International Journal of Cardiology 260 (2018) 82–87

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

# Usefulness of a clinical risk score to predict the response to cardiac resynchronization therapy

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ARTICLE INFO

*Article history:*
Received 9 December 2017
Received in revised form 18 January 2018
Accepted 2 February 2018

*Keywords:*
Responders
Heart failure
Risk stratification
Score
Mortality
DAI-PP

ABSTRACT

*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 1301 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 1959 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, 95% CI 1.26–3.45), NYHA class ≤ III (OR = 2.71, 95% CI 1.63–4.52), left ventricular ejection fraction ≥ 25% (OR = 1.75, 95% CI 1.27–2.41), QRS duration ≥ 150 ms (OR = 1.70, 95% CI 1.25–2.30) and estimated glomerular filtration rate ≥ 60 mL/min (OR = 2.01, 95% CI 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.



*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.

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[1] See Appendix.

https://doi.org/10.1016/j.ijcard.2018.02.012
0167-5273/

## 1. 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.

## 2. Methods

### 2.1. Derivation cohort and derivation of the risk prediction model

Among the participants of the DAI-PP cohort (*Défibrillateur Automatique Implantable-Prévention Primaire*; NCT01992458), 1301 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 (NYHA) functional class, 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).

### 2.2. 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.

### 2.3. 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].

## 3. Results

### 3.1. 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

**Table 1**
Baseline sample characteristics.

| Variable | DAI-PP derivation cohort ($n = 1301$) | Validation cohort ($n = 1959$) | $P$ |
|---|---|---|---|
| Age | 64.5 ± 10.5 | 67.1 ± 11.9 | <0.001 |
| Female gender | 15.8% (206) | 27.7% (542) | <0.001 |
| Primary prevention | 100% (13013) | 91.1% (1784) | <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 ≥ 150 ms | 52.7% (685) | 65.9% (1291) | <0.001 |
| LBBB morphology | N.A. | 79.4% (1472) | N.A. |
| Atrial fibrillation | 24.5% (314) | 40.9% (789) | <0.001 |
| Ischemic CM | 47.6% (615) | 49.6% (948) | 0.334 |
| DM | N.A. | 26.5% (451) | N.A. |
| eGFR ≥ 60 mL/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.