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Prediction of survival and magnitude of reverse remodeling using the ST2-R2 score in heart failure: A multicenter study

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ABSTRACT

Background: Cardiac remodeling and its reversibility are key in HF outcomes.
The ST2-R2 score was recently developed to predict relevant left ventricular (LV) reverse remodeling (R2) in patients with heart failure (HF). In the present study we sought to validate the ST2-R2 score for grading improvement in LV ejection fraction (EF) and LV size at one year, and to evaluate its prognostic implication up to 4 years.
Methods: A total of 569 patients with baseline LVEF <40% from three international cohorts (Barcelona, TIME-CHF, and PROTECT) were included in the study. Patients were classified into four strata based on their ST2-R2 score, which took into account concentrations of the biomarker ST2, non-ischemic etiology, absence of left bundle branch block, HF duration, baseline LVEF, and β-blocker treatment.
Results: A significant relationship was observed between ST2-R2 scores and changes in LVEF and indexed LV sizes. LVEF recovery (from +5.6% to +17.3%; $p < 0.001$), percentage reduction in LV end-systolic volume index (from −6.1% to −32.1%; $p < 0.001$) and in LV end-systolic diameter index (from −1.1% to −18.6%; $p < 0.001$) increased over the ST2-R2 strata. A similar trend was observed with diastolic parameters. Improvement in LV function and size was inversely predictive of mortality. Hazard ratios for risk of death, using the lower ST2-R2 score strata (<9) as a reference, were 0.49 ($p < 0.001$; score 9–11), 0.27 ($p < 0.001$; score 12–14), and 0.17 ($p < 0.001$; score 15–17).
Conclusions: The ST2-R2 score predicts reverse LV remodeling in HF patients and is useful for predicting mortality up to 4 years.

1. Introduction

Outcomes in heart failure (HF) are related in part to left ventricular (LV) remodeling, a process characterized by progressive ventricular dilatation and impaired systolic function in HF with reduced ejection fraction (HFrEF) [1]. The existence of a new category of HF beyond HFrEF and HF with preserved ejection fraction has been recently proposed, the so called HF with recovered ejection fraction (HF-Recovered) [2]. This population represents a distinct HF phenotype with biochemical properties and natural history that differs from the traditional HFrEF population; and the need to identify characteristics and predictors of both reverse remodeling (R2) and myocardial recovery in advanced HF has been highlighted [2].

Biomarkers have been useful for the diagnosis of HF and risk stratification [3] and are being evaluated to guide therapy [4]. Additionally, data now suggest that biomarkers may also be useful to predict or monitor LV R2 [5–10]. In this regard, a clinical score that includes a remodeling biomarker was developed recently to predict relevant R2, the ST2-R2 score, which contains five clinical variables (i.e., non-ischemic etiology, absence of left bundle branch block, HF duration, baseline LV ejection fractions (LVEF), and β-blocker treatment) and a biomarker closely associated with LV remodeling (ST2) (Supplemental Table 1) [11]. This score was recently shown to predict relevant R2 and was internally and externally validated using the derivation and an external validation cohort [11].

Abbreviations: HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction; LBBB, Left bundle branch block; LV, Left ventricular; LVEF, Left ventricular ejection fraction; LVEDDi, Left ventricular end-diastolic diameter index; LVESDi, Left ventricular end-systolic diameter index; LVEDVi, Left ventricular end-diastolic volume index; LVESVi, Left ventricular end-systolic volume index; R2, Reverse remodeling; ST2, Soluble ST2.

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In the initial analysis of the ST2-R2 score, we did not examine links between the magnitude of R2 and long-term prognosis, however. Indeed, predicting the magnitude of R2 could have important prognostic implications [1,11–16], and its identification may help stratify risk beyond symptom improvement and other classical risk factors. Accordingly, the objectives of the present study were 1) to extend the understanding of the ST2-R2 score regarding LVEF improvement and LV size in a larger pooled cohort of patients with HFrEF and 2) to examine the prognostic implications of the ST2-R2 score during extended follow up in a large multicenter cohort.

2. Methods

2.1. Study cohort

Patients with baseline LVEF <40% and available baseline and one year echocardiograms were included from three well-defined HF cohorts: Barcelona [11], TIME-CHF trial [17], and PROTECT [18]. Long-term follow-up (up to 4 years, that means 3 years after de second echocardiogram) was conducted by regular quarterly visits at the Barcelona cohort and by telephone contact and chart review at the TIME-CHF and the PROTECT cohorts. Fatal events were identified from the clinical records (chart review) or by contacting the patient's relatives. Further verification was performed with the databases of the Catalan and Spanish Health Systems (Barcelona), as well as with Social Security Death Index (PROTECT).

All participants provided written informed consent and local ethics committees approved the studies. All study procedures were conducted in accordance with the ethical standards outlined in the Helsinki Declaration of 1975 as revised in 1983.

2.2. Biomarker assay

ST2 was measured in all patients using a high-sensitivity sandwich monoclonal immunoassay (Presage® ST2 assay, Critical Diagnostics, San Diego, CA, USA). The antibodies used in the Presage assay were generated from recombinant protein based on the human complementary deoxyribonucleic acid clone for the complete soluble ST2 sequence. The ST2 assay had a within-run coefficient of <2.5%, a total coefficient of variation of 4%, and a limit of detection of 1.31 ng/mL.

2.3. Statistical analysis

Categorical variables were described as frequencies and percentages. Continuous variables were described as mean (standard deviation), or median (Q1–Q3 percentile) for cases with skewed distribution. Normal distribution was assessed with Q–Q plots. Differences among the patients from the three cohorts were assessed by chi-square, means' comparison (ANOVA), or Kruskal–Wallis test as appropriate. Echocardiographic data were analyzed as continuous variables; for the purposes of this analysis, we considered LVEF, LV end-diastolic volume index and diameter index (LVEDVi and LVEDDi respectively) and LV end-systolic volume and diameter index (LVESVi and LVESDi respectively) as measures of remodeling.

Four strata of the ST2-R2 score were defined (<9, 9–11, 12–14, and 15–17), gathering every 3 scoring points, except for patients with scores below 9 that were grouped in only one strata due to small numbers and for homogeneity. Differences among the patients from the four strata were assessed by chi-square and means' comparison (ANOVA). P values for trend along these strata regarding changes in the echocardiographic data were assessed using Rho Spearman correlation. Univariate and multivariate Cox regression analyses were performed and survival curves were plotted based on the predefined ST2-R2 strata. All-cause death up to 4 years of follow-up (3 years after the second echocardiogram) was the primary endpoint for this analysis.

P-values <0.05 from two-sided tests were considered significant. The analyses were performed using SPSS 15 (SPSS Inc., Chicago, IL).

3. Results

A total of 569 patients that met the inclusion criteria from January 2003 to September 2012 were included. Table 1 provides the demographic, clinical, biochemical, echocardiographic characteristics and treatments during follow-up of the studied patients. Mean follow-up for survivors (up to 4 years) was 3.5 (0.8) years. As clearly shown in the table patients characteristics differ significantly among the three cohorts.

Patients were divided into 4 strata depending on their ST2-R2 score. Characteristics of these subjects are depicted in Supplemental Table 2. Based on these ST2-R2 score strata, a significant association was observed between LVEF recovery and the percentage reduction of LVESVi and LVESDi (Table 2). Fig. 1 shows box plots of the relative changes in LVEF and LVESVi relative to the ST2-R2 subgroups. Diastolic remodeling parameters evolved similarly (Table 2).

Considering patients as a function of mortality by 4 years, age, New York Heart Association functional class III–IV, treatment with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and ST2-R2 score were associated with mortality in the

Table 1
Characteristics of patients of each single and the entire cohorts.

	Total cohort	Barcelona	PROTECT	TIME-CHF	P value
	N = 569	N = 304	N = 116	N = 149	
Age, years	68.2 (12.6)	66.1 (12.4)	63.4 (13.7)	76.1 (7.4)	<0.001
Female sex	135 (23.7%)	62 (20.4%)	17 (14.7%)	56 (37.6%)	<0.001
NHYA functional class					<0.001
I–II	335 (58.9%)	239 (78.6%)	56 (48.3%)	40 (26.8%)	
III–IV	234 (41.1%)	65 (21.4%)	60 (51.7%)	109 (73.2%)	
Non-ischemic etiology	258 (45.3%)	133 (43.8%)	59 (50.9%)	66 (44.3%)	0.41
Duration of HF < 12 months	276 (48.5%)	186 (61.2%)	27 (23.3%)	63 (42.3%)	<0.001
No LBBB	444 (78%)	247 (81.3%)	96 (82.8%)	101 (67.8%)	0.002
ST2 < 48 ng/mL	383 (67.3%)	190 (62.5%)	85 (73.3%)	108 (72.5%)	0.03
LVEF < 24%	172 (30.2%)	81 (26.6%)	41 (35.3%)	50 (33.6%)	0.13
ST2-R2 score	10.5 (3.6)	10.7 (3.5)	10.8 (3.4)	9.8 (3.7)	0.03
ST2, ng/mL	37.9 (28.5–53.3)	40.8 (32.7–56.3)	35.9 (25.6–48.7)	34.2 (23.6–48.9)	<0.001
Baseline LVEF	27.4 (7.4)	28.0 (6.7)	27.0 (8.9)	26.3 (7.1)	0.08
Baseline LVESVi	60.5 (45.5–78)	59.2 (45.7–73.7)	57.3 (45.4–82.7)	63.7 (45.7–78.9)	0.34
Baseline LVESDi	27.8 (5.7)	28.0 (5.9)	26.2 (5.1)	28.7 (5.6)	0.002
Baseline LVEDVi	82.7 (68–103.7)	84.1 (66.2–99.7)	81.4 (68.9–103.9)	88.8 (68.5–107.2)	0.14
Baseline LVEDDi	33.2 (5.5)	34.3 (5.4)	30.2 (4.8)	33.4 (5.2)	<0.001
Treatments (Follow-up)					
β-blocker	548 (96.3%)	287 (94.4%)	113 (97.4%)	148 (99.3%)	0.01
ACEi-ARB	539 (94.7%)	286 (94.1%)	105 (90.5%)	148 (99.3%)	0.001
ARM	363 (63.8%)	206 (67.8%)	61 (52.6%)	96 (64.4%)	0.02
Loop diuretic	516 (90.1%)	278 (91.4%)	105 (90.5%)	133 (89.3%)	0.76
Digoxin	173 (30.4%)	107 (35.2%)	30 (25.9%)	36 (24.2%)	0.03
CRT	75 (13.2%)	31 (10.2%)	44 (37.9%)	1 (0.01%)	<0.001
ICD	119 (20.9%)	47 (15.5%)	66 (56.9%)	6 (4.0%)	<0.001

Data are presented as mean (standard deviation), median (Q1-Q3 percentile) or N (%).
LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; NHYA: New York Heart Association; HF: heart failure; ST2: soluble form of ST2; LVESVi: left ventricular end-systolic volume index (n = 402); LVESDi: left ventricular end-systolic diameter index (n = 530); LVEDVi: left ventricular end-diastolic volume index (n = 418); LVEDDi: left ventricular end-diastolic diameter index (n = 534).