1698 (66)	924 (59)	0.0001
Hospitalization for HF within previous 6 mo, n (%)	1816 (44)	1139 (44)	677 (43)	1
Medical history, n (%)				
Hypertension	3650 (88)	2303 (90)	1347 (86)	0.0089
Angina symptoms	1652 (40)	1116 (44)	536 (34)	<0.0001
Unstable angina	315 (8)	174 (7)	141 (9)	0.3478
Myocardial infarction	969 (23)	626 (24)	343 (22)	1
PCI or CABG	548 (13)	286 (11)	262 (17)	<0.0001
Atrial fibrillation	1209 (29)	717 (28)	492 (31)	0.6228
Diabetes mellitus	1134 (27)	653 (25)	481 (31)	0.0089
Stroke or transient ischemic attack	399 (10)	233 (9)	166 (11)	1
QOL				
Score on the Minnesota Living with HF Scale				
Median	42	43	40	0.4121
Interquartile range	28–58	28–58	25–56	
Laboratory measurements				
Hemoglobin				
Mean, g/dL	13.9±1.9	13.9±1.9	13.7±1.9	0.0262
Anemia, n (%)	514 (13)	293 (11)	221 (16)	0.0087
Creatinine, mg/dL	1±0.33	0.99±0.3	1.02±0.37	0.0887

(*Continued*)

Table 1. Continued

Characteristic	Full Cohort (n=4128)	Full Data Cohort (n=2563)	Missing Data Cohort (n=1656)	*P* Value
Estimated GFR				
Mean, mL/min/1.73 m^2 body surface area	73±22	73±22	72±23	1
<60 mL/min/1.73 m^2, n (%)	1245 (31)	763 (30)	482 (33)	1
Potassium, mmol/L	4.4±0.47	4.4±0.46	4.4±0.5	1
NT-proBNP, pg/mL				
Median	339	320	410	1
Interquartile range	134–963.5	126–928	153–1043	
Outcome, n (%)				Log-rank *P*
Primary outcome	1505 (36)	904 (35)	601 (38)	0.0068
All-cause mortality	881 (21)	517 (20)	364 (23)	0.0032
Composite HF outcome	716 (17)	445 (17)	271 (17)	0.6060

PCI indicates percutaneous coronary intervention; CABG, coronary artery bypass graft.

occurred, including 447 all-cause deaths and 1058 prespecified cardiovascular hospitalizations. Overall, there were 881 all-cause deaths and 716 HF events, including 125 fatal HF events.

Table 2 shows the 10 strongest variables from univariate analysis for the 3 outcomes. For each of the 3 outcomes, the strongest associated factors were log plasma level of NT-proBNP, age, renal function assessed either by blood urea nitrogen or by estimated GFR and a history of a HF hospitalization within 6 months before entry.

The rate of event increased progressively with increasing age and log NT-proBNP. In contrast, a different pattern was observed for EF and estimated GFR: For the former, the rate of event increased for EF values below 60% and was constant above 60% for all 3 outcomes, whereas for the latter, the rate increased below 90 mL/min/1.73 m^2 and was constant above 90 for all 3 outcomes (supplemental material: Figure A, B, C, and D).

Table 3 shows the final models in descending order of variable strength for each of the 3 modeled outcomes. Log NT-proBNP was the strongest independent factor associated with primary outcome and all-cause mortality and the second strongest for HF composite. Previous HF hospitalization was the strongest factor correlated with the HF composite. Age, diabetes mellitus, heart rate, poor QOL, comorbidities such as chronic obstructive pulmonary disease or impaired renal function, EF, and previous myocardial infarction or ischemic etiology were also identified as associated with poor outcome. Overall, there was consistency across the 3 models as to the most important factors associated with outcome.

Figure 1 illustrates the correlative power of the final models: Kaplan–Meier curves for each outcome by septile of the risk scores from the Cox models are shown. For each outcome, patients in the 2 septiles with the higher risk score had a particularly poor outcome.

Figure 2 shows model calibrations of the observed and expected 3-year rates of primary outcome, all-cause mortality, and HF composite by septiles of risk. Predicted and observed scores were well in line with only minor deviations from equality in each outcome.

For the 3 outcomes, there was at least a 7-fold increase in event rate for the highest septile of the risk score compared with the lowest septile. The actual 3-year event rate in the highest septile was 59.9% for the primary outcome, 36.5% for all-cause mortality, and 38.9% for the HF composite. By contrast, it was only 8.2%, 2.7%, and 2.1%, respectively, in the lowest septile. The upper cutoffs of the septiles of risk score are shown in Table 4.

The discrimination ability of the models was robust, with Harrell C-statistics of 0.711 (primary outcome), 0.736 (all-cause mortality), and 0.765 (HF composite), respectively. Results from internal validation resampling showed no overinflation of the models' discrimination ability, with averaged C-indices of 0.711, 0.735, and 0.765, respectively.

Discussion

This study identified a set of clinical, demographic, and biological variables that were strongly associated with cardiovascular morbidity, all-cause death, and HF events in a large sample of older patients with HF-PEF enrolled in I-PRESERVE.

Although NT-proBNP was moderately increased in the overall population, a finding in line with other observations,[16–19] baseline NT-proBNP was the most powerful independent factor for the primary event and all-cause mortality models. This observation has important clinical implications for the identification of high-risk patients with this condition and strongly supports using natriuretic peptides as an inclusion criterion in future studies involving HF-PEF patients.

Age was another powerful factor associated with outcome in our study. Older age has also been reported as a strong prognostic factor in HF patients with low EF[20–23] and in a clinical trial spanning the full range of left ventricular dysfunction.[24] Because patients enrolled in I-PRESERVE were, by protocol, 60 years of age or older, we were unable to verify if there was a threshold value below which age had little impact, as described in the CHARM program.[24]

The presence of diabetes mellitus was also associated with a poor outcome. Although diabetes mellitus has been associated with poor outcome in patients with HF with low EF,[24–26] a population in which ischemic cardiomyopathy predominates, our finding underlines the importance of this comor-

Table 2. Strongest Univariate Association of Candidate Variables With Each Outcome

Variable	Hazard Ratio (95% CI)	χ^2 Value	*P* Value
Ten strongest variables from univariate analysis for primary composite			
NT-proBNP: log, pg/mL	1.592 (1.525, 1.661)	458.6	<0.0001
Age per 1-y increase	1.055 (1.048, 1.063)	209.9	<0.0001
BUN: log >3.1	4.281 (3.535, 5.183)	172.6	<0.0001
eGFR <90 by 1-unit decrease	1.019 (1.016, 1.022)	159.4	<0.0001
Hosp for HF last 5 mo: Yes vs no	1.915 (1.729, 2.120)	157.6	<0.0001
Atrial fibrillation: Yes vs no	1.926 (1.737, 2.136)	146.3	<0.0001
Creatinine, μmol/L	1.926 (1.771, 2.095)	135.5	<0.0001
Neutrophil count: log	2.268 (1.945, 2.644)	110.1	<0.0001
Albumin: log	2.261 (1.936, 2.639)	107	<0.0001
EF <60% by 1%	1.048 (1.038, 1.058)	83.8	<0.0001
Ten strongest variables from univariate analysis for all-cause mortality			
NT-proBNP: log, pg/mL	1.715 (1.621, 1.813)	363.7	<0.0001
Age per 1-y increase	1.071 (1.061, 1.081)	197.1	<0.0001
BUN: log >3.1	4.774 (3.792, 6.010)	134.6	<0.0001
eGFR<90 by 1-unit decrease	1.021 (1.017, 1.025)	118.4	<0.0001
Creatinine, μmol/L	2.080 (1.876, 2.305)	107	<0.0001
EF <60% by 1%	1.059 (1.046, 1.073)	76.3	<0.0001
Pulmonary congestion: Yes vs no	1.795 (1.569, 2.053)	72.6	<0.0001
Atrial fibrillation Yes vs no	1.792 (1.567, 2.050)	68.9	<0.0001
Neutrophil count: log	2.316 (1.898, 2.825)	68.9	<0.0001
Albumin: log	2.292 (1.874, 2.803)	66.5	<0.0001
Ten strongest variables from univariate analysis for HF composite			
NT-proBNP: log, pg/mL	1.735 (1.631, 1.846)	307.7	<0.0001
Hosp for last 6 mo: Yes vs no	2.924 (2.502, 3.417)	196.9	<0.0001
eGFR <90 by 1-unit decrease	1.026 (1022, 1.030)	145.9	<0.0001
Atrial fibrillation: Yes vs no	2.517 (2.173, 2.915)	144.9	<0.0001
BUN: log >3.1	5.847 (4.543, 7.525)	139.7	<0.0001
Age per 1-y increase	1.065 (1.054, 1.076)	136.5	<0.0001
Atrial fibrillation or flutter: Yes vs no	2.364 (2.013, 2.778)	95.7	<0.0001
Creatinine, μmol/L	2.053 (1.841, 2.289)	89.7	<0.0001
Neutrophil count: log	2.508 (2.008, 3.131)	66	<0.0001
Albumin: log	2.517 (2.012, 3.149)	65.3	<0.0001

BUN indicates blood urea nitrogen; eGFR, estimated GFR (mL/mn/m^2); and Hosp, hospitalization. Neutrophil count is measured as 1000 cells/μL and albumin as g/dL.

bidity in a population consisting exclusively of HF-PEF with lower overt ischemic heart disease.

The presence of a previous hospitalization for HF was associated with a >2-fold increase in the rate of subsequent HF events as it is in patients with HF with low EF.[24] Our observation confirms that patients with a recent admission for HF, regardless of their EF, are a high-risk group for readmission and a population that should be targeted in designing future trials on HF-PEF.

EF is a known predictor of outcome in HF with low EF.[21,24] We found that EF was also associated with the primary outcome and all-cause mortality in the I-PRESERVE population, although the relationship was observed only when EF was <60%. A weaker association was seen for the HF outcome. Our results are similar to those of the CHARM program, although their results found increased morbidity and mortality risk for subjects with an EF <45%.[24] Heart rate was identified as a factor associated with all-cause mortality and with HF events. The relationship of heart rate to morbidity and mortality has been reported previously[27–31] in coronary artery disease and in HF with low EF. It has been postulated that increased heart rate is associated with increased oxygen consumption and reduced myocardial oxygen supply resulting in myocardial energy imbalance. Our study suggests that the relationship between heart rate and poor outcome is also present in patients with HF-PEF.

Table 3. Final Model Summaries

Variable	Hazard Ratio (95% CI)	Coefficient	Standard Error	χ^2 Value	*P* Value
Final model for primary composite					
NT-proBNP: log, pg/mL	1.251 (1.201, 1.304)	0.224	0.021	114.5	<0.0001
Age per 5-y increase	1.198 (1.151, 1.246)	0.180	0.020	79.3	<0.0001
Hosp for HF last 6 mo	1.541 (1.386, 1.714)	0.433	0.054	64.5	<0.0001
Diabetes mellitus	1.433 (1.285, 1.597)	0.359	0.056	40.4	<0.0001
Neutrophils: log, pg/mL	1.458 (1.261, 1.686)	0.377	0.074	26.5	<0.0001
EF per 5% decrease <60	1.135 (1.078, 1.195)	−0.127	0.026	22.8	<0.0001
COPD or asthma	1.413 (1.215, 1.643)	0.356	0.770	18.6	<0.0001
GFR per 5-unit decrease <90	1.031 (1.015, 1.047)	−0.031	0.008	15.2	0.0001
QOL per 5-unit increase >50	1.044 (1.021, 1.068)	0.043	0.012	13.3	0.0002
Ischemic etiology	1.199 (1.052, 1.367)	0.182	0.067	7.3	0.0066
Myocardial infarction	1.177 (0.849, 1.029)	0.163	0.069	5.6	0.0176
Heart rate per 5-bpm increase	1.021 (0.997, 1.045)	0.021	0.012	2.9	0.0869
Final model for all-cause mortality					
NT-proBNP: log, pg/mL	1.341 (1.271, 1.415)	0.293	0.027	115.1	<0.0001
Age per 5-y increase	1.277 (1.211, 1.345)	0.244	0.027	83.3	<0.0001
Diabetes mellitus	1.482 (1.287, 1.706)	0.393	0.072	28.7	<0.0001
EF per 5% decrease <60	1.174 (1.099, 1.253)	−0.160	0.034	22.2	<0.0001
Heart rate per 5-bpm increase	1.058 (1.027, 1.090)	0.056	0.015	13.2	0.0003
Neutrophils: log, pg/mL	1.387 (1.153, 1.668)	0.327	0.094	12.2	0.0005
Hosp for HF last 6 mo	1.225 (1.065, 1.410)	0.203	0.071	8.1	0.0043
QOL per 5-unit increase >50	1.045 (1.014, 1.076)	0.044	0.015	8	0.0047
COPD or asthma	1.320 (1.086, 1.604)	0.277	0.099	7.3	0.0068
GFR per 5-unit decrease <90	1.027 (1.007, 1.047)	−0.026	0.010	6.8	0.0092
Ischemic etiology	1.192 (1.006, 1.413)	0.176	0.087	4	0.0442
Myocardial infarction	1.194 (1.003, 1.421)	0.178	0.089	3.9	0.0472
Final model for HF composite					
Hosp for HF last 6 mo	2.235 (1.901, 2.627)	0.8	0.083	100.2	<0.0001
NT-proBNP: log, pg/mL	1.274 (1.201, 1.352)	0.24	0.030	64.7	<0.0001
Age per 5-y increase	1.216 (1.148, 1.288)	0.2	0.029	44.7	<0.0001
Diabetes mellitus	1.688 (1.447, 1.969)	0.52	0.079	42.3	<0.0001
GFR per 5-unit decrease <90	1.056 (1.033, 1.079)	−0.05	0.011	32.2	<0.0001
COPD or asthma	1.528 (1.244, 1.878)	0.42	0.105	14.9	0.0001
Neutrophils: log, pg/mL	1.381 (1.123, 1.698)	0.32	0.105	9.5	0.0020
Heart rate per 5-bpm increase	1.045 (1.014, 1.083)	0.05	0.017	7.6	0.0059
EF per 5% decrease <60	1.110 (1.030, 1.196)	−0.1	0.038	7.3	0.0068
QOL per 5-unit increase >50	1.045 (1.012, 1.079)	0.04	0.016	6.9	0.0087
Ischemic etiology	1.128 (0.931, 1.366)	0.12	0.098	1.5	0.2207
Myocardial infarction	1.085 (0.890, 1.323)	0.08	0.101	0.6	0.4229

Hosp indicates hospitalization; COPD, chronic obstructive pulmonary disease.

The presence of lung disease was associated with a marked increase in rate of event in the 3 models and particularly in the rate of HF events. This is consistent with previous reports and reflects the complexity of elderly patients with HF-PEF, who often have multiple comorbidities and of their management.[32–34] Because by study design, severe pulmonary disease was excluded, the impact of this comorbidity on outcome could be even greater in an unselected population of HF-PEF.

Some factors such as renal function and prior myocardial infarction were not as prominent as in other populations.

Renal function assessed by estimated GFR, univariately, was strongly associated with poor outcome, but the χ^2 value suggests that renal impairment only had a moderate impact multivariately when the other variables were included. The importance of renal dysfunction as a powerful marker of poor outcome has been recognized in several studies or surveys of patients with low EF as well as in HF-PEF patients.[21,22,35–36] The lack of a stronger correlative value observed in the present study may, in part, reflect the exclusion of patients with severe renal impairment or anemia in I-PRESERVE.

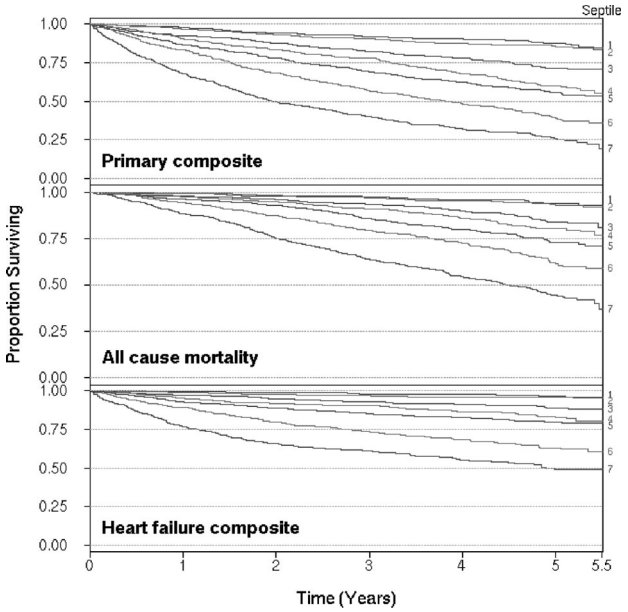

Figure 1. Kaplan–Meier curves of risk septiles for each outcome.

Also, none of the previous analyses have included NT pro-BNP, which may have altered the strength of renal function as associated with outcome.

Log neutrophil count was also correlated to outcome in our 3 models. The association of neutrophil count and outcome has been reported previously in HF with low EF[37] and after myocardial infarction,[38] and increased neutrophil lifespan has been described in this condition.[39] This marker might reflect the deleterious role of chronic inflammation in HF with associated prothrombotic and proatherogenic effects.

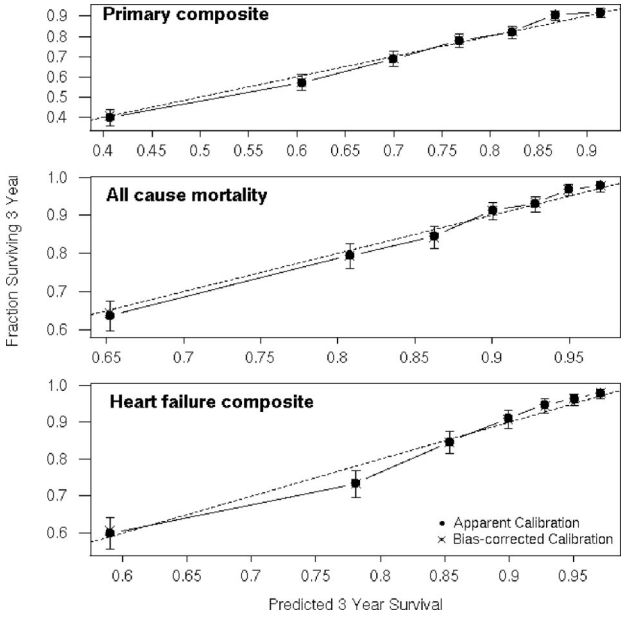

Figure 2. Calibration of model selection by using Efron bootstrap, with B=200 resamples and 7 equally divided groups of patients by 3-year survival probability. Fraction surviving (*y*-axis) is from Kaplan–Meier estimates. Predicted survival (*x*-axis) is from Cox proportional hazard model.

Table 4. Upper Cutoff of Risk Score Septiles

	Septile of Risk						
Outcome	1st	2nd	3rd	4th	5th	6th	7th
Primary composite	29.72	33.09	36.16	39.12	42.19	46.00	65.09
All-cause mortality	42.09	46.01	49.54	52.83	56.36	60.44	83.84
HF composite	35.08	39.04	42.95	46.43	50.72	55.62	79.26

Previous models have provided useful prognostic information in HF. Although some of our independent factors are similar to those identified in the CHARM overall population,[24] the CHARM trial included HF patients spanning the full range of EF values, and the prognostic analysis did not include laboratory parameters. The lack of laboratory values is also true for the SEATTLE model, which was constructed in low-EF HF only.[40]

Overall, the 3 models developed in the present study show that a limited set of simple clinical, demographic, and biological variables provides important information for the association with all-cause mortality, cardiovascular morbidity, or HF events. These models are based on a large sample of patients with HF-PEF enrolled in I-PRESERVE with documented inclusion criteria and on a long follow-up period. They have been developed out of a large number of events adjudicated by an end point committee based on predefined criteria. Moreover, the consistency of the variables associated with the 3 different outcomes suggests that these models are robust.

The goodness of fit of our models to predict any individual's risk of each outcome was also confirmed by the consistency between predicted and observed rates of events and its internal validity verified by C-statistic values. Simple demographic, clinical, and biological data allow to group patients in very low or very high risk groups. In particular, NT-proBNP, age, previous HF hospitalization, and diabetes mellitus are strongly correlated with outcome and should be carefully taken into consideration when assessing risk in HF-PEF. These factors could also enrich populations to be studied in future trials with HF-PEF.

Limitations

The I-PRESERVE population was studied in the context of a clinical trial with exclusion criteria. This population is therefore selective compared with patients with HF-PEF in clinical practice. In particular, patients with moderate or severe renal dysfunction were excluded from the trial. Also diabetes mellitus was reported by investigators but no specific criterion was used for the diagnosis of this important factor. The study cohort was nearly exclusively White and therefore may not be generalizable to other ethnicities.

Further, our model was built based on a subset of the total population albeit a moderate but nonetheless substantial and similar subgroup of 2563 patients for which the full set of baseline variables was available. Moreover, after checking the effect of the missing data by imputation and refitting the models, the effect on the model estimates between the 2 cohorts were marginal and we therefore proceeded to use the entire cohort with imputed data to report our final models.

Finally, the prognostic power of our models was not validated in an independent cohort, though it is supported by statistical techniques such as bootstrapping. Further validation should be performed in other populations.

Conclusion

We report models of associations for 3 important prespecified outcomes in elderly patients with HF-PEF included in the I-PRESERVE trial. We have identified a limited set of demographic, clinical, and biological variables that provide important and independent prognostic information and are consistent across the 3 models developed. These models allow the identification of a subgroup of patients at very high risk of events and should be validated in existing data bases and in future trials on HF-PEF.

Sources of Funding

The I-PRESERVE trial was supported by Bristol-Myers-Squibb and Sanofi Aventis.

Disclosures

Drs Komajda, Carson, McKelvie, Zile, and Massie received consulting fees from Bristol-Myers-Squibb as Executive Committee Members of the I-PRESERVE trial. Dr McMurray received support from Bristol-Myers-Squibb to Glasgow University. Scott Hetzel and Dr DeMets are employed by the Statistical Data Analysis Center at the University of Wisconsin-Madison, which conducted statistical analysis for the study supported by Bristol-Myers-Squibb and Sanofi-Aventis. Dr Ptaszynska is an employee of and has an equity interest in Bristol-Myers-Squibb.

References

1. Lenzen MJ, Scholte OP, Reimer WJ, Boersma E, Vantrimpont PJMJ, Follath F, Swedberg K, Cleland J, Komajda M. Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeartFailure Survey. *Eur Heart J*. 2004;25:1214–1220.
2. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251–259.
3. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med*. 2006;355:260–269.
4. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function: epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol*. 2004;43:317–327.
5. Yancy CW, Lopatin M, Stevenson LW, de Marco T, Fonarrow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) database. *J Am Coll Cardiol*. 2006;47:76–84.
6. Philbin EF, Rocco TA Jr, Lindenmuth NW, Ulrich K, Jenkins PL. Systolic versus diastolic heart failure in community practice: clinical features, outcomes, and the use of angiotensin-converting enzyme inhibitors. *Am J Med*. 2000;109:605–613.
7. Fonarrow GC, Stough WG, Abraham WT, Albert N, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB, for the OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with Preserved Systolic Function Hospitalized for Heart Failure. *J Am Coll Cardiol*. 2007;50:768–777.
8. Somaratne JB, Berry C, McMurray JJ, Poppe KK, Doughty RN, Whalley GA. The prognostic significance of heart failure with preserved left ventricular ejection fraction: a literature-based meta-analysis. *Eur J Heart Fail*. 2009;11:855–862.
9. Carson P, Massie BM, McKelvie R, McMurray J, Komajda M, Zile M, Ptaszynska A, Frangin G, for the I-PRESERVE Investigators. The Irbesartan in heart failure with Preserved Systolic Function (I-PRESERVE) trial: rationale and design. *J Card Fail*. 2005;11:576–585.
10. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A, for the I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med*. 2008;359:2456–2467.
11. Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota living with heart failure questionnaire as a measure of therapeutic response to enalapril or placebo. *Am J Cardiol*. 1993;71:1106–1107.
12. de Groot JAH, Janssen KJM, Zwinderman AH, Moons KGM, Reitsma JB. Multiple imputation to correct for partial verification bias revisited. *Stat Med*. 2008;27:5880–5889.
13. Harrell FE Jr. *Regression Modelling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York: Springer-Verlag New York, Inc; 2001.
14. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation: Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461–470.
15. Harrell FE Jr, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. *Stat Med*. 1984;3:143–152.
16. Hogg K, McMurray J. Neurohormonal pathways in heart failure with preserved systolic function. *Prog Cardiovasc Dis*. 2005;47:357–366.
17. Maisel AS, McCord J, Nowak RM, Hollander JE, Wu AHB, Duc P, Omland T, Storrow AB, Krishnaswamy P, Abraham WT, Clopton P, Steg G, Aumont MC, Westheim A, Wold Knudsen CW, Perez A, Kamin R, Kazanegra R, Hermann HC, McCullough PA, for the Breathing Not Properly Multinational Study Investigators. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. *J Am Coll Cardiol*. 2003;41:2010–2017.
18. Gradman A, Deedwania P, Cody R, Massie B, Packer M, Pitt B, Goldstein S. Predictors of total mortality and sudden death in mild to moderate heart failure. *J Am Coll Cardiol*. 1989;14:564–570.
19. McKelvie RS, Komajda M, McMurray J, Zile M, Ptaszynska A, Donovan M, Carson P, Barry MM, for the I-PRESERVE Investigators. Baseline plasma NT-proBNP and clinical characteristics: results from the irbesartan in heart failure with preserved ejection fraction trial. *J Card Fail*. 2010;16:128–134.
20. Kearney MT, Nolan J, Lee AJ, Brooksby PW, Prescott R, Shah AM, Zaman AG, Eckberg DL, Lindsay HS, Batin PD, Andrews R, Fox KA. A prognostic index to predict long-term mortality in patients with mild to moderate chronic heart failure stabilised on angiotensin converting enzyme inhibitors. *Eur J Heart*. 2003;5:489–497.
21. Brophy JM, Dagenais GR, McSherry F, Williford W, Yusuf S. A multivariate model for predicting mortality in patients with heart failure and systolic dysfunction. *Am J Med*. 2004;116:300–304.
22. Eichhorn EJ. Prognosis determination in heart failure. *Am J Med*. 2001;110:14S–36S.
23. Rich MW, McSherry F, Williford W, Yusuf F. Effect of age on mortality, hospitalizations and response to digoxin in patients with heart failure: the DIG study. *J Am Coll Cardiol*. 2001;38:806–813.
24. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJC, Swedberg KB, Ostergren J, Michelson EL, Pieper KS, Granger CB, on behalf of the CHARM Investigators. Predictors of mortality and morbidity in patients with chronic heart failure. *Eur Heart J*. 2006;27:65–75.
25. Domanski M, Krause-Steinfrauf H, Deedwania P, Follmann D, Ghali JK, Gilbert E, Haffner S, Katz R, Lindenfeld J, Lowes BD, Martin W, McGrew F, Bristow MR, BEST Investigators. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. *J Am Coll Cardiol*. 2003;42:914–922.
26. Das SR, Drazner MH, Yancy CW, Stevenson LW, Gersh BJ, Dries DL. Effects of diabetes mellitus and ischemic heart disease on the progression from asymptomatic left ventricular dysfunction to symptomatic heart failure: a retrospective analysis from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial. *Am Heart J*. 2004;148:883–888.
27. Disegni E, Goldbourt U, Reicher-Reiss H, Kaplinsky E, Zion M, Boyko V, Behar S. The predictive value of admission heart rate on mortality in patients with acute myocardial infarction. *J Clin Epidemiol*. 1995;48:1197–1205.
28. Lechat PH, Hulot JS, Escolano S, Mallet A, Leizorovicz A, Werhlen-Grandjean M, Pochmalicki G, Dargie H, on behalf of the CIBIS II Investigators. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. *Circulation*. 2001;103:1428–1433.
29. Kjekshus J, Gullestad L. Heart rate as a therapeutic target in heart failure. *Eur Heart J*. 1999;1:H64–H69.

30. Fox K, Ford I, Steg G, Tendera M, Robertson M, Ferrari R, on behalf of the BEAUTIFUL Investigators. Heart rate as a prognostic risk factor in patients with coronary artery disease and left ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet*. 2008;372:817–821.
31. Böhm M, Swedberg K, Komajda M, Borer J, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L, on behalf of the SHIFT Investigators: heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial *Lancet*. 2010;376:886–894.
32. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, Wu AW. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol*. 2003;42:1226–1233.
33. Macchia A, Monte S, Romero M, d'Ettore A, Tognoni G. The prognostic influence of chronic obstructive pulmonary disease in patients hospitalized for chronic heart failure. *Eur J Heart Fail*. 2007;9:942–948.
34. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail*. 2009;11:130–139.
35. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, Granger CB, Michelson EL, Ostergren J, Cornel JH, de Zeeuw D, Pocock S, van Veldhuisen DJ. Candesartan in heart failure: assessment of reduction in mortality and morbidity (CHARM) Investigators. *Circulation*. 2006;113:671–678.
36. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. *Circulation*. 1997;95:2660–2667.
37. Anand IS, Yen J, Folre AVG, Hester A, Glazer R, Latinin R, Maggioni A, Cohn JN. Prognostic role of neutrophil and lymphocyte counts in heart failure: results from Val-HEFT. *J Am Coll Cardiol*. 2004;43:229A.
38. Arruda-Olson AM, Reeder GS, Bell MR, Weston SA, Roger VL. Neutrophilia predicts death and heart failure after myocardial infarction. *Circulation*. 2009;2:656–662.
39. Tracchi I, Ghigliotti G, Mura M. Garibaldi S, Spallarossa P, Barisione C, Boasi V, Brunelli M, Corsiglia L, Barsotti A, Brunelli C. Increased neutrophil lifespan in patients with congestive heart failure. *Eur J Heart Fail*. 2009;11:378–385.
40. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The SEATTLE heart failure model: prediction of survival in heart failure. *Circulation*. 2006;113:1424–1433.

CLINICAL PERSPECTIVE

Recent surveys suggest that up to half of patients with heart failure have a preserved ejection fraction. In this condition, which is associated with poor outcome and in particular a high rate of rehospitalization, identification of factors predicting mortality or morbidity remains largely unexplored, in contrast to patients with heart failure and low ejection fraction. We evaluated data from 4128 patients in the I-PRESERVE trial (Irbesartan in Heart Failure with Preserved Ejection Fraction Study). We report an analysis identifying clinical, demographic, and biological factors associated with the primary end point outcome (all-cause mortality or cardiovascular hospitalization), all-cause mortality, and heart failure death or hospitalization. We found that log N-terminal pro–B-type natriuretic peptide, age, diabetes mellitus, previous hospitalization for heart failure, ejection fraction, and other simple clinical or biological variables were associated with a more unfavorable outcome. The models were able to identify subgroups of patients at very high and very low risk. Our analysis provides new tools for the prognostic evaluation of heart failure with preserved ejection fraction and the factors that should be taken into consideration when assessing the prognosis of patients with heart failure and preserved ejection fraction.

Circulation
Heart Failure

Factors Associated With Outcome in Heart Failure With Preserved Ejection Fraction: Findings From the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-PRESERVE)

Michel Komajda, Peter E. Carson, Scott Hetzel, Robert McKelvie, John McMurray, Agata Ptaszynska, Michael R. Zile, David DeMets and Barry M. Massie

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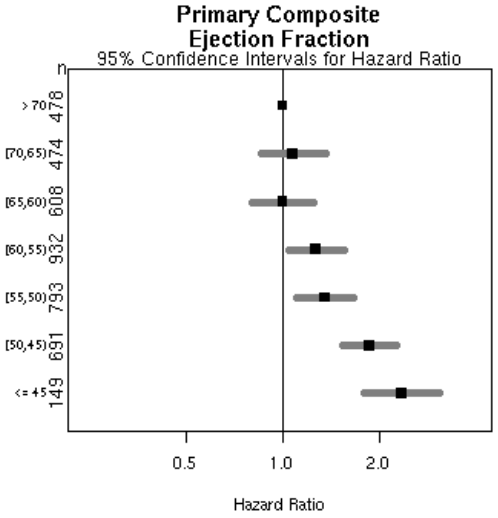
Supplemental Material

Figure. A: Hazard ratios by 5% groups of ejection fraction for each of the three outcomes. **B**: Hazard ratios by septiles of log NT-proBNP plasma level for eache of the three outcomes. **C:** Hazard ratios by groups of 10 units of estimated glomerular filtration rate (GFR) for the three outcomes. **D:** Hazard ratios by septiles of age for the three outcomes.


Primary Composite
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> 70 478
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[50,45) 691
<= 45 149
0.5
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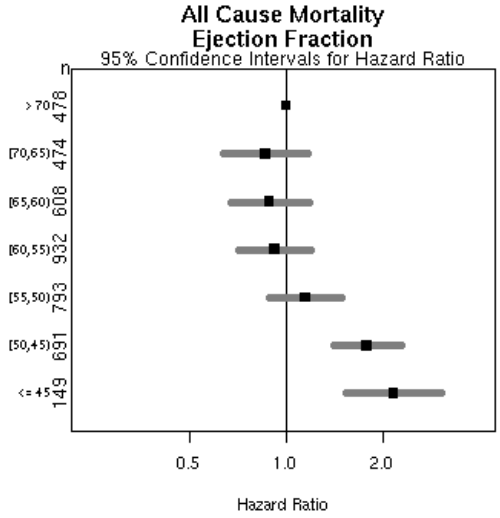
2.0
Hazard Ratio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<= 45 149
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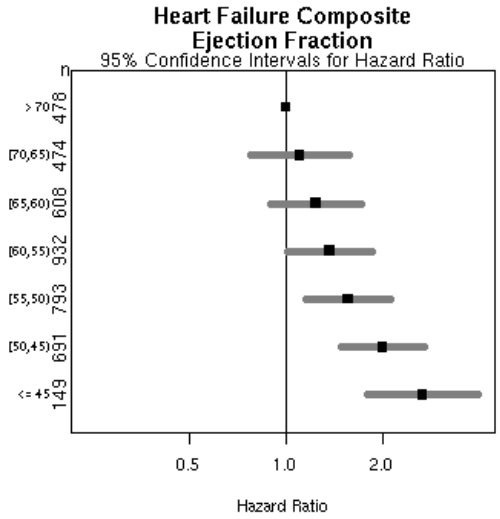
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[50,45) 691
<= 45 149
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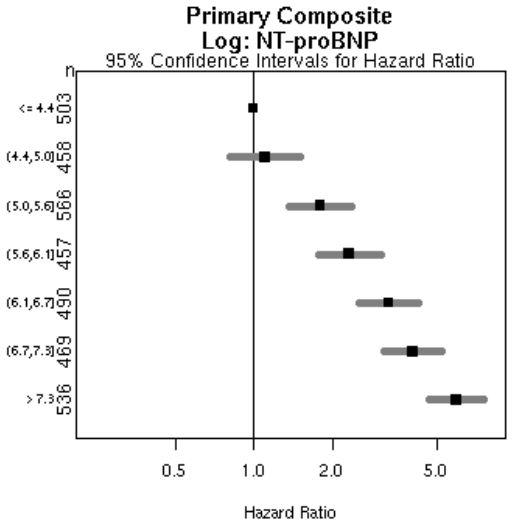
Hazard Ratio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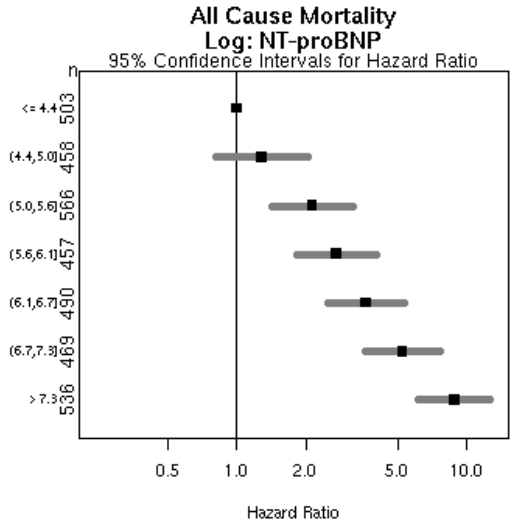
(5.6,6.1] 457
(6.1,6.7] 490
(6.7,7.3] 469
> 7.3 536
0.5
1.0
2.0
5.0
Hazard Ratio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Log: NT-proBNP
95% Confidence Intervals for Hazard Ratio
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(5.6,6.1] 457
(6.1,6.7] 490
(6.7,7.3] 469
> 7.3 536
0.5
1.0
2.0
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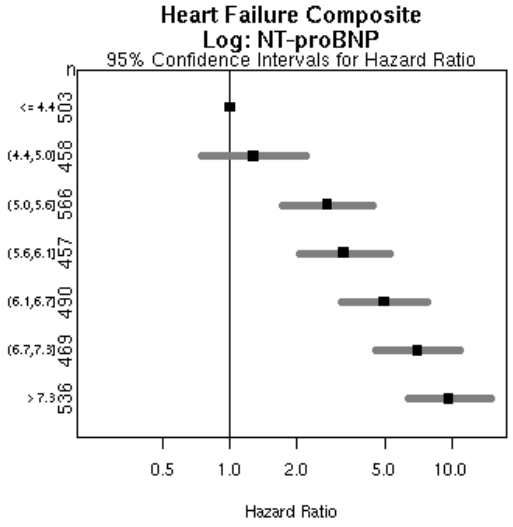
Hazard Ratio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95% Confidence Intervals for Hazard Ratio
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(5.6,6.1] 457
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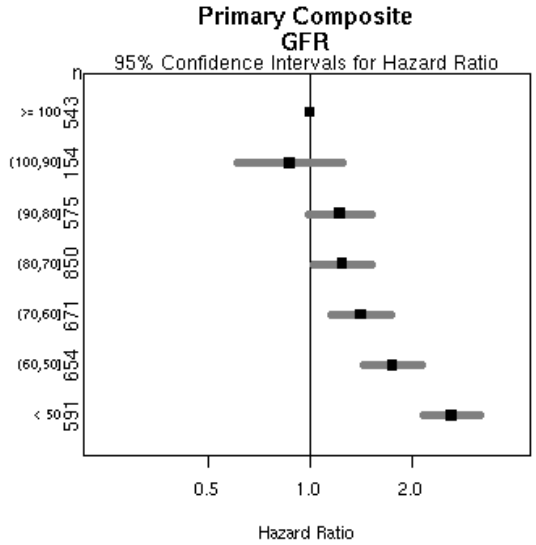
10.0
Hazard Ratio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GFR
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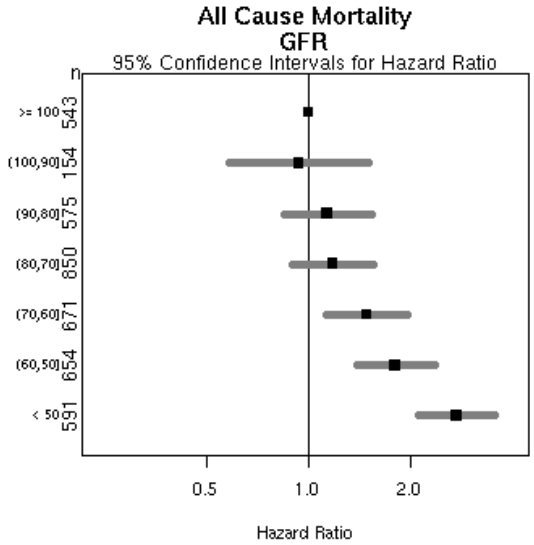
(60,50] 654
< 50 591
0.5
1.0
2.0
Hazard Ratio


All Cause Mortality
GFR
95% Confidence Intervals for Hazard Ratio
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>= 100 543
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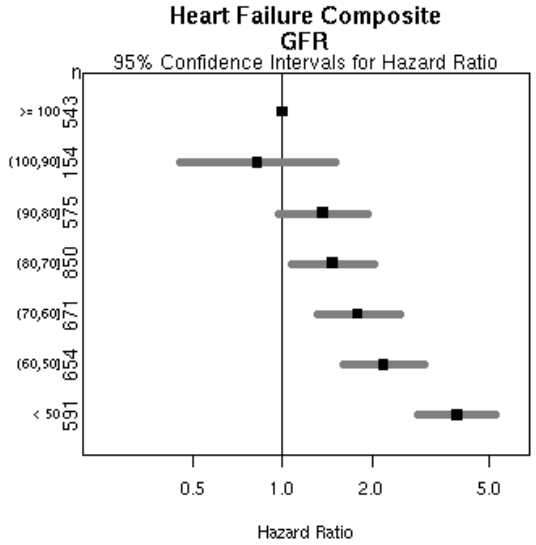
Heart Failure Composite
GFR
95% Confidence Intervals for Hazard Ratio
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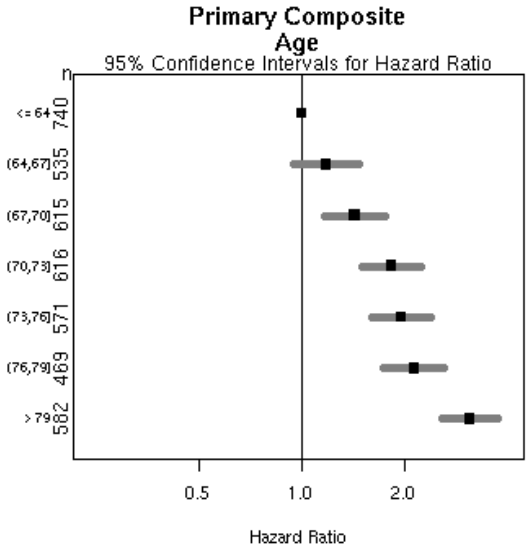
Hazard Ratio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(76,79] 469
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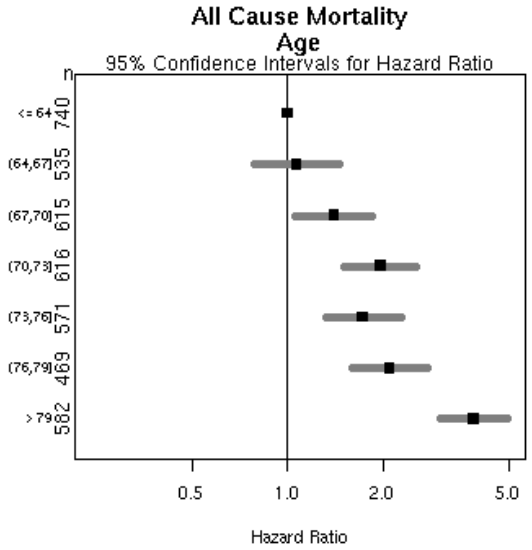
1.0
2.0
Hazard Ratio


All Cause Mortality
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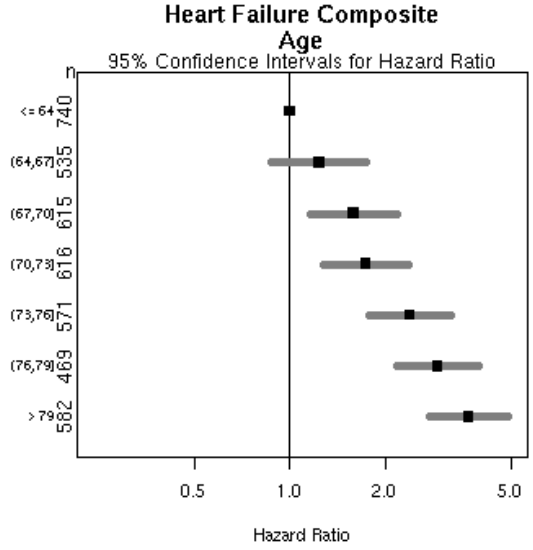
Hazard Ratio


Heart Failure Composite
Age
95% Confidence Intervals for Hazard Ratio
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(70,73] 616
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(76,79] 469
> 79 582
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Hazard Ratio