Abstract   **Words:** 249

Background: Almost 1/3 of heart failure patients fail to respond to cardiac resynchronization therapy(CRT). A simple clinical score to predict who these patients are at the moment of referral or at time of implant may be of importance for early optimization of their management.

Methods: Observational study. A risk score was derived from factors associated to CRT response. The derivation cohort was composed of 1,301 patients implanted with a CRT defibrillator in a multi-center French cohort-study. External validation of this score and assessment of its association with CRT response and all-cause mortality and/or heart transplant was performed in 1,959 CRT patients implanted in 4 high-volume European centers.

Results: Independent predictors of CRT response in the derivation cohort were: female gender (OR=2.08, CI95%1.26-3.45), NYHA class≤III (OR=2.71, CI95%1.63-4.52), left ventricular ejection fraction≥25% (OR=1.75, CI95%1.27-2.41), QRS duration≥150ms (OR=1.70, CI95%1.25-2.30) and estimated glomerular filtration rate≥60ml/min (OR=2.01, CI95%1.48-2.72). Each was assigned 1 point. External validation showed good calibration (Hosmer-Lemeshow test-P=0.95), accuracy (Brier score=0.19) and discrimination (c-statistic=0.67), with CRT response increasing progressively from 37.5% in patients with a score of 0, to 91.9% among those with score of 5 (Gamma for trend= 0.44, P<0.001). Similar results were observed regarding all-cause mortality or heart transplant.

Conclusion: The ScREEN score (Sex category, Renal function, ECG/QRS width, Ejection fraction and NYHA class) is composed of widely validated, easy to obtain predictors of CRT response, and predicts CRT response and overall mortality. It should be helpful in facilitating early consideration of alternative therapies for predicted non-responders to CRT therapy.

Keywords: responders; heart failure; risk stratification; score; mortality; DAI-PP.

Abbreviations

CRT – cardiac resynchronization therapy; AF – atrial fibrillation; NYHA - New York Heart Association functional class (NYHA); eGFR - Estimated glomerular filtration rate; LVEF – left ventricular ejection fraction.

Background

Cardiac resynchronization therapy (CRT) has emerged as a highly effective treatment option in patients with advanced systolic heart failure [1, 2]. Unfortunately, almost one third of patients do not gain significant benefit from this therapy, and develop episodes of heart failure, referral for heart transplantation or die prematurely [3].

Different predictors of CRT response have been identified [4-7], but to date these have not yet been incorporated into an externally validated clinical scoring system that allows simple and easy-to-use categorization of patients based on their likelihood of responding to this therapy.

After correcting all reversible medical conditions leading to non-response, like anaemia, optimizing device AV and V-V interval programming, and heart failure medication, non-responders to standard CRT therapy may be potential candidates to novel approaches like multipoint pacing [8], use of dynamic auto-optimization algorithms [9], LV endocardial pacing [10], new pharmacological approaches as they become available [11, 12] or other investigational approaches. As an alternative, non-responders should be referred early to transplant centers, and kept under close monitoring to make sure that, in the absence of CRT response, they can still meet criteria for heart transplantation and have a chance to survive.

Methods

Derivation Cohort and Derivation of the Risk Prediction Model

Among the participants of the DAI-PP cohort (*Défibrillateur Automatique Implantable-Prévention Primaire*; NCT01992458), 1,301 were implanted with CRTs and provided data

regarding their responder status (definition of CRT response provided below). Briefly, between 2002 and 2012, all patients aged ≥18 years at the time of implantable cardioverter defibrillator (ICD) implantation, with ischemic or non-ischemic cardiomyopathy, stable on maximally tolerated medical therapy, implanted with an ICD (biventricular, single or dual chamber) in the setting of primary prevention in 12 French reference centers were considered and enrolled in the DAI-PP follow-up program [13].

Exclusion criteria included secondary prevention ICD recipients, those without structural heart disease (including channelopathies) or other types of structural heart disease (e.g. hypertrophic cardiomyopathy, non-compaction and arrhythmogenic right ventricular cardiomyopathy). For our derivation cohort, we selected only patients implanted with cardiac resynchronization therapy defibrillators (CRT-Ds) and whose responder status was available.

The study was funded by private and public sources, including the *Arrhythmia Association from Toulouse* (ART), the *French Institute of Health and Medical Research* (INSERM) and the French Society of Cardiology, and was coordinated by *Clinique Pasteur*, Toulouse and the *Paris Cardiovascular Research Center*, *European Georges Pompidou Hospital*, Paris, in France. The study complied with the *Declaration of Helsinki*, and the data file of the DAI-PP study was declared to and authorized by the French data protection committee (*Commission Nationale Informatique et Liberté,* CNIL).

All variables at the time of the procedure were defined and categorized according to the literature or common practice. In addition to New York Heart Association functional class (NYHA), assessed by the local DAI-PP investigator at the time of device implantation, we collected the aetiology of the underlying heart disease (ischemic or dilated cardiomyopathy). Estimated glomerular filtration rate (eGFR), was calculated using the *Modification of Diet in Renal Disease Study Equation* (MDRD) and categorized into 2 categories (≥60 and <60

mL/min). Atrial fibrillation (AF) was defined as a history of AF (paroxysmal or persistent), documented on standard ECG or 24-hour Holter monitoring.

Follow-up information was obtained from appointments every 4-6 months for device evaluation, according to French guidelines [14]. Endpoints included: i) Response to CRT therapy, defined as an improvement of ≥1 NYHA functional class and/or ≥5% left ventricular ejection fraction (LVEF) in the absence of hospitalization for congestive heart failure within the 12 months after implant; ii) Survival free from all-cause mortality or heart transplant.

Data was entered into a pre-defined data introduction electronic sheet made available to all participant centers. After completion of follow-up, data from all DAI-PP Centers was merged and analysed at the *Paris Cardiovascular Research Center* (Inserm U970, Cardiovascular Epidemiology Unit) using SAS program v9.3 (SAS Institute Inc, Cary, North Carolina).

Derivation of the risk prediction model

Logistic regression was used to determine independent predictors of CRT response in the derivation cohort. Cut-off values for quantitative variables were chosen using the Youden index (best combination of sensitivity and specificity). These were then combined, and based on their relative ratios, which were similar, each was assigned one point, and composed our model.

This score was tested in the derivation cohort to monitor its association with the primary endpoint, CRT response, and subsequently with the secondary endpoint of survival free from death and or transplant.

Assessment of the score was also performed in DAI-PP patients implanted with non-CRT ICDs, which acted as controls, as confirmation the score truly reflected CRT response and not only overall frailty. If this was true, the risk prediction model should have a close association with all-cause mortality and/or transplant in CRT patients only.

External Validation and Model Assessment

External validation with regard to CRT response and survival free from all-cause mortality and/or transplant was performed using a contemporary cohort of CRT patients from 4 high-volume European Centers.

We assessed the calibration, discrimination and accuracy of our model both in the derivation and validation cohort, using the *Hosmer–Lemeshow* goodness-of-fit test statistic to assess calibration (whether or not the observed event rates match expected event rates in subgroups of the model population; a non-significant result, P-value > 0.05, for this test indicates that the model is a good fit [15]), and receiver-operator characteristic curve (area under the curve or c statistic) to assess discrimination. Discrimination describes a model's ability to distinguish between patients who do or do not experience the outcome of interest. This was assessed through the area under the receiver-operator characteristic curve (area under the curve or c statistic) [16].

C-statistic to evaluate the performance of a continuous score to predict an outcome is well established and has been extended to the application when that score is a linear combination of several factors, using coefficients from a logistic regression model. This use of a logistic regression model is not well suited to analysis of probability of disease onset when disease is observed over follow-up periods that vary in length by person, since probability of onset usually varies by length of observation period [17]. Sensitivity and specificity and c-statistic are all defined in terms of probability of disease onset, so they are also time-dependent when follow-up period is not fixed. Accordingly, we have assessed discrimination of our model according to follow-up duration, to ascertain the time interval where it was more useful.

As a measure of accuracy, we calculated the *Brier* score, which is the averaged squared

difference between predicted and observed values. It describes how well a particular model predicts the likelihood of an outcome in an individual patient. The *Brier* score ranges from 0 to 1: lower scores being better, a 0 indicates a perfect model [18]. Usually, a model is only considered useful if Brier score is < 0.25.

SPSS 19.0 for descriptive and inferential statistical analysis. Preparation of this report was in accordance with the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) statement for reporting of observational studies [19].

Results

Sample Characterization

Baseline characterization of the derivation cohort from DAI-PP study and its comparison to the external validation cohort is shown in Table 1. DAI-PP patients were younger but average age was still in the mid-sixties, with a higher proportion of male patients (almost 85%). In the derivation cohort there were 90 individuals (6.9%) in NYHA=4. All were stable in ambulatory class IV. NYHA classes I, II, and III, accounted for 50 (3.8%) 366 (28.1%), and 795 (61.1%) patients, respectively. Patients in NYHA class I were implanted on the basis of qualifying for an ICD and having a pacing indication (therefore were implanted with CRT-Ds). LVEF ≥25% was observed in 70.4% (n=916) in the same cohort. Unlike in the external validation cohort, no CRT-Ps or secondary prevention indications were present in the derivation sample. The prevalence of ischemic cardiomyopathy was similar in both samples and accounted for approximately 50%. Similar mean left ventricle ejection fraction and NYHA values were observed in the two samples, but statistical power was high enough to account for statistically significant differences. Finally, in the derivation cohort a lower

prevalence of AF (only a quarter of patients at baseline) was observed, and more than half of DAI-PP patients had eGFR ≥ 60mL/min (10% more than in the external validation cohort).

Derivation of ScREEN

In the French sample, 75.8% of patients met criteria for CRT response. On multivariate analysis female gender, eGFR ≥60mL/min, QRS width ≥150ms, LVEF ≥ 25% and NYHA class I to III were the only five independent predictors of CRT response (Table 2). As these had relatively similar odds ratios (ranging from 1.70 to 2.71), and because no predictor odds ratio value was twice that of the others, and as a way of preserving simplicity in the model, one point was assigned to each variable to constitute the ScrEEN score, which ranged between 0 and 5, according to the number of variables observed for each patient. The acronym ScREEN is derived from the variables: Sex category, Renal function, ECG (QRS width), Ejection fraction, and New York Heart Association class (Figure S-1. Supplementary Material). Accordingly, patient with the highest chance of responding to CRT therapy, with the highest ScREEN scores, were assigned 4 or 5 points and accounted for 30% of the sample, and patients least likely to respond, with lowest ScREEN scores, had 0 or 1 points and corresponded to nearly 10%.

Age, ischaemic CM and AF were associated with survival or survival free from all-cause mortality or heart transplant, but not with CRT response (Table S-1).

Performance of ScREEN in the Derivation Sample to Predict CRT Response and Survival

Assessment of the rate of CRT responders across the different values of ScREEN score shows that < 50% of patients (46.7%) with a score of 0 met criteria for response, while > 90% of individuals (93.9%) with the maximum score of 5 were responders, with progressive increase

in the intermediate levels (Gamma for trend =0.47, P<0.001) (Figure 1). ScREEN had reasonable discriminative power (c-statistic =0.67, 95%CI 0.63-0.70, P<0.001), was well-calibrated (*Hosmer-Lemeshow* P=0.65), and appeared to be accurate based on *Brier* score (value of 0.17) for CRT response in the derivation cohort.

Even though use of beta-blockers was 15% lower in patients with a score of 0 or 1 (Supplementary material – Table S-2), multivariate analysis shows that use of these agents, angiotensin-II receptor antagonists, angiotensin-converting enzyme inhibitors, and aldosterone antagonists did not add any additive predictive value to the ScREEN score.

During a median follow-up of 2.5 years (IQR 1.2-4.1) 24.4% of patients died or underwent heart transplantation. Survival free from all-cause mortality and/or heart transplant also rose in parallel with ScREEN score (log rank P<0.001; Gamma for trend =0.46, P<0.001) (Figure S-2.A. Supplementary Material).

Furthermore, in the non-CRT ICD population of the DAI-PP survey (single and dual chamber ICDs), the ScREEN score did not predict the primary endpoint, with different score strata intersecting and overlapping each other, and ranging from 60 to 80% across all patient groups at 5 year's survival (Figure S-2.B. Supplementary Material). This demonstrates that the ScREEN score is a valid and specific discriminator of CRT response and survival free from all-cause mortality and/or heart transplant in the CRT population.

Hosmer-Lemeshow goodness of fit test confirmed that the model was well calibrated (P=0.71), and assessment of discrimination over time showed that best c-statistic value, 0.70, was observed at 3 years (Table S-3). Based on *Brier* score values the model can be considered accurate as they fall below the 0.25 threshold.

External validation

71.6% of patients in the validation cohort were CRT responders. During a median follow-up of 3.6 years (IQR 1.9-5.9) 45.0% of patients died or underwent heart transplantation. The bar chart in Figure 1 illustrates the rate of CRT response in the different strata of ScREEN, rising progressively from 37.5% in patients with a score of 0, to 91.9% in patients with a score of 5 (*Gamma* for trend =0.44, P<0.001) (Figure 1). Discrimination was satisfactory (c-statistic 0.67, 95% CI 0.62-0.71, P<0.001), and the score was well calibrated (*Hosmer-Lemeshow* P= 0.95), and accurate (Brier score = 0.19).

The *Kaplan-Meier* curve in Figure 2.A. illustrates that survival increased progressively from the lowest ScREEN scores (0 and 1, with some degree of overlap), to intermediate levels in values 2 and 3, and was highest for scores of 4 or 5 (overall log rank P<0.001; Gamma for trend =0.45, P<0.001). Grouping patients in 3 categories according to ScREEN scores (0 and 1, lowest chances of CRT response; 2 and 3 intermediate chances of CRT response; 4 and 5 highest chances of CRT response) showed that almost 75% of patients in the highest category of response were alive at 10 years, while nearly 50%, or only 25% were alive in the intermediate and lowest chance of response group, respectively (Figure 2.B and Table S-4). Interestingly, not only did the individuals with lowest chance of CRT response have lower survival, but also half of these patients were dead within 2 years. Graphical analysis of the results in each of the 4 centers (scores from 0 to 5) displayed separately shows that discrimination and performance were comparable (Figure S-3. Supplementary Material). Table S-4 (Supplementary Material) provides survival rates and incidence of events in the first 10 years of follow-up for each risk strata and the three aforementioned categories.

Hosmer-Lemeshow goodness of fit test confirmed that the model was well calibrated (P=0.36), and assessment of discrimination over time showed good c-statistic value (0.72) in the first 4 years (c-statistic 0.71 to 0.72). Based on *Brier* score values the model could be considered accurate as they fall below the 0.25 threshold.

Table S-5 (Supplementary material) shows data on the performance of the ScREEN score in different sub-populations of the validation cohort (patients with and without AF, CRT-Ds and CRT-Ps, primary and secondary prevention, ischemic and non-ischemic cardiomyopathy, Diabetes and no Diabetes, presence vs. absence of left bundle branch block), with a c-statistic ranging from 0.64 to 0.71, and the 95% confidence intervals of complementary subpopulations (e.g. AF vs. no AF) overlapping, and showing comparable discrimination.

Discussion

The ScREEN score, composed of readily available data from echocardiogram, ECG and clinical evaluation, is able to predict CRT response and overall survival prior to implantation. This model performed well, with good calibration, accuracy and discrimination, in both the derivation and validation cohorts. To date and to the best of our knowledge, this is the first score to predict CRT response and hard clinical outcomes (survival free from all-cause mortality and heart transplant) with appropriate external validation. Its performance is reproducible with good results within the DAI-PP derivation cohort and in 4 European high volume centers which constitute the validation cohort. This classification may be an important way of:

i. Reinforcing the benefit of referring individuals with a high chance of CRT response, improving patient selection and referral;

ii. Providing prognostic information to physicians and patients;

iii. Identifying a group of likely non-responders to CRT who may benefit from early referral to other interventions e.g. cardiac transplant, or offered investigational drugs, devices or pacing modalities.

iv. Detecting CS leads in sub-optimal location in patients predicted as having high chances of response and not improving after CRT

In spite of having been derived from a cohort of patients implanted with CRT-Ds, the ScREEN score performed equally well in the external validation cohort, which comprised nearly half of patients treated with CRT-Ps, supporting its application in both the CRT-D and CRT-P populations.

Female gender [4], left ventricular ejection fraction [5], QRS width [6], and New York Heart Association class [1, 7] have long been known to be associated with response to CRT therapy and outcomes in CRT recipients. This may occur as a result of more pronounced electrical dyssynchrony, lower scar burden [20] and contractile reserve [21], which associates with higher chances of reverse remodeling.

Liu et al. have shown that for same levels of LVEF, patients with eGFR <60mL/min presented with reduced systolic function, as measured through longitudinal LV strain, circumferential strain and strain rate [22]. This makes a case for using eGFR as a marker for potential deterioration of LV systolic function beyond LVEF [20].

We live in an era in which scores are being developed for different clinical scenarios at a rapid pace. However, only a minority of such scores will make their way into our routine clinical practice. In this setting, it seems obvious that simplicity of models and reliability of incorporated measurements may be a common point in widely used clinical prognostic scores [23, 24]. Also, experience seems to show that more complex models, especially when extensive variable selection has been performed, tend to give overoptimistic predictions [25], but complexity may deter clinicians from using them routinely. We believe the ScREEN score offers the best of these characteristics, as it is composed from variables that are universal, easy to obtain, use, and recall in a busy clinical practice. In addition, its prognostic information can easily be remembered using the following "25% rule": score of 0 or 1 corresponds to approximately 25% survival or freedom from heart transplantation at 10 years, in patients with score of 2 or 3, this number rises to 50%, and in patients with higher chances of response, score 4 or 5, survival is almost 75%.

Other risk schemes have been proposed for predicting mortality in CRT patients [26, 27], but so far none has assessed CRT response.

Finally, the existence of the ScREEN score will be of importance when discussing treatment alternatives with patients and relatives. More and more, patients want to know what to expect from a treatment option, and are more frequently requesting to be empowered in decisions regarding their management [28]. In patients meeting guideline criteria, when chances of response are low discussion may involve the choice between a CRT-D or a CRT-P device [29], or considering novel approaches like LV endocardial pacing [10], or multipoint pacing [8] at an early stage if non-responder status if confirmed. Use of auto-optimization algorithms [9], and optimization of medical therapy with novel drugs [11, 12] should be pursued in this group of patients to optimize chances of response and survival in this group. If all of the abovementioned options fail, it is important that these patients, identified at the time of implant and kept under very close surveillance, get promptly referred to a transplant centre before they get too deteriorated, to make sure they do not lose the window of opportunity for a heart transplant. The aforementioned reasons reinforce the role of and usefulness of the ScREEN score at the time of CRT referral or implant. CRT indications are clearly stated in the guidelines [30], and this score should not by any means considered as a way of denying CRT to patients who are less likely to respond.

A word of caution should be added regarding the use of the ScREEN use in cases where leads cannot be advanced to adequate positions. It is likely that the likelihood of response in those cases will be lower than the estimated by the score. Even though our data do not allow us to say the amount of reduction in response rate, we may be able to provide an adjustment factor in the future when we gather a reasonable number of cases which can provide the adequate statistical power for addressing that matter.

Further validation of the ScREEN score using LV volumes and heart failure hospitalizations as endpoints will be pursued by our group in the near future. A prospective

randomized study assigning patients to "CRT-on" vs. "CRT-off" during the initial period after the device implant (e.g. initial 6 months) may the ideal setting for testing the usefulness of CRT across the different strata of the score.

Our investigation has some limitations that should be highlighted. When using all-cause mortality as part of our secondary endpoint, we acknowledge that some CRT patients will have died from non-cardiovascular causes or causes unrelated to lack of CRT response. It was a conscious decision to use this metric, which by definition is binary and not open to interpretation. Furthermore, this endpoint represents a worst case scenario analysis, meaning that if a score is capable of demonstrating its utility with such a hard endpoint (providing an acceptable c-statistic of 0.72). One would speculate it might perform significantly better if it was assessing something more specific like heart failure or cardiovascular mortality, and we think this is worthy of future study. Left bundle branch block status was not present in the derivation cohort (only QRS width was available). For that reason its potential inclusion in the score could not be tested. However, assessment of ScREEN in patients with left bundle branch block and in the minority of patients without left bundle branch block provided similar c-statistic values (Table S-5). Finally, there are multiple definitions of CRT response and there is no consensus regarding which one is the best. Therefore, this score still lacks validation for definitions different from the one we used in this study, namely those using different cut-offs for LVEF, or volume, or haemodynamic parameters.

Conclusion

The ScREEN score (Sex category, Renal function, ECG (QRS width), Ejection fraction and New York Heart Association class) is composed of widely validated, simple, easy to obtain predictors of CRT response and appears predictive for survival and CRT response. The

ScREEN score should be helpful in reinforcing which patients have higher chances of responding to CRT, and facilitating consideration of alternative therapies, before, or early after CRT implant for predicted non-responders. This may have an impact on patient survival and is likely to improve the management of CRT patients.

Figure Legends

Figure 1. Responder rate (% in y axis) according to ScREEN value

Figure 2. Survival free from all-cause mortality and/or heart transplant according to ScREEN score value (3.A) and probability of CRT response (3.B) in the validation cohort.

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Table 1. Baseline sample characteristics.

Variable	DAI-PP Derivation cohort (n=1,301)	Validation cohort (n=1,959)	P
Age	64.5±10.5	67.1±11.9	<0.001
Female Gender	15.8% (206)	27.7% (542)	<0.001
Primary Prevention	100% (1,3013)	91.1% (1,784)	<0.001
CRT-P	0% (0)	42.7% (837)	<0.001
NYHA class	2.7±0.6	2.8±0.6	<0.001
QRS width ≥150ms	52.7% (685)	65.9% (1,291)	<0.001
LBBB morphology	N.A.	79.4% (1,472)	N.A.
Atrial Fibrillation	24.5% (314)	40.9% (789)	<0.001
Ischaemic CM	47.6% (615)	49.6% (948)	0.334
DM	N.A.	26.5% (451)	N.A.
eGFR ≥60ml/min	55.4% (721)	45.5% (892)	<0.001
LVEF (%)	26±6	27±9	<0.001

Legend: DAI-PP - *Défibrillateur Automatique Implantable-Prévention Primaire*; CRT – cardiac resynchronization therapy; NYHA – New York Heart Association Class; CM – cardiomyopathy; DM – diabetes mellitus; eGFR – estimated glomerular filtration rate; LVEF – left ventricular ejection fraction.

Table 2. Independent predictors of CRT response in the DAI-PP cohort.

Predictor	Univariate OR	Univariate 95%CI	Univariate P	Multivariate OR	Multivariate 95%CI	Multivariate P
Age ≥ 72.5	1.30	1.00-1.69	0.049	-	-	-
♀	1.56	1.12-2.18	0.008	2.08	1.26-3.45	0.004
NYHA ≤III	3.39	2.23-5.17	<0.001	2.71	1.63-4.52	<0.001
Ischaemic CM	0.59	0.47-0.74	<0.001	-	-	-
Atrial Fibrillation	0.58	0.45-0.74	<0.001	-	-	-
QRS ≥150ms	1.75	1.37-2.23	<0.001	1.70	1.25-2.30	0.001
LVEF ≥25%	1.31	1.03-1.67	0.028	1.75	1.27-2.41	0.001
eGFR ≥60ml/min	2.05	1.55-2.71	<0.001	2.01	1.48-2.72	<0.001

Legend: CRT – cardiac resynchronization therapy; DAI-PP - *Défibrillateur Automatique Implantable-Prévention Primaire*; OR – odds ratio; CI – confidence interval; NYHA – New York Heart Association Class; CM – cardiomyopathy; eGFR – estimated glomerular filtration rate; LVEF – left ventricular ejection fraction.

Appendix

The following investigators and institutions participated in the conception of the registry, and in the organization, collection, storage, and analysis of the data:

Co-principal Investigators:

Serge Boveda, MD, Clinique Pasteur, Toulouse; Eloi Marijon, MD, PhD, Hopital Europeen Georges Pompidou, Paris, France. Conceived, designed and organized the registry in 2009.

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