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Biomarker-assist score for reverse remodeling prediction in heart failure: The ST2-R2 score

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ABSTRACT

Background: Limited data exists regarding biomarker use to predict left ventricular (LV) reverse remodeling (R2). Our aim was to examine the value of soluble ST2 (ST2), N-terminal-pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), and galectin-3 relative to LV-R2 in systolic heart failure (HF), and to develop a clinical score for LV-R2 prediction.
Methods: R2 was defined as a) LV ejection fraction (LVEF) increase ≥15%, or b) LVEF increase ≥10% plus reduction of LV end-systolic diameter index ≥20% or LV end-systolic volume ≥40%, for 12 months.
Results: We studied 304 patients (79.6% men, mean age 66.1 ± 12.3 years) with baseline LVEF <40%. R2 was observed in 104 patients (34.2%). In univariable logistic regression, factors associated with R2 were age ($p = 0.02$), non-ischemic etiology of HF ($p < 0.001$), NYHA functional class ($p = 0.02$), baseline LVEF ($p = 0.005$), absence of left bundle branch block (LBBB; $p = 0.002$), ST2 ($p = 0.004$), NT-proBNP ($p = 0.005$), and hs-cTnT ($p < 0.001$); HF duration achieved borderline significance ($p = 0.08$). In multivariable analysis, ST2 remained the only biomarker associated with LV-R2. We developed the ST2-R2 score for use in clinical practice for predicting R2; variables included were ST2 <48 ng/mL, non-ischemic etiology, absence of LBBB, HF duration <12 months, baseline LVEF <24%, and β-blocker treatment. The score had an area under the curve of 0.79 in the derivation cohort and 0.73 in a separate validation cohort.
Conclusions: The ST2-R2 score, which includes the novel biomarker ST2 and five clinical variables, reasonably predicts LV-R2 in systolic HF patients. ST2 was the only studied biomarker that was independently associated with R2.

1. Introduction

Heart failure (HF) has become a true epidemic and has an ominous prognosis despite major advances in diagnosis and treatment. Adverse outcomes clearly relate to cardiac remodeling and progressive ventricular dilatation, with impairment of systolic function [1]. Biomarkers have been used in HF for diagnostic purposes [2,3], prognostic prediction of outcomes [3–7], and more recently to guide therapy [8,9]. The rationale for including biomarkers in risk stratification is their demonstrated benefit in terms of discrimination, calibration and reclassification [5,7] that permit better selection of higher risk patients, who may need a closer follow-up or more aggressive neurohormonal blockade. Limited data exists regarding the use of biomarkers to predict left ventricular (LV) reverse remodeling (R2) and LV function recovery [10–13], although changes in several biomarkers have been reported after successful ventricular R2 [12–17]. Whether biomarkers can predict R2 is crucial, because R2 has prognostic implications [1,18–22] and its identification might substantially influence long-term risk stratification above and beyond the improvement of symptoms. Accordingly, the objectives of this

Abbreviations: HF, heart failure; hs-cTnT, high-sensitivity cardiac troponin T; 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; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association functional class; R2, reverse remodeling; ST2, soluble ST2

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[1] These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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study were to examine whether clinical variables plus serum concentrations of soluble ST2 (ST2), N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), and galectin-3 predict R2; as a secondary goal we sought to develop an easy and user-friendly score to estimate R2.

2. Methods

2.1. Derivation cohort

The source of the study population from which this cohort is derived and the methodology underlying the biomarker assays have been described elsewhere [5,23]. In summary, all patients were ambulatory HF patients treated at a multidisciplinary unit. Patients were referred to the unit by cardiology or internal medicine departments, and to a lesser extent from emergency or other hospital departments. The principal referral criterion was HF according to the European Society of Cardiology guidelines irrespective of etiology, at least one HF hospitalization, and/or reduced left ventricular ejection fraction (LVEF) [5,23]. The present cohort inclusion criteria were baseline echocardiogram and LVEF <40%, baseline biomarker measurement, and an echocardiogram available at 12 months.

All participants provided written informed consent, and the local ethics committee approved the study. All study procedures were in accordance with the ethical standards outlined in the Helsinki Declaration of 1975 as revised in 1983. The regular visitation schedule is reported elsewhere [5,23].

2.2. Definition of reverse remodeling

Two-dimensional transthoracic echocardiography was performed at the first visit (baseline) and at the 1-year follow-up to assess left ventricular remodeling. Cardiac structural measurements were made according to current recommendations and guidelines [24]. Echocardiographic measurements for the study included LVEF calculated from 4- and 2-chamber views using Simpson's method, LV end-diastolic diameter index (LVEDDi), LV end-systolic diameter index (LVESDi), LV end-diastolic volume index (LVEDVi) and LV end-systolic volume index (LVESVi).

R2 during the 1-year follow-up was defined as:

- LVEF increase ≥15% or;
- LVEF increase ≥10% + LVESDi reduction ≥20% or LVESVi reduction ≥40%.

2.3. Biomarker assays

Blood samples were obtained by venipuncture between 09.00 and 12.00 during conventional ambulatory visits, and adequate centrifugation serum samples were stored at −80 °C with a single freeze–thaw cycle. All biomarkers were analyzed from the same blood sample.

2.3.1. ST2 assay

ST2 was measured using a high-sensitivity sandwich monoclonal immunoassay (Presage® ST2 assay, Critical Diagnostics, San Diego, CA, USA).

2.3.2. Galectin-3 assay

For galectin-3 measurement, we used an enzyme-linked fluorescent assay (ELFA; BioMerieux ref. 411191) on a mini-VIDAS® analyzer (BioMerieux, France).

2.3.3. NT-proBNP assay

NT-proBNP levels were determined using an electrochemiluminescence immunoassay on the Modular Analytics E 170 (Roche Diagnostics, Switzerland).

2.3.4. hs-cTnT assay

Troponin levels were measured using an electrochemiluminescence immunoassay on the Modular Analytics E 170 (Roche Diagnostics, Switzerland).

2.4. Validation cohort

An external validation was performed with the subset of patients with serial echocardiographic data from the cohort of the Pro-B Type Natriuretic Peptide Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study [11].

2.5. Statistical analysis

Categorical variables were described as frequencies and percentages. Continuous variables were described as mean ± standard deviation (SD), and median with 25th–75th percentiles (P_{25}–P_{75}) for cases with skewed distribution. Normal distribution was assessed with normal Q–Q plots. Statistical differences between groups in the echocardiographic data were assessed using Student's *t*-test. Binomial univariate and multivariate logistic regression analysis were performed to assess the relationship between significant R2 (dependent variable) and clinical and analytical (biomarkers) parameters. To fulfill the assumption of linearity of the co-variables galectin-3, hs-cTnT, ST2, and NT-proBNP, we used the logarithmic functions of galectin-3, NT-proBNP, and hs-cTnT; and also ST2/10 plus the quadratic term of ST2/10. Variables with p-value < 0.1 in the univariable analysis, or that were considered clinically important to be included in the score (such as β-blocker treatment), were included in the multivariable analysis. To exclude biomarker collinearity in the multivariable analysis a backward step approach was also performed.

Next, continuous significant variables in the multivariable logistic regression analysis were dichotomized using clinical criteria (such as HF duration <12 months vs. ≥12 months) or using better cut-off points according to bootstrapping methods (LVEF and ST2). Then two predictive models with these dichotomous variables were evaluated (with and without the inclusion of the biomarker ST2); their performance in predicting R2 was tested using the following different measures of performance:

Discrimination. The ability of the score to discriminate between patients who will have and will not have the event (R2) was measured by means of the C-statistic (expressed with area under the curve [AUC]). Differences between AUC were assessed with the DeLong test.

Calibration. How well the observed incidence rate fit the predicted probability was measured by Nam–D'Agostino statistics using the Hosmer–Lemeshow test. Also the Brier score and the Akaike information criterion were calculated for predictive models; lower values indicate a better model. The global goodness-of-fit of the models was evaluated by likelihood ratio tests. A significant p value in this test means that adding a new variable to the model significantly improves the accuracy of the model.

Reclassification. The integrated discrimination improvement (changes in the estimated prediction probabilities as a continuous variable) and the net reclassification improvement (changes in the estimated prediction probabilities that imply a change from pre-established categories) were used.

Finally, a user-friendly score was developed from β-coefficients obtained in a new logistic regression analysis with the dichotomous

variables (1 point was assigned to the lowest β-coefficient [0.421 for baseline LVEF] with proportional values assigned to the rest). This score was then evaluated by means of discrimination, calibration and generalization or validation. To assess internally how the results of the models can be generalized to an independent dataset, a 10-fold cross-validation technique was used; the mean C-statistic was calculated, and the process was repeated for all 1000 samples. The external validation was performed by calibration and discrimination methods.

Finally, Cox regression event-free survival curves were plotted based on the presence or absence of R2 according to the established definition. For this analysis event was defined as cardiovascular mortality or HF hospital admission.

p-Values < 0.05 from two-sided tests were considered to indicate statistical significance. The analyses were performed using SPSS 15 (SPSS Inc., Chicago, IL) and the software R (version 2.11.1) statistical package (Foundation for Statistical Computing, Vienna, Austria).

3. Results

From May 2006 to September 2012, 304 consecutive patients that met the inclusion criteria were included in the study. Flow-chart inclusion is shown in Online Supplementary Fig. 1. Table 1 provides demographic, clinical, and biochemical characteristics of the studied patients with respect to the presence or absence of R2. This R2 was observed in 104 patients (34.2%). In univariable logistic regression analysis, factors associated with R2 were age, non-ischemic etiology of HF, NYHA functional class, baseline LVEF, absence of left bundle branch block (LBBB), ST2, NT-proBNP, and hs-cTnT; HF duration achieved borderline significance (Table 1). Galectin-3 concentrations were similar in patients with and without R2 and did not show any relationship with it. After multivariable regression logistic analysis, ST2 remained the only biomarker associated with R2, together with non-ischemic etiology of HF, absence of LBBB, HF duration, and baseline LVEF (Table 1).

Table 2 shows baseline and 1-year echocardiographic data for the entire cohort and with respect to the presence or absence of R2. Differences in LVEF improvement and LV diameter/volume reduction were highly significant between groups. In patients with LVEF increase ≥15%, the changes observed in LVESDi and LVESVi were −20.2% and −41.2%, respectively.

We tested a predictive model that comprised of 6 variables (baseline ST2 <48 ng/mL, non-ischemic etiology, absence of LBBB, HF duration <12 months, baseline LVEF <24%, and β-blocker treatment) and obtained a C-statistic (area under the curve) of 0.79. The same predictive model but without ST2 levels was also tested in order to ascertain how much the incorporation of this biomarker modified the performance of the model. In Table 3 the performance of the two models is depicted. Discrimination and reclassification were significantly improved with the addition of ST2. The best calibration was also obtained with the addition of the biomarker.

Next, we developed a simple score from obtained β-coefficients (the ST2-R2 score) for use in clinical practice (Table 4). R2 estimation ranged from 10% in patients with a low score (2 to 5 points) to a remarkable 86% in patients with a score of 15–17 (Fig. 1). Among the five patients who had a score of 2 points, none of them experienced R2; no patient scored 0 or 1. The C-statistic (area under the curve) of the ST2-R2 score virtually superimposed the C-statistic obtained with the predictive model using dichotomous variables (Fig. 2). The Hosmer–Lemeshow test did not reveal any significant differences between predicted and observed results (Fig. 3). Internal 10-fold cross-validation test revealed an average C-statistic of 0.79 (Fig. 4).

The external validation PROTECT cohort showed a good calibration (Hosmer–Lemeshow test chi-square 2.66, p = 0.62, Online Supplementary Fig. 3) and the score had an AUC of 0.73. Online Supplementary Fig. 4 depicts R2 percentage in the PROTECT cohort relative to ST2-R2 score punctuation quintiles. Online Supplementary Table 1 shows echocardiographic changes observed in the subset of patients with available LV volumes in the derivation and in the validation cohorts.

Follow-up after the second echocardiogram up to 3 years (mean 2.2 ± 0.9 years) revealed 70 patients suffered an event (cardiovascular death or HF hospitalization). Patients with R2 had significantly better outcomes (HR 0.36 [95% CI 0.18–0.72], p = 0.003) as depicted in Online Supplementary Fig. 2.

4. Discussion

The term ventricular remodeling refers to alteration in ventricular architecture, with associated increased volume and altered chamber configuration, driven at a histological level by a combination of

Table 1
Characteristics of the entire cohort and association with reverse remodeling.

	Total	Reverse remodeling	No reverse remodeling	Univariable logistic regression			Multivariable logistic regression		
	N = 304	N = 104	N = 200	OR	95% CI	p	OR	95% CI	p
Age, years	66.1 ± 12.3	63.7 ± 13.2	67.3 ± 11.7	0.98	0.96–1.00	0.018	1.01	0.98–1.04	0.50
Female sex	62 (20.4%)	21 (20.2%)	41 (20.5%)	0.98	0.54–1.77	0.950	–	–	–
Non-ischemic etiology	133 (43.8%)	72 (69.2%)	61 (30.5%)	5.13	3.07–8.57	<0.001	4.7	1.87–11.93	<0.001
Baseline LVEF	28.0 ± 6.7	26.4 ± 7.4	28.7 ± 6.3	0.95	0.92–0.99	0.005	0.93	0.88–0.97	0.003
Duration of HF (months)[a]	4 (1–36)	3.5 (1–24)	6 (1–48)	0.89	0.78–1.01	0.079	0.82	0.69–0.98	0.03
NYHA functional class	2.16 ± 0.5	2.1 ± 0.47	2.2 ± 0.5	0.56	0.34–0.92	0.023	0.74	0.39–1.41	0.36
No LBBB	247 (81.3%)	95 (91.3%)	152 (76%)	3.33	1.56–7.10	0.002	4.7	1.87–11.83	0.001
β-Blocker treatment	287 (94.4%)	100 (96.2%)	187 (93.5%)	1.74	0.55–5.47	0.345	2.33	0.50–10.81	0.28
ACEI–ARB treatment	286 (94.1%)	97 (93.3%)	189 (94.5%)	0.81	0.30–2.15	0.667	–	–	–
Ivabradine treatment	38 (12.5%)	12 (11.5%)	26 (13%)	0.87	0.42–1.81	0.715	–	–	–
MRA treatment	140 (46.1%)	50 (48.1%)	90 (45%)	1.17	0.72–1.90	0.531	–	–	–
CRT[b]	19 (5.3%)	7 (6.7%)	9 (4.5%)	1.53	0.55–4.24	0.412	–	–	–
Galectin-3[a], ng/mL	16.4 (13–21.2)	16.3 (12.6–20.2)	16.5 (13.2–22.8)	0.77	0.42–1.42	0.406	–	–	–
NT-proBNP[a], ng/L	1828 (854–3893)	1307 (703–2772)	2390 (1044–4298)	0.74	0.61–0.91	0.005	0.77	0.55–1.07	0.12
hs-cTnT[a], ng/L	26.8 (12.8–44.5)	21.4 (7.5–32.8)	28.8 (14.5–48.5)	0.62	0.47–0.81	<0.001	0.95	0.65–1.38	0.78
ST2[c], ng/mL	40.1 (32.7–56.3)	38.3 (32–47.5)	43.8 (33.0–59.9)	0.71	0.56–0.90	0.004	0.69	0.50–0.94	0.02

ACEI–ARB: angiotensin converting enzyme inhibitor–angiotensin II receptor blocker; CRT: cardiac resynchronization therapy; hs-cTnT: high-sensitivity cardiac troponin T; NT-proBNP: N-terminal pro-B-type natriuretic peptide; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; MRA: mineral-corticoid receptor antagonist; NYHA: New York Heart Association; HF: heart failure; and ST2: soluble form of ST2.

Data are presented as mean values ± standard deviation, median values (25th–75th percentile) or N (%).

N for galectin-3 = 268 total, 80 with R2, 150 without R2.

N for hs-cTnT = 264 total, 80 with R2, 150 without R2.

[a] For logistic regression the logarithmic forms of duration of heart failure, galectin-3, NT-proBNP, and hs-cTnT were used.

[b] Five patients treated with CRT were considered as non-CRT-treated because they underwent less than 6 months of therapy before control echocardiography.

[c] ST2 per every 10 ng/mL. p-Value for the quadratic form of ST2/10 = 0.068.

Table 2
Echocardiographic data with respect to the presence or absence of reverse remodeling.

	Total	Reverse remodeling	No reverse remodeling	p
Baseline LVEF, %	28.0 ± 6.8	26.4 ± 7.4	28.7 ± 6.3	0.005
Baseline LVESDi, mm/m^2	28.2 ± 5.9	28.8 ± 6.0	27.6 ± 5.8	0.10
Baseline LVEDDi, mm/m^2	34.3 ± 5.4	34.8 ± 5.3	34.1 ± 5.4	0.30
Baseline LVESVi, mL/m^2	61.0 ± 24.3	60.2 ± 23.9	61.4 ± 24.6	0.78
Baseline LVEDVi, mL/m^2	83.8 ± 28.9	81.7 ± 27.7	84.9 ± 29.6	0.52
1-Year LVEF, %	37.2 ± 11.4	48.8 ± 8.1	31.2 ± 7.6	<0.001
1-Year LVESDi, mm/m^2	26.1 ± 5.9	22.3 ± 4.3	28.1 ± 5.7	<0.001
1-Year LVEDDi, mm/m^2	33.2 ± 5.2	30.5 ± 3.6	34.6 ± 5.2	<0.001
1-Year LVESVi, mL/m^2	50.0 ± 26.8	32.9 ± 17.3	58.2 ± 26.7	<0.001
1-Year LVEDVi, mL/m^2	76.7 ± 29.9	63.8 ± 26.5	83.0 ± 29.6	<0.001
Mean change in LVEF, %	+9.3 ± 11.7	+21.9 ± 7.9	+2.5 ± 10.8	<0.001
Mean change in LVESDi, %	−5.2 ± 19.6	−21.0 ± 13.6	+3.04 ± 171	<0.001
Mean change in LVESVi, %	−14.3 ± 35.1	−41.6 ± 25.2	−0.8 ± 31.3	<0.001

LVEF: left ventricular ejection fraction; LVESDi: left ventricular end-systolic diameter index; LVEDDi: left ventricular end-diastolic diameter index; LVESVi: left ventricular end-systolic volume index (n = 151); and LVEDVi: left ventricular end-diastolic volume index (n = 151).

pathological myocyte hypertrophy, myocyte apoptosis, myofibroblast proliferation, and interstitial fibrosis. Although originally described after myocardial infarction, it develops in response to a variety of forms of myocardial injury and increased wall stress [1]. Ventricular remodeling has a long history of being associated with worse prognosis [1]. LVEF, the most common metric of cardiac performance in clinical practice, is influenced by the degree of LV remodeling more than by any other factor [20] and can be used as a measure of ventricular remodeling. Other, more precise metrics of remodeling, such as LV dimensions, volumes, and mass, have received greater focus in clinical trials than in clinical practice [1], yet these measurements relate closely to prognosis.

It is very remarkable that the processes that can lead to LV remodeling may be reversible when the stress is removed or attenuated, with the LV capable of being restored to its normal size and shape [25]. Although there is no universal definition of R2, the term can be applied to this regression phenomenon of ventricular remodeling. Many studies only use statistically significant increases in LVEF or reduction in LV dimensions or volumes; others (as we did) use defined cut-offs for LVEF improvement (5–20 percentage points) and/or a reduction of ≥10–20% in LV dimensions or volumes [18,26,27] to consider R2 as clinically significant. We used strict and demanding criteria for meaningful R2 by selecting patients with clinically significant LV performance improvement.

Table 3
Performance of the predictive model without and with ST2 levels for the prediction of reverse remodeling.

	Reference model	Model with ST2
Discrimination		
C-statistic	0.765 (0.707 to 0.823) Reference	0.791 (0.745 to 0.846) p = 0.041
Calibration		
H–L	Chi-square: 2.3 p = 0.13	Chi-square: 3.2 p = 0.08
Brier score	0.173	0.164
AIC	333	321
Likelihood ratio	Reference	p < 0.01
Reclassification		
IDI	Reference	4.0 (1.9 to 6.2) p < 0.001
NRI	Reference	14.8 (5.4 to 24.2) p = 0.002

Reference model: non-ischemic etiology, absence of LBBB, HF duration <12 months, baseline LVEF <24%, and β-blocker treatment.
Model with ST2: reference model + baseline ST2 <48 ng/mL.
AIC = Akaike information criterion; H–L = Hosmer–Lemeshow test; IDI = integrated discrimination improvement; NRI = net reclassification improvement; ST2 = high-sensitivity soluble ST2.

There are limited data regarding the use of biomarkers to predict LV remodeling, and even less regarding their use to predict LV function recovery or R2 [10–13]; however, changes in several biomarkers have been reported after successful LV R2 [12–17]. Some of the biomarkers assessed are not usually included in clinical practice [13–15]. In the PROTECT study [11], galectin-3 concentration >20 ng/mL was associated with an increase in LVEF but not with changes in LV volume; furthermore, no therapies appeared to reduce galectin-3 concentrations in this cohort, and a reduction in galectin-3 was not linked to R2 in PROTECT either. In a substudy of the CARE-HF trial, neither galectin-3 nor other markers of collagen turnover reflective of extracellular cardiac matrix remodeling did predict response to cardiac resynchronization [28]. In our study, galectin-3 was not associated with R2; while ST2, NT-proBNP, and hs-cTnT serum concentrations were associated with R2 in the univariable analysis, only ST2 remained statistically independently associated with it in the multivariable analysis. These results are consistent with those from Gaggin and colleagues, who recently reported changes in ST2 concentration predicted remodeling in PROTECT [17]. For these reasons, ST2 was the biomarker selected to construct the score.

ST2 is a commercially available biomarker, approved by the United States Food and Drug Administration, which has recently obtained the American College of Cardiology/American Heart Association class II recommendation for determination of prognosis in chronic HF [29]. ST2 is a member of the interleukin 1 receptor family and exists in two forms, a transmembrane receptor (ST2L) and a soluble decoy receptor (ST2) [30]. The ligand of ST2L is interleukin 33, which is involved in reducing fibrosis and hypertrophy in mechanically strained tissues. ST2L transduces the effects of interleukin 33 in in vitro and in vivo models, while excess soluble ST2 leads to cardiac fibrosis and ventricular dysfunction [31–33]. Our data suggest that ST2 values in excess of 48 ng/mL are associated with a reduced likelihood of achieving R2 during follow-up owing to excess myocardial fibrosis. In other words, ST2 measurement provides a strong serologic overview of the cumulative myocardial

Table 4
Dichotomized variables used for score construction.

	Multivariate logistic regression (N = 304)				
	OR	95% CI	p	β	Assigned points
Non-ischemic etiology	6.33	3.52–11.39	<0.001	1.845	5
No LBBB	5.56	2.37–13.05	<0.001	1.716	4
ST2 < 48 ng/mL	2.96	1.62–5.39	<0.001	1.084	3
Duration of HF <12 months	2.13	1.18–3.84	0.01	0.754	2
β-Blocker treatment	1.89	0.52–6.86	0.34	0.634	2
Baseline LVEF <24%	1.52	0.81–2.88	0.20	0.421	1

LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; HF: heart failure; and ST2: soluble form of ST2.

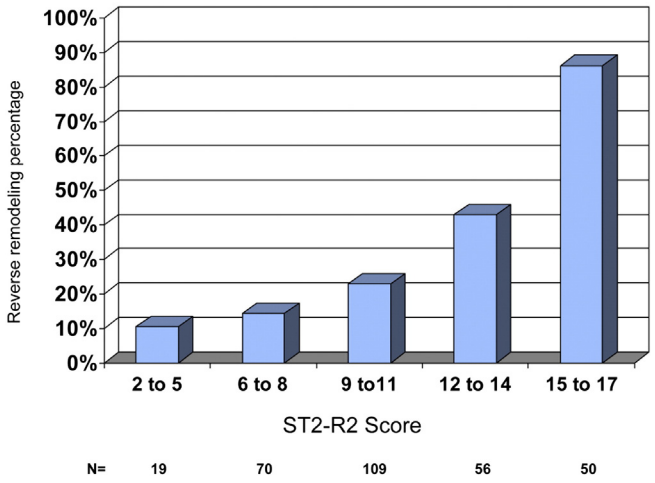

Fig. 1. Probability of R2 with respect to ST2-R2 score. The probability of reverse remodeling ranges progressively from 10% in the lowest-scoring group (2–5 points) to 86% in the highest-scoring group (15–17 points).

fibrotic process and ultimately is a relevant addition to the predictive ability of the practicing clinician to identify R2.

Non-ischemic etiology of HF was the variable with a stronger association with R2; thus, it scores the highest in our developed ST2-R2 score. Although some studies have observed R2 irrespective of HF etiology [27], cardiac resynchronization therapy studies demonstrate a consistent benefit in cases with non-ischemic etiology [22,34,35]. Earlier β-blocker treatment studies also suggest this phenomenon [36]. Merlo et al. [18] observed LV R2 in 37% of patients with idiopathic dilated cardiomyopathy, a similar rate to our study. It is remarkable that the absence of LBBB was (very importantly) associated with LV R2 in our study, similar to the Merlo et al. study, despite the inclusion of patients with ischemic etiology of HF.

Several treatments (drugs and devices) have been widely associated with ventricular R2. Kramer et al. [21] used a comprehensive meta-analytic approach to demonstrate that β-blocker treatment is associated with the greatest improvement in LVEF and greater reductions in both

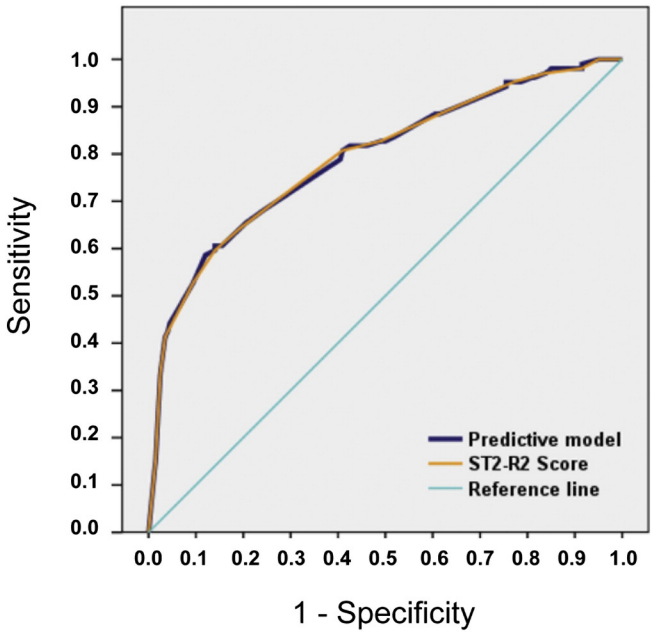

Fig. 2. AUC for predictive model and ST2-R2 score. The AUC of the ST2-R2 score was practically identical to that obtained with the predictive model using dichotomous variables.

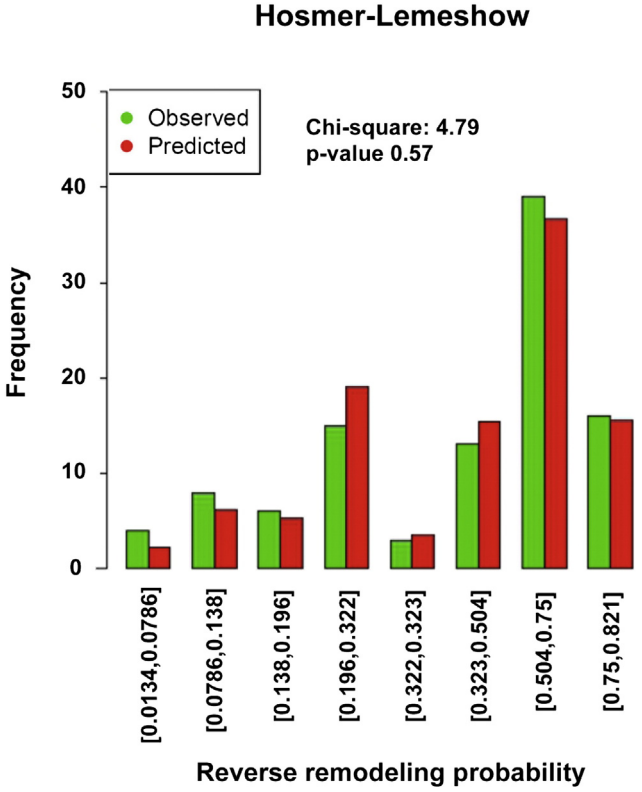

Fig. 3. The Hosmer–Lemeshow test for the ST2-R2 score. Calibration of the ST2-R2 score using the Hosmer–Lemeshow test did not reveal any statistically significant differences between predicted and observed results.

end-systolic and end-diastolic LV volumes. The literature is consistently very strongly in favor of such treatment [37,38], which is the main reason we decided to include β-blocker treatment in the ST2-R2 score.

As previously reported [1,18–22], R2 also had significant prognostic implications in our cohort. Patients with R2 suffered 3-fold lower clinical events, defined as cardiovascular death or HF hospitalization, during follow-up. Validation of the ST2-R2 score was dual, both internal and using a validation external cohort, and in both instances the score performed reasonably well.

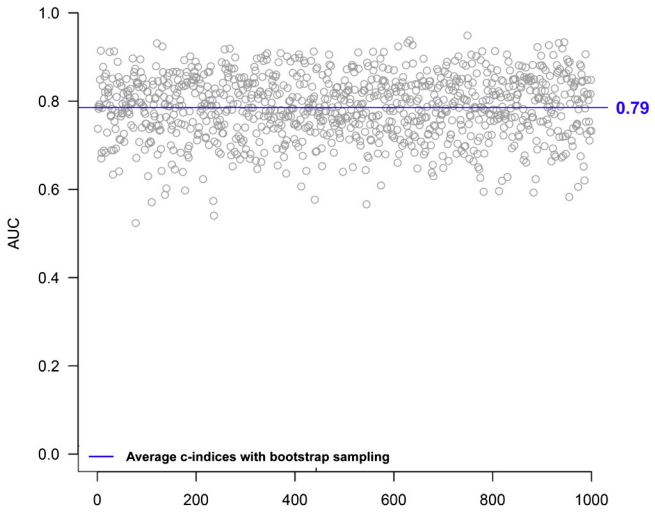

Fig. 4. The C-statistic in 10-fold cross-validation with 1000 bootstrapping. The average AUC for the ST2-R2 score after 1000 bootstrapping was 0.79.

The strength of our work is the validation of the ST2-R2 score in a geographically and demographically distinct cohort of patients from Boston. In the validation group, the ST2-R2 score showed an AUC of 0.73 to predict R2, with consistent links between lower score and lower likelihood for improved LV size and function.

Eventually, the addition of elaborated electrophysiologic, imaging and/or genetic parameters might have an impact on the score. Future studies will have to demonstrate their true value in terms of discrimination/calibration/reclassification analysis.

4.1. Limitations

Although we recognize that the superiority of contrast echocardiography in the evaluation of LV remodeling parameters has been demonstrated [39], often it is only used in selected patients, and we did not use such a technique in a generalized way. Indeed, more contemporary techniques, such as 3-dimensional echocardiography and cardiac magnetic resonance imaging, would measure LV function and volumes more precisely; however, these techniques are not widely used in clinical practice and were not available for our study. We used indexed LV diameters to estimate LV size and LV volumes in a subset of patients in which they were available; notably 100% of the validation cohort had available volume index for both end-systolic and diastolic parameters. We have no data on mitral regurgitation or dyssynchrony changes that might be significant in patients with R2. As in all published studies of remodeling, our analyses have been performed in "completers," that is, patients who have both baseline and final echocardiography data for analysis, and the score is also derived from those patients. It is not possible to predict the effect that the "non-completers" might have had on the analysis if their information had been available. Lastly, we did not examine the serial use of the ST2-R2 score to evaluate whether changes in serial measurement of the score would inform greater understanding regarding the presence and tempo of R2. To the extent that the PROTECT study suggested that serial ST2 measurement provided superior information about predicting R2 [17], it is reasonable to suspect serial calculation of the score would be of value, and should be the focus of future efforts.

5. Conclusions

The ST2-R2 score, which includes the novel biomarker ST2 and five conventional risk parameters, reasonably predicted R2 in systolic HF patients. Of the four studied biomarkers, ST2 was the only biomarker that was independently associated with R2 as defined. This validated score provides proof of concept that R2 is a predictable phenomenon; such knowledge may influence treatment decision making.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.02.019.

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Conflict of interest

Dr. A. Bayes-Genis has received lecture honoraria from Roche Diagnostics and Critical Diagnostics and Dr. J. Lupón from Roche Diagnostics. Drs. A. Bayes-Genis and J. Lupón report their relationship with Critical Diagnostics.

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