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## **The additive prognostic value of the cardiopulmonary exercise test in elderly patients with heart failure**

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*Short title: Cardiopulmonary exercise test in the elderly*

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## Abstract

*Objectives:* The role of the cardiopulmonary exercise test (CPET) for risk stratification in elderly HF patients with depressed or preserved ventricular function has not yet been evaluated. We analysed whether CPET is useful in predicting outcome in this population.

*Methods and Results:* 220 NYHA class I-III HF patients  $\geq 70$  years performed maximal CPET (peak expiratory exchange ratio  $> 1.00$ ). Median age was 75 years, 23% had NYHA class III; 59% had preserved ventricular systolic function (ejection fraction  $\geq 40\%$ ). Median peak oxygen uptake was 11.9 mL/Kg/min, median slope of the ventilation to CO<sub>2</sub> production ratio (VE/VCO<sub>2</sub> slope) was 33.2; 45% showed enhanced ventilatory response to exercise (EVR, VE/VCO<sub>2</sub> slope  $\geq 34$ ). During 19-month follow-up, 94 patients (43%) met the combined end point of death and hospital admission for worsening HF, arrhythmias or acute coronary syndromes.

By Cox multivariable analysis, a creatinine clearance  $< 50$  ml/min (HR 1.657, 95% CI 1.055 to 2.602) and EVR (HR 1.965, 95% CI 1.195 to 3.231) were the best predictors of outcome, while ventricular function had no influence on prognosis.

*Conclusions:* In elderly HF patients, a steeper VE/VCO<sub>2</sub> slope provides additional information for risk stratification across the spectrum of ventricular function and identifies a high risk population, commonly not considered in exercise test guidelines.

*Keywords:* Elderly; Heart Failure; Cardiopulmonary exercise test; Preserved left ventricular ejection fraction heart failure

## 1. Introduction

Heart failure (HF) is a common chronic diseases in the elderly. While relief of symptoms and acceptable quality of life are the main goals of treatment in frail patients with multiple disabling comorbidities, “robust” elderly subjects, with no relevant strength or mobility problems, may have an outlook similar to younger patients, and should be carefully assessed for up-to-date treatment.

When assessing prognosis in elderly HF patients, certain predictors are particularly relevant, in view of their prevalence in older age. Renal dysfunction, common in the elderly and frequent in HF, increases mortality across the whole spectrum of ventricular impairment [1-2]. In the elderly, HF with preserved left ventricular ejection fraction (PLVEF-HF) is a common and costly clinical entity, with mortality and one-year readmission rates [3-4] similar to HF with depressed systolic function (SHF). Increasing evidence links diastolic dysfunction to exercise intolerance [5] .

Among laboratory investigations, the cardiopulmonary exercise test with gas exchange measurement (CPET), when technically feasible, is an accurate tool in routine clinical evaluation and risk stratification of HF patients [6-7]. Reduced peak oxygen consumption ( $\text{PVO}_2$ ) and ventilatory abnormalities, such as an enhanced ventilatory response to exercise (EVR) provide objective and non-invasive evaluation of functional capacity and were shown to predict prognosis in a large subset of SHF and PLVEF-HF patients [8-11]. Our group previously demonstrated the feasibility and safety of CPET in elderly HF patients [12].

Brain natriuretic peptide (BNP), a composite marker of systolic and diastolic function and neurohormonal activation, is a prominent prognostic parameter, even in elderly patients [13-14]. Recent clinical reports have focused on the prognostic usefulness of BNP and  $\text{PVO}_2$  in

HF patients. [15-16], yet CPET-derived parameters of ventilatory efficiency may be superior to BNP in predicting prognosis in SHF patients [17].

Aim of our study was to address the additive prognostic role of ventilatory parameters to clinical, neurohormonal and echocardiographic variables in stable elderly outpatients with mild to moderate SHF and PLVEF-HF on optimized medical treatment, followed-up at a dedicated HF clinic.

## 2. Methods

### 2.1 Study population

Between October 2001 and January 2006, 331 consecutive outpatients aged  $\geq 70$  years with a diagnosis of HF since at least 3 months were screened for CPET evaluation and 95 were excluded for reasons detailed in Figure 1. Patients were in NYHA class I-III on stable drug doses without worsening symptoms or need for intravenous inotropic support during the last 4 weeks. Among the 236 consenting subjects who were able to perform a CPET test, 220 with a  $\text{PVO}_2 < 25$  mg/kg/min and a respiratory exchange ratio (RER)  $> 1.00$  at CPET, indicating the achievement of anaerobic exercise conditions, were enrolled; 16 subjects with a  $\text{RER} \leq 1$  were excluded.

The study protocol was approved by the Institutional Ethics Committee and complies with the ethical rules for human experimentation that are stated in the Declaration of Helsinki.

Baseline laboratory assessment was performed according to standard laboratory methods. Creatinine clearance was determined using the Cockcroft e Gault equation.

Patients were followed up at the outpatient HF clinic of our hospital; outcome data of patients who did not attend their scheduled appointments ( $<10\%$  of those enrolled) were obtained by telephone interview of the patient or his/her family; none of these patients had

been admitted to hospital. The primary combined study end-point was defined as the occurrence of death and hospital admission for worsening HF, arrhythmias or acute coronary syndromes.

## 2.2 Exercise test

A standard bicycle exercise ramp protocol was used, with increments of 10 watts/min. Details of test protocol have been published previously [12, 17]. Before each test, oxygen and carbon dioxide analyzers and a flow mass sensor were calibrated by use of available precision gas mixtures and a 3-L syringe, respectively. To stabilize gas measurement, patients were asked to remain still for at least 3 minutes before beginning an upright graded bicycle exercise testing, using a continuous protocol, which was continued until exhaustion.

A 12-lead electrocardiogram was continuously recorded (MAX-1, Marquette Electronics, Milwaukee, Wis, USA). Blood pressure was recorded every minute by a cuff sphygmomanometer. Indications to stop the test were exhaustion, dyspnoea, angina, ST-segment depression  $\geq 3$  mm, high-degree AV block or ventricular tachycardia  $\geq 5$  consecutive beats at a rate  $\geq 120$ /min, new-onset atrial fibrillation, or systolic blood pressure  $\geq 260$  mmHg, as well as a progressive decrease in blood pressure.

Oxygen uptake ( $\text{VO}_2$ ), carbon dioxide production ( $\text{VCO}_2$ ) and minute ventilation were measured by breath-by-breath gas analysis with use of a computerized metabolic cart (V max 29, SensorMedics, Yorba Linda, Ca, USA).

$\text{PVO}_2$  was recorded as the mean value of  $\text{VO}_2$  during the last 30 seconds of the test and expressed as mL per kilogram per minute.  $\text{PVO}_2$  was measured and expressed as absolute and percent predicted value from the individual age, sex, and body weight-corrected mean normal values (%  $\text{PVO}_2$ ). The %  $\text{PVO}_2$  was calculated for each patient using Wasserman's equation.

The O<sub>2</sub> uptake at the anaerobic threshold was determined by use the V-slope method [18].

Other considered parameters were:

- a) ventilation (VE) and expired O<sub>2</sub> ratio (VE/VO<sub>2</sub>),
- b) VE/CO<sub>2</sub> production ratio (VE/VCO<sub>2</sub>), (VE, VO<sub>2</sub> and VCO<sub>2</sub> L/min);
- c) VE/VCO<sub>2</sub> slope, calculated in every subject as the slope of the regression line relating VE to CO<sub>2</sub> output during exercise testing, with the exclusion of the final non-linear portion after the onset of acidotic drive to ventilation.

A VCO<sub>2</sub>/VO<sub>2</sub> ratio > 1.00 was selected for the definition of maximal exercise.

The VE/VCO<sub>2</sub> slope was used as the main index of the ventilatory response to exercise. We defined EVR as a VE/VCO<sub>2</sub> slope  $\geq$  34 [19]. The ratio of VE/VCO<sub>2</sub> slope to PVO<sub>2</sub>, previously suggested as a better predictor of prognosis than either variable alone [20] was also analysed.

### 2.3 Doppler echocardiography

Doppler echocardiography was performed using a Philips MS Sonos 5.500 D device equipped with a multiband 1.8–3.6 MHz probe. Left ventricular ejection fraction (LVEF) was measured by two blinded expert operators according to the modified Simpson's biplane method, in the apical-four and two-chamber views. Biplane volumes were calculated from area tracings using the disc summation method (modified Simpson's rule). Pulmonary systolic pressure (PAP) was calculated by means of right ventricular/ right atrial gradient in patients with detectable tricuspid regurgitation (peak ventricular/atrial gradient + 8-10 mmHg). Transmitral flow velocity was determined by the pulsed-wave Doppler approach using a 2-4 mm sample volume placed at the mitral leaflet tips level in the apical four-chamber view. The transmitral pulsed-wave Doppler blood flow velocities were calculated off-line from 5 consecutive cardiac cycles to measure early diastolic (E) peak velocity (cm/sec), late diastolic

(A) peak velocity (cm/sec), E/A velocity ratio and E velocity deceleration time (msec). A restrictive filling pattern was defined as presence of a E/A ratio  $> 2.0$  cm/sec and a E deceleration time  $< 140$  ms. In patients with atrial fibrillation, the restrictive filling pattern was defined by a E deceleration time  $< 140$  ms calculated off-line from 10 consecutive cardiac cycles. Preserved left ventricular ejection fraction (PLVEF) was defined as LVEF  $\geq 40\%$  [ 21-23].

#### 2.4 Measurement of BNP plasma levels

Before exercise test, blood was collected by venipuncture from an antecubital vein, after 10 min of rest in the sitting position. A point-of-care test (Triage BNP test, Biosite Diagnostics®), based on immunofluorometric assay for quantitative determination of BNP in whole blood or plasma was used. Normality range values are 0-40 pg/mL. BNP concentrations were determined by nurses blinded to the cardiopulmonary exercise test results.

#### 2.5 Statistical analysis

Categorical variables are presented as frequency percents and continuous variables as median values [interquartile range]. Between-group differences were tested by chi-square test and Student's t-test or non parametric testing according to normal or non normal variable distribution. A  $p$  value  $< 0.05$  was considered statistically significant.

To determine the independent predictors of the primary combined end point of occurrence of death and hospital admission for major cardiovascular events, we entered variables significant by univariable analysis ( $p < 0.004$  Bonferroni correction) in a multivariable Cox proportional hazards model. in sequential diagnostic blocks of clinical and laboratory,

echocardiographic and CPET information, to mimick the sequence of information obtained in clinical practice. Relevant covariates were selected through a forward selection procedure. Hazard ratios (HR) are presented with 95% confidence intervals (CI). Non categorical variables were entered as continuous values and HR are expressed as risk per 10-unit change. In the final model, clinically relevant cut-off values were also used. Differences between Kaplan Meier event-free survival curves according to the predefined cut-off values were assessed by the log rank test.

All statistical tests were two-tailed. Data were analyzed using SPSS 10 (Microsoft ®) .

### 3. Results

Clinical features and laboratory findings of our population are described in Table 1. Median age was 75 [72, 79] years. LV function was mildly reduced in this series: PLVEF was found in 131 patients (59%). EVR was present in 123 out of 220 patients (56 %).

During a median follow-up of 19 [10, 40] months, 68 patients were admitted at least once for worsening HF (45) arrhythmias (12) or acute coronary syndromes (11) , and 32 died (17 of progressive HF, 9 of sudden death, 4 of other cardiovascular causes and 2 of cancer). Among patients with left bundle branch 12 ( 5,4 % ) underwent to resincronization therapy. Using a time-to first-event approach , overall 94 patients (43%) achieved the study end point of death or hospital admission. The significant predictors of major events by univariable analysis ( $p$  value  $< 0.004$  using Bonferroni correction, Table 2) were entered in multiple multivariable Cox proportional hazard models in a sequential approach. Hazard ratios and related 95% CI per 10-unit increments and according to clinically relevant cut off values are shown in Table 3.

In the first model, among 5 clinical, laboratory and echocardiographic variables, only renal dysfunction and higher BNP levels were predictive of the end point. In the final model including 4 CPET parameters, only renal dysfunction and a steeper VE/VCO<sub>2</sub> slope were significantly associated to outcome.

Survival rates free from HF admission by the Kaplan Meier method according to renal dysfunction, BNP levels and VE/VCO<sub>2</sub> slope are shown in Figures 2-4.

#### 4. Discussion

The present prospective study is among the largest carried out to define, in a multimodal assessment, the additive prognostic role of CPET in an elderly population with mild to moderate HF and depressed or preserved LV function. Our data demonstrate that, in the “robust” elderly with HF able to perform maximal exercise, CPET is a crucial step in prognostic assessment and ventilatory parameters, together with evidence of renal dysfunction, have a key role in risk stratification over and beyond the level of LV function.

In advanced age morbidity, with its attendant impact on quality of life, is a relevant target for HF management beyond extension of life, so we chose to assess outcome in terms of hospital admissions for major cardiac events besides mortality: 43 % of the patients met, over a median period of 19 months, the combined end point.

Renal dysfunction, an established risk factor for adverse outcome in HF [1-2], was in our elderly population a main independent prognostic predictor across the spectrum of ventricular impairment. This finding has important clinical implications: pharmacological management, focused on kidney protection to prevent or slow progression of renal impairment, may prove valuable also to improve outcome in elderly HF patients.

Our data further underscore the relevance of PLVEF-HF in the elderly: although LV function predicted outcome by univariable analysis, both renal dysfunction and BNP, a

composite marker of systolic and diastolic function and neurohormonal activation [13], showed a stronger independent association with prognosis. Actually, the role of LVEF is far less important when morbidity, with its attending health care costs and detrimental impact on quality of life, is considered: in overt HF event-free survival does not differ among patients with depressed or preserved LV function [3, 21-23]. Moreover a recent clinical trial, which enrolled 556 HF patients with both preserved ( $EF > 50\%$ ) or reduced systolic function ( $EF < 50\%$ ), [24] demonstrated that PLVEF-HF presented a higher 6 months mortality rate than HF patients with depressed ejection fraction. These findings are also supported by another recent retrospective study [25], that showed a similar post-discharge mortality and hospitalization rate in patients with preserved ( $EF > 40\%$ ) and reduced ( $EF < 40\%$ ). The heterogeneous etiology, the high prevalence in the older population and the under-use of the optimal pharmacological treatment are probably the reason of the high morbidity and mortality rate of patients with PLVEF-HF and of the reduced prognostic significance of EF in this group of patients.

Our main aim in this study was to assess the additive prognostic role of CPET, an established test for risk stratification in other clinical HF settings, in elderly patients, who so far have been substantially neglected in the literature. Controversy still exists on the best ventilatory prognostic predictor in general [11]. Peak exercise  $VO_2$  has been found superior in large series [8] and recent studies [26], and the anaerobic threshold in other studies of younger HF patients [27]. Other reports stressed the optimal value of ventilatory efficiency as marker of adverse outcome [10-12, 28]. Old age per se might well determine differences in the definition of the most useful CPET parameters for outcome assessment. Peak exercise  $VO_2$  is known to be influenced, besides age and gender, by comorbidities and noncardiac factors, such as muscle deconditioning, motivation, anemia, all highly prevalent in the elderly, and might therefore be less useful as prognostic marker in this population, as highlighted by our

findings.  $\text{VO}_2\text{AT}$ , the anaerobic threshold, an objective parameter of cardiopulmonary exercise capacity that can be derived from submaximal exercise testing, previously found useful to predict 6-month mortality [27], could not be determined in about 15% of our study patients and was not independently associated to prognosis in this group.

So far, only three studies have analysed the prognostic value of CPET in patients of an age similar to ours [29-31]. Both Davies et al [29] and Mejhert et al. [30] demonstrated in small series the prominent predictive role of  $\text{VE}/\text{VCO}_2$  slope, but their analyses were restricted to patients with SHF. In a larger study by Cicoira et al [31], among 102 SHF or PLVEF-HF patients with a maximal CPET ( $\text{RER} > 1$ ) both  $\text{PVO}_2$  and  $\text{VE}/\text{VCO}_2$  slope were mortality predictors. The inclusion of subjects with hypertrophic or restrictive cardiomyopathy and dynamic flow obstruction; the different end point (death vs mortality and morbidity), and the underuse of beta-blockers (15% vs 56%) may explain the different prognostic weight of LVEF in Cicoira's and our experience. In none of these studies was CPET compared to BNP as a risk stratification tool.

In a group of patients with SHF and a median age of 71 years, we previously demonstrated the prognostic superiority of ventilatory and diastolic function parameters in comparison with BNP [17]. In the present series, although independently predictive in the clinical model, as anticipated by its significant relationship with ventilatory parameters, BNP lost its power when ventilatory parameters, namely  $\text{VE}/\text{VCO}_2$  slope, were included in the multivariable model. Based on these findings, when CPET cannot be adequately performed in the elderly, BNP may be used as reliable surrogate predictor of prognosis.

The prognosis of elderly pts with CHF is poor, and NYHA classification, a simple and widely-used approach to the assessment of their functional status, seems unreliable for risk stratification.

CPX, an inexpensive and reliable tool for testing cardio-pulmonary function can be safely performed in the vast majority of older patients, adding important information on disease severity and thus providing a guide for a tailored CHF treatment also in this population normally neglected by exercise test guidelines.

## 5. Study limitations

Our study population was relatively small and included only clinically stable “robust” outpatients with mild to moderate HF, who did not have important comorbidities and were furthermore able to perform a CPET. Therefore our conclusions cannot be extended to all elderly HF patients.

Beta-blockers reduced mortality and hospital admissions in the landmark HF trials, but did not predict outcome in the present series. One possible explanation is the relatively low proportion of sudden deaths with respect to worsening HF in our patients. Furthermore stratification of ventilatory parameters by beta-blocker treatment did not show significant differences.

We did not measure plasma N-terminal pro-BNP, recently presented as an accurate prognostic predictor in HF, as point-of-care testing, easier to perform, was not yet available for NT-pro-BNP. at the time the study was performed. Patients with advanced renal dysfunction were excluded from the study because of the non-specific elevation of plasma BNP in this clinical condition. However, even in this relatively healthy population, mild degrees of renal dysfunction were one of the strongest predictors of outcome independently of BNP levels.

We did not assess the value of other emerging ventilatory parameters such as the oxygen uptake efficiency slope [32]. Indeed others [28] have recently reasserted the superior

prognostic characteristics of the VE/VCO<sub>2</sub> slope over both peak VO<sub>2</sub>, both at maximal and submaximal testing, in younger HF patients treated by beta-blockers in a proportion similar to our series.

## 6. Conclusion

In robust elderly patients with mild to moderate congestive HF and impaired or PLVEF, reduced estimated glomerular filtration rate and a steeper VE/VCO<sub>2</sub> slope provide additional independent prognostic information across the spectrum of ventricular function and identify a high risk population commonly not considered in exercise test guidelines. These findings authorize to extend some clinical applications of CPX validated in middle-aged pts to older populations with CHF not eligible for heart transplantation suggesting a wider use of this technique.

## Acknowledgments

The corresponding author affirms that she has listed everyone who contributed significantly to the work. None of the authors has any conflict of interest, such as financial or personal conflicts; moreover no circumstance or competing interest that could be construed or perceived as influencing the interpretation of the results occurred.

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## FIGURE LEGENDS

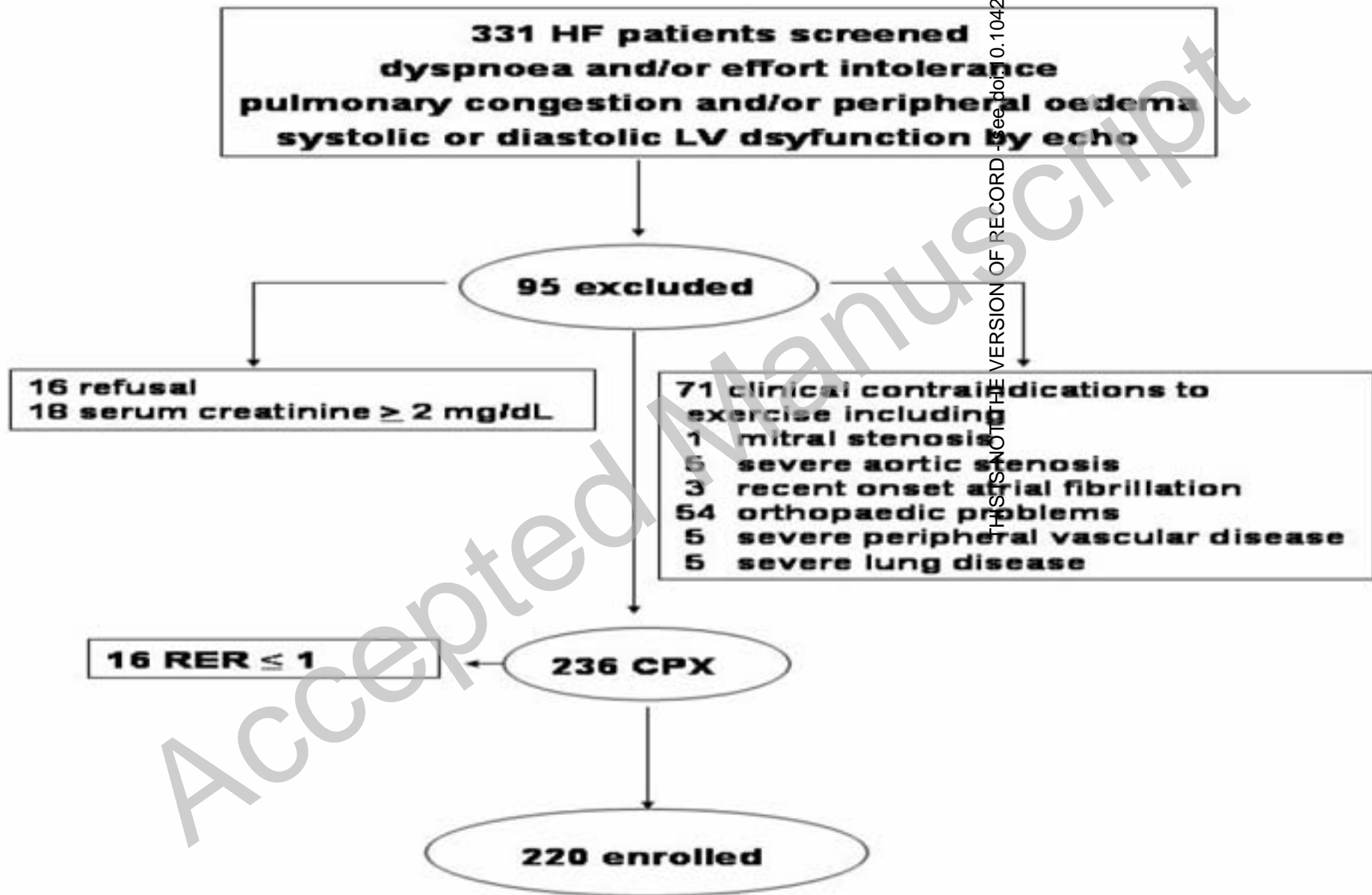
**Fig.1** Study flow chart detailing exclusion criteria

**Fig. 2** Event free survival rates in patients with an eGFR (estimated glomerular filtration rate, creatinine clearance calculated by the Cockcroft e Gault equation)  $\geq 50$  or  $<50$  ml/min (log rank  $p < 0.005$ )

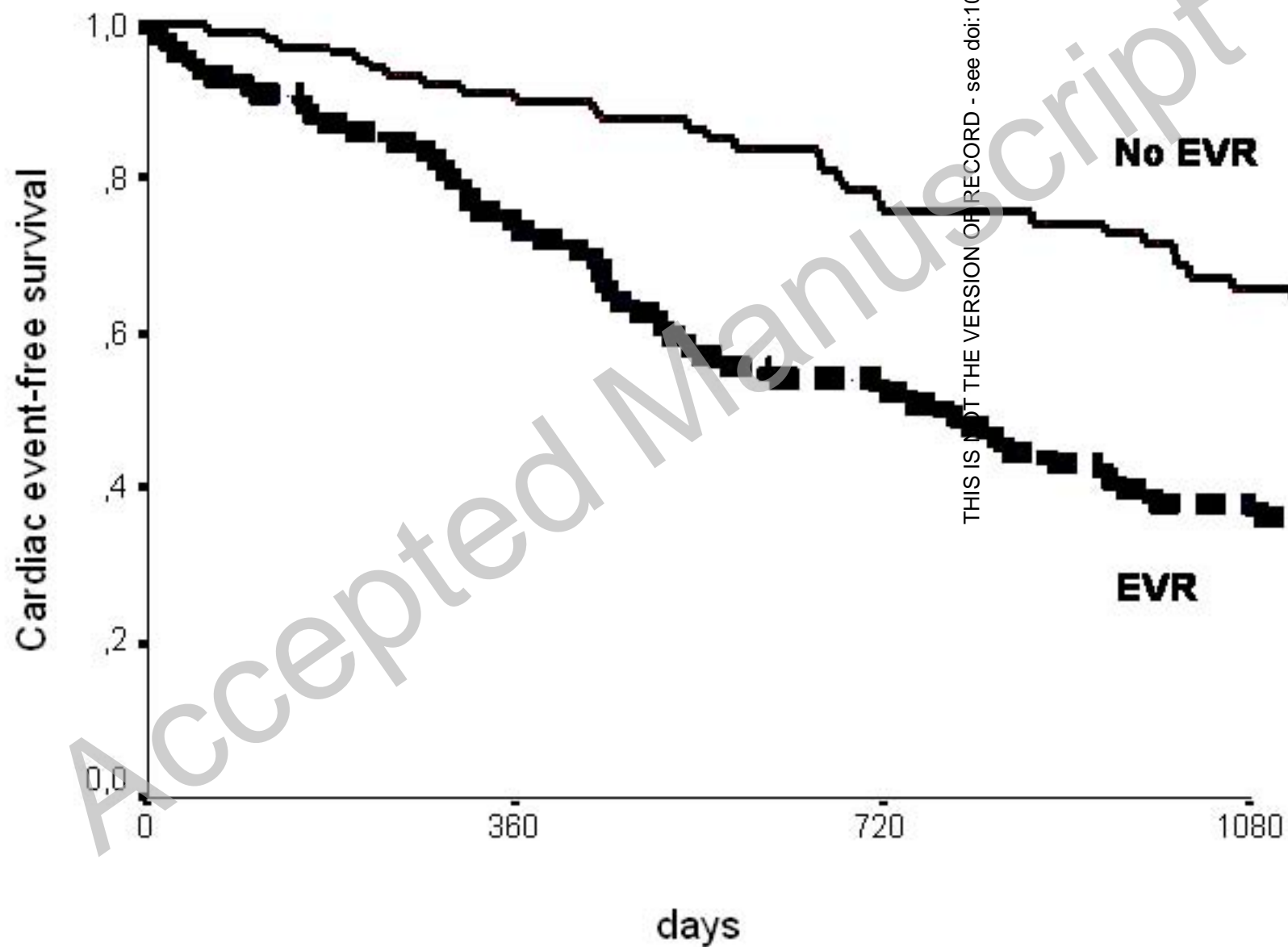
**Fig. 3** Event free survival rates in patients with BNP  $\leq 140$  or  $>140$  pg/ml (log rank  $p$  value  $<0.0001$ )

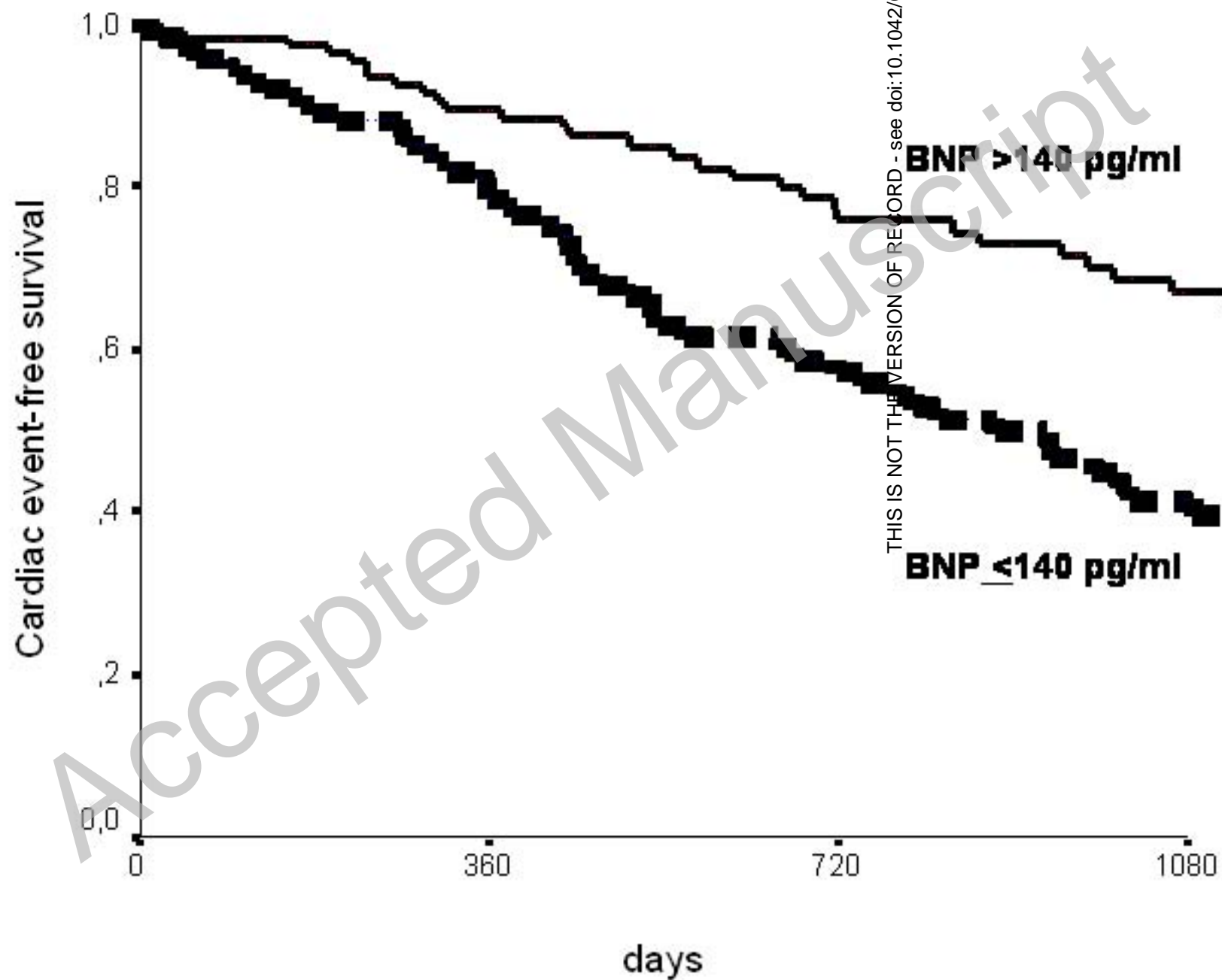
**Fig. 4** Event free survival rates in patients without or with EVR (enhanced ventilatory response to exercise) (log rank  $p$  value  $<0.001$ )

## Study flow-chart



**Figure 1**





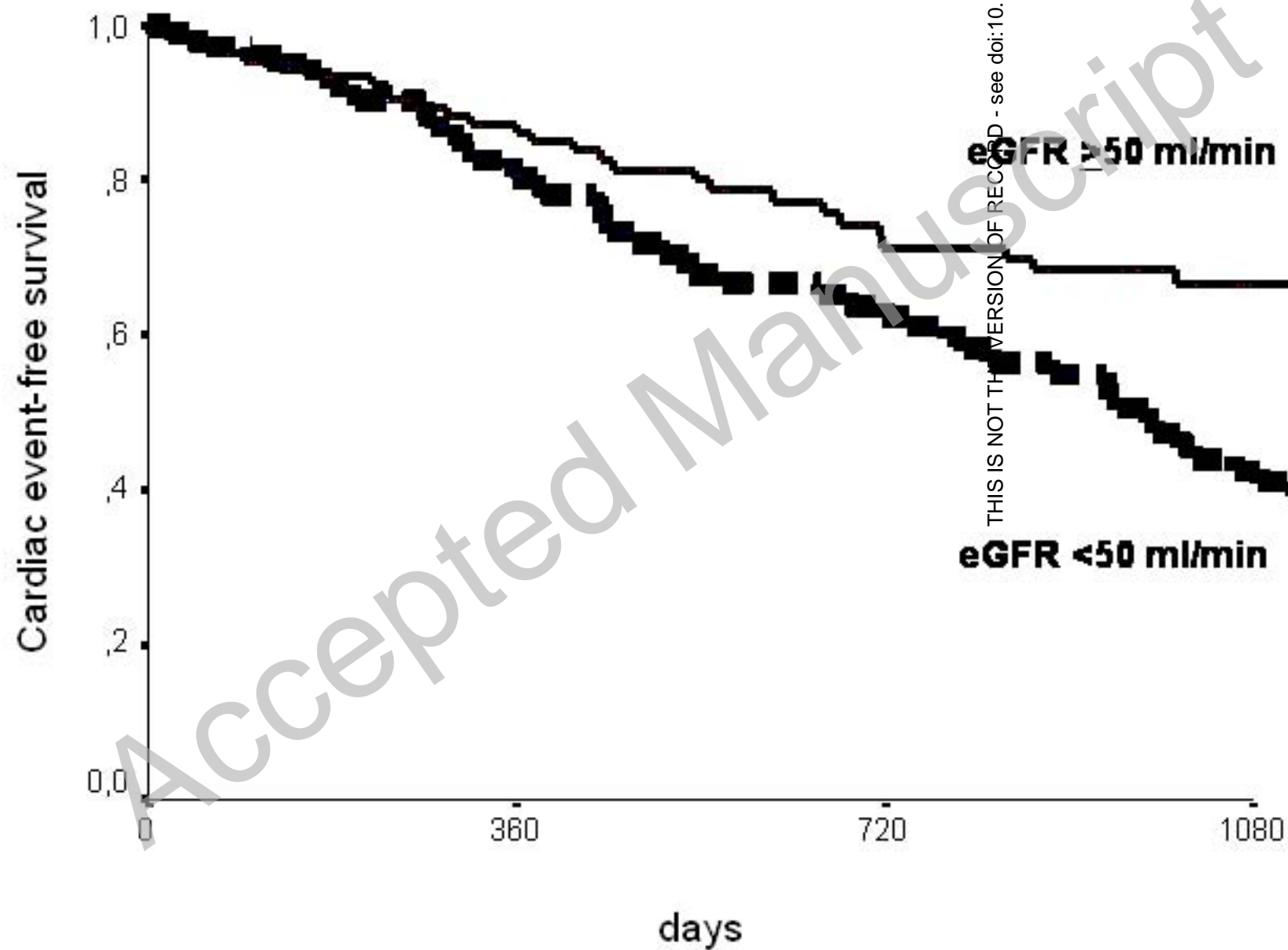


Table 1  
Clinical characteristics and main parameters in the 220 study patients

| Clinical characteristics             | N (%)     | Median [Interquartile range]                    |                   |
|--------------------------------------|-----------|---|-------------------|
| Female gender                        | 70 (32 %) | <b>Laboratory findings</b>                      |                   |
| Ischemic etiology of CHF             | 101 (46%) | Hemoglobin ( g/ dl )                            | 12.7 [11.7, 13.7] |
| NYHA functional class III            | 51 (23 %) | Serum Sodium (mmol/l)                           | 140 [138, 142]    |
| Left bundle branch block             | 62 (28%)  | Creatinine cl. (ml/min )                        | 50 [38, 63]       |
| Chronic atrial fibrillation          | 33 (15%)  | BNP pg / ml                                     | 141 [56, 365]     |
| Diabetes                             | 68 (31 %) | <b>Echocardiographic variables</b>              |                   |
| Anamnestic mild BPCO                 | 51 ( 23%) |   |                   |
| ACE-inhibitors                       | 196 (89%) | <b>Echocardiographic variables</b>              |                   |
| ARB                                  | 18 8%)    |   |                   |
| Beta-Blockers                        | 123 (56%) | LVED volume (ml)                                | 129 [103, 160]    |
| Non K <sup>+</sup> sparing diuretics | 194 (88%) | LVES volume (ml)                                | 70 [50, 105]      |
| K <sup>+</sup> sparing diuretics     | 53 (24%)  | LVEF (%)  | 42 [34, 51]       |
| Digitalis                            | 13 (6%)   | E deceleration time (msec)                      | 200 [150, 225]    |
| Nitrates                             | 123 (56%) | PAP (mmHg)                                      | 31 [25, 44]       |
| Oral anticoagulants                  | 31 (14%)  | Restrictive filling pattern                     | 40 (22%)          |
| CRT                                  | 5 (2%)    | <b>Cardiopulmonary exercise test parameters</b> |                   |
| ICD                                  | 5 (2%)    | PVO <sub>2</sub> (ml/kg/min)                    | 11.9 [9.76, 14]   |
|                                      |           | % PVO <sub>2</sub> (%)                          | 63 [51, 74]       |
|                                      |           | VO <sub>2</sub> AT(n=185)(ml/kg/min)            | 9.20 [7.8, 10.5]  |
|                                      |           | VE/VO <sub>2</sub>                              | 42 [37, 50]       |
|                                      |           | VE/VCO <sub>2</sub>                             | 37 [34, 43]       |
|                                      |           | VE/VCO <sub>2</sub> slope                       | 33.2 [29, 38.1]   |
|                                      |           | VCO <sub>2</sub> slope/ PVO <sub>2</sub> ratio  | 2.78 [2.24, 3.72] |
|                                      |           | Workload ( Watt )                               | 61 [48, 77]       |

ACE, angiotensin converting enzyme ; ARB, angiotensin receptor blocking; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; LVED, left ventricular end diastolic; LVES, left ventricular end systolic; PAP, pulmonary artery systolic pressure; PVO<sub>2</sub>, peak oxygen uptake; % PVO<sub>2</sub>, percent predicted PVO<sub>2</sub>; VE, ventilation; VE/VCO<sub>2</sub>, relation between minute ventilation and carbon dioxide production; VE/VCO<sub>2</sub> slope, slope of the regression line relating VE to carbon dioxide production; VE/VO<sub>2</sub>, relation between minute ventilation and expired oxygen; VO<sub>2</sub>AT, anaerobic threshold.

Table 2 Univariable predictors of outcome

|   | <i>p</i> | HR    | 95% CI      |
|---|----------|-------|-------------|
| Age   | 0.353    | 1.020 | 0.978-1.063 |
| Female gender                                     | 0.718    | 0.923 | 0.597-1.426 |
| Ischemic etiology of CHF                          | 0.102    | 1.404 | 0.935-2.109 |
| NYHA III functional class                         | 0.118    | 1.452 | 0.909-2.318 |
| Left bundle branch block                          | 0.018    | 1.656 | 1.092-2.510 |
| Chronic atrial fibrillation                       | 0.178    | 1.440 | 0.847-2.446 |
| Beta-Blockers                                     | 0.327    | 0.817 | 0.545-1.224 |
| Hemoglobin ( g/ dl )                              | 0.061    | 0.873 | 0.757-1.006 |
| Serum Sodium (mmol/l                              | 0.680    | 0.989 | 0.939-1.042 |
| Creatinine clearance (ml/min )                    | 0.003    | 0.982 | 0.969-0.995 |
| BNP ( pg/ ml )                                    | 0.001    | 1.001 | 1.000-1.002 |
| Left ventricular end diastolic volume (ml)        | 0.220    | 1.002 | 0.999-1.006 |
| Left ventricular end systolic volume (ml)         | 0.094    | 1.004 | 0.999-1.008 |
| LVEF (%)  | 0.019    | 0.979 | 0.962-0.997 |
| PAP (mmHg)  | 0.001    | 1.020 | 1.008-1.033 |
| E deceleration time (msec)                        | 0.003    | 0.995 | 0.992-0.998 |
| Restrictive filling pattern                       | 0.001    | 2.079 | 1.330-3.249 |
| PVO <sub>2</sub> (mL/Kg/min)                      | 0.006    | 0.915 | 0.859-0.974 |
| % PVO <sub>2</sub>                                | 0.099    | 0.991 | 0.980-1.002 |
| VO <sub>2</sub> AT                                | 0.010    | 0.867 | 0.777-0.967 |
| VE/VO <sub>2</sub>                                | 0.000    | 1.039 | 1.018-1.060 |
| VE/VCO <sub>2</sub>                               | 0.000    | 1.040 | 1.019-1.061 |
| VE/VCO <sub>2</sub> slope                         | 0.000    | 1.043 | 1.020-1.067 |
| VE/VCO <sub>2</sub> slope/ PVO <sub>2</sub> ratio | 0.000    | 1.218 | 1.096-1.354 |
| Workload ( Watt )                                 | 0.006    | 0.987 | 0.978-0.996 |

*p* < 0.004 (Bonferroni correction) for inclusion in the multivariable model. See Table I for other abbreviations

Table 3

Multivariable predictors of death or hospitalization

|  | <i>p</i> | HR    | 95% CI |       |
|--|----------|-------|--------|-------|
| <i>1. Clinical, BNP and ECHO variables</i>       |          |       |        |       |
| Per 10-unit increments                           |          |       |        |       |
| Creatinine clearance (ml/min)                    | 0.020    | 0.852 | 0.795  | 0.914 |
| BNP ( pg /ml )                                   | 0.000    | 1.010 | 1.009  | 1.012 |
| Cut off values                                   |          |       |        |       |
| Creatinine clearance <50 vs ≥ 50 ml/min          | 0.014    | 1.748 | 1.122  | 2.724 |
| BNP >140 vs ≤140 pg/ml                           | 0.001    | 2.171 | 1.388  | 3.396 |
| <i>2. Clinical, BNP, ECHO and CPET variables</i> |          |       |        |       |
| Per 10-unit increments                           |          |       |        |       |
| Creatinine clearance (ml/min)                    | 0.024    | 0.852 | 0.795  | 0.914 |
| VE/VCO2 slope                                    | 0.001    | 1.492 | 1.323  | 1.682 |
| Cut off values                                   |          |       |        |       |
| Creatinine clearance <50 vs ≥ 50 ml/min          | 0.028    | 1.657 | 1.055  | 2.602 |
| VE/VCO2 slope ≥ 34 (EVR)                         | 0.008    | 1.965 | 1.195  | 3.231 |

EVR, enhanced ventilatory response to exercise; HR, hazard ratios