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EAARN score, a predictive score for mortality in patients receiving cardiac resynchronization therapy based on pre-implantation risk factors

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Aims The beneficial effects of CRT in patients with advanced heart failure, wide QRS, and low LVEF have been clearly established. Nevertheless, mortality remains high in some patients. The aims of our study were to identify the predictors of mortality in patients treated with CRT and to design a risk score for mortality.

Methods and results A cohort of 608 consecutive patients treated with CRT from 2000 to 2011 in our centre was prospectively analysed. Baseline clinical and echocardiography variables were analysed and mortality data were collected. During a mean follow-up of 36.2 ± 29.2 months, 174 patients died: 123/174 (71%) due to cardiovascular causes, 25/174 (14%) non-cardiac causes, and 26/174 (15%) unknown aetiology. In a multivariate analysis the predictors of mortality were NYHA class IV [hazard ratio (HR) 2.54, 95% confidence interval (CI) 1.7–3.7, $P < 0.001$], glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 (HR 1.61, 95% CI 1.14–2.30, $P = 0.008$), AF (HR 1.67, 95% CI 1.19–2.3, $P = 0.01$), age ≥70 years (HR 1.44, (95% CI 1.04–2.00, $P = 0.02$), and LVEF <22% (HR 1.83, 95% CI 1.33–2.52, $P \leq 0.001$). The EAARN score (EF, Age, AF, Renal dysfunction, NYHA class IV) summarizes the predictors. Each additional predictor increased the mortality: one predictor, HR 3.28 (95% CI 1.37–7.8, $P = 0.008$); two, HR 5.23 (95% CI 2.24–12.10, $P < 0.001$); three, HR 9.63 (95% CI 4.1–22.60, $P < 0.001$); and four or more, HR 14.38 (95% CI 5.8–35.65, $P < 0.001$).

Conclusion The predictors of mortality have a significant add-on predictive effect on mortality. The EAARN score could be useful to stratify the prognosis of CRT patients.

Keywords Mortality • Age • Atrial fibrillation • Cardiac resynchronization therapy • Glomerular filtration rate • Ejection fraction • NYHA functional class

Introduction

Cardiac resynchronization therapy (CRT) in heart failure patients has been shown to improve both functional capacity and quality of life, and to decrease hospital admissions and mortality.[1] The short-term response to CRT and decreased mortality have been extensively investigated.[1] Previous studies have shown a 3-year mortality of 24.7% in CRT recipients vs. 38.1% in the control population.[2] Mortality in CRT has been associated with several pre-implant risk factors that predict mortality.[3–5] Most of these studies have focused on isolated risk factors and their effect on mortality. The aims of our study were to identify the predictors of mortality in patients treated with CRT and to design a risk score for mortality, considering the add-on effects of the predictors.

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Methods

A cohort of 608 consecutive patients who received a CRT device was prospectively included in the study.

Inclusion criteria

All patients with symptomatic heart failure (NYHA class II–IV) despite optimal drug therapy, LVEF ≤35%, and QRS duration >120 ms were included, as well as patients with LVEF ≤35% with complete atrioventricular block who received a pacemaker or defibrillator and were in functional class II or higher, regardless of QRS duration.

Patients were seen at the outpatient clinic at 6- to 8-month intervals and at any other time they required further evaluation due to a worsened clinical condition.

Patients were classified as having permanent AF if they had experienced permanent AF for at least 3 months and previous attempts to restore sinus rhythm (SR) had failed. No rhythm control interventions were pursued in these patients.

Measures of clinical outcome

All patients underwent a 12-lead ECG, echocardiography, and clinical evaluation prior to implant and at 6 and 12 months follow-up. Heart failure symptoms, functional capacity, and quality of life were assessed by NYHA functional class, the 6 min walk test (6MWT)[7], and the Minnesota Living with Heart Failure test,[6] respectively. Pharmacological treatment was recorded.

The glomerular filtration rate (GFR) was measured according to the MDRD (Modification of Diet in Renal Disease) formula: GFR (mL/min/1.73 m^2) = 175 × (Scr) −1.154 × (Age) − 0.203 × (0.742 if female).

Mortality data were collected by reviewing outpatient clinical history or by phone interviews with relatives. Two cardiologists reviewed the data and assigned, by consensus, the mode of death. Deaths were categorized as cardiac, non-cardiac, or unknown. Cardiac deaths were classified as sudden (not preceded by HF or ischaemic symptoms) or due to HF, according to Epstein *et al.*[8] When the cause of death could not be determined, it was classified as unknown.

Echocardiographic evaluation

Two-dimensional echocardiography was performed with the patient in left lateral decubitus position, using a commercially available system (Vingmed Vivid-7, Milwaukee, WI, USA) equipped with a 3.5-MHz probe. Standard M-mode and two-dimensional images were acquired at a depth of 16 cm and stored in cine-loop format of three consecutive beats. The LV volumes and EF were calculated by Simpson's rule from the two- and four-chamber apical views. The presence of mitral regurgitation was assessed systematically. Colour Doppler echocardiography was performed in all views after optimizing gain and Nyquist limit. The severity of valvular regurgitation was determined on a qualitative scale according to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with valvular heart disease: mild (grade 1), moderate (grade 2), and severe (grades 3–4).[9]

Device implantation and programming

Right ventricular (RV) leads were positioned at the RV apex in most of the procedures. Conventional atrial leads were used only in patients in SR or paroxysmal AF. The LV electrode was inserted through the coronary sinus into a lateral vein whenever possible. If the LV lead could not be satisfactorily positioned, it was implanted epicardially.

Patients in SR, minimum heart rate 50 b.p.m., were programmed in DDD mode or DDDR in the case of sick sinus syndrome. Patients with AF were programmed in VVIR mode at 70–75 b.p.m., with maximum heart rate set at 85% of the maximum theoretical heart rate. In the AF group, the algorithm trigger by RV sense was programmed on, according to the physician's criteria. Atrioventricular node ablation was performed when the ventricular pacing was <85%.

Statistical analysis

Continuous variables are presented as the mean value ± standard deviation (SD). Categorical variables were expressed as total number and percentages. Event-free survival was evaluated with the Kaplan–Meier method. The effect of different variables on survival was investigated using the Cox proportional hazards model. Variables that showed a statistically significant effect on survival in univariate analyses were entered in a multivariate Cox proportional hazards model, using a backward stepwise selection to obtain the final model. At each step, the least significant variable was discarded from the model until all variables in the model reached a *P*-value <0.10. The number of variables that could enter the multivariate model was limited using the $P < m/10$ rule to prevent overfitting the model. The Cox proportional hazards model assumptions were validated in the final model. All significance testing was two-tailed, and a *P*-value <0.05 was considered statistically significant. Analysis was performed using R software for Windows version 2.15.0 (R project for statistical computing; Vienna, Austria).

An internal validation of our predictive model was made by bootstrap analysis of 1000 samples.[10] In the bootstrap procedure, repeated samples of the same number of observations as the original database were randomly selected with replacement from the original set of observations. For each sample, the hazard ratio (HR) for the EAARN score was calculated.

Results

A total of 608 patients were included in the study. The baseline characteristics of the patients are summarized in *Table 1*.

Overall mortality

Eight patients (1.3%) were lost to follow-up and excluded from analysis due to the impossibility of checking their vital status. During a mean follow-up of 36 ± 29 months, 174 patients died (28%). Of these deaths, 123/174 (71%) were due to cardiac and 25/174 (14%) to non-cardiac causes; in 26/174 patients (15%) the aetiology of the death could not be determined and was classified as unknown.

Of the 123 cardiac deaths, 109 (88.6%) were end-stage of heart failure and 14 (11.4%) were sudden cardiac death.

Of the deaths from all causes, 34% (59/174) occurred during the first 12 months, increasing to 48% (84/174) at 24 months following CRT implantation.

Cumulative mortality was 10% [95% confidence interval (CI) 9–13]; 16% (95% CI 13–19), and 37% (95% CI 50–62) at 1, 2, and 5 years.

Table 1 Baseline patient characteristics ($n = 600$)

Age (years)	66.9 ± 9.8
Sex (male)	468 (77%)
Ischaemic aetiology	253 (42%)
QRS duration (ms)	167.8 ± 32.1
Atrial fibrillation	155 (25%)
Complete A-V block	90 (15%)
CRT-D	404 (68%)
NYHA functional class	
II	135 (23%)
III	406 (67%)
IV	59 (10%)
6MWT (m)	269.6 ± 141.4
Minnesota test (points)	45.6 ± 23.3
GFR (mL/min/1.73 m^2)	63.5 ± 25.1
LVEDV (mL)	236.8 ± 85.0
LVESV (mL)	177.5 ± 73.9
LVEF (%)	24.8 ± 6.6
MR, severe	126 (21%)
Beta-blockers	420 (69%)
ACE inhibitors/ARB	438 (72%)
Spironolactone	286 (47%)
Furosemide	511 (84%)

A-V, atrioventricular; CRT-D, cardiac resynchronization therapy-defibrillator; GFR, glomerular filtration rate; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; 6MWT, 6 min walk test.

Among patients in AF, the percentages of ventricular pacing were 97 ± 4% in the patients with atrioventricular junction ablation and 94 ± 5% in patients without atrioventricular junction ablation ($P = 0.48$).

Predictors of all-cause mortality

Predictors of mortality are listed in *Table 2*. Significant univariate predictors were age, NYHA class IV, AF, renal dysfunction, ischaemic cardiomyopathy, LVEF, severe mitral regurgitation, and type of CRT device. After adjusting for these variables in a Cox regression model, the independent predictors of mortality were baseline NYHA functional class IV (HR 2.54, 95% CI 1.7–3.7, $P < 0.001$), GFR <60 mL/min/1.73 m^2 (HR 1.61, 95% CI 1.14–2.30, $P = 0.008$); AF (HR 1.67, 95% CI 1.19–2.3, $P = 0.01$); age >70 years (HR 1.44, 95% CI 1.04–2.00, $P = 0.02$); and LVEF <22 (HR 1.83, 95% CI 1.33–2.52, $P < 0.001$).

EAARN score

Based on data obtained in our multivariate analysis, a predictive score was designed to represent an add-on predictive score for overall mortality. EAARN is the acronym for EF < 22%, AF, Age ≥70 years, Renal function (GFR <60 mL/min/1.73 m^2), and baseline NYHA class IV (*Figure 1*). In the cohort of 608 patients, 142 (23.3%) had no risk factors, 210 (34.5%) had 1 risk factor, 149 (24.5%) had 2 risk factors, 77 (12.6%) had 3 risk factors, and 30 (5%) had ≥4 risk factors.

Overall mortality increased with the accumulation of risk factors (*Figure 2*). Each additional predictor significantly increased the risk of mortality: 1 predictor, HR 3.28 (95% CI 1.37–7.83, $P < 0.01$); 2 predictors, HR 5.23 (95% CI 2.25–12.17, $P < 0.001$); 3 predictors, HR 9.63 (95% CI 4.10–22.60), $P < 0.001$]; and ≥4 predictors, HR 14.38 (95% CI 5.80–35.66, $P < 0.001$). Bootstrap HR estimation confirmed the internal validity of this analysis: 1 predictor, HR 3.28 [95% CI 3.22 (1.54–10.62)]; 2 predictors, HR 5.23 [95% CI 5.01 (2.61–16.66), $P < 0.001$]; 3 predictors, HR 9.63 [95% CI 10.28 (4.67–33.25), $P < 0.001$); and ≥4 predictors, HR 14.38 (95% CI 6.83–48.67, $P < 0.001$).

Overall mortality was 21.4 per 100 person-year in the subgroup of patients with an EAARN score ≥3, compared with 7 per 100 person-year in the EAARN score 0–1 group (HR 4.04, 95% CI 2.9–6.5, $P < 0.001$).

In comparison with the EAARN ≤1 group, patients with an EAARN score ≥3 were older, had a higher prevalence of AF, a worse renal function, a poorer functional capacity, and a lower LVEF. In addition, the EAARN score ≥3 patients had wider QRS but low percentage of LBBB morphology, and were less likely to receive a CRT-D (*Table 3*).

Discussion

The present study evaluates the long-term clinical outcomes and predictors of mortality in a large cohort of consecutive patients treated with CRT. Moreover, a risk score was designed to stratify the prognosis of these patients according to the addition of risk factors.

Our series also included patients with relatively narrow QRS, mild heart failure, and complete atrioventricular block requiring CRT or a CRT upgrade. Nevertheless, the percentages of these patients were similar to published results from a large European multicentre registry.[11]

Cumulative mortality at the end of follow-up (mean of 36 ± 29 months) was 29%. One-year and 2-year mortality were similar to those reported in other CRT studies.[2,5] Worsening heart failure was the main cause of death during follow-up.

Predictors of mortality

Renal dysfunction

Most of the patients with chronic heart failure had mild or moderate renal dysfunction. Impairment of renal function was directly correlated with the prognosis of these patients.[12] Stage 3 renal failure (GFR <60 mL/min/1.73 m^2)[13] was associated with a significant increase in mortality. Results were in accordance with previously published registries.[3,5,12,14] High creatinine levels were also predictive of poor outcomes in patients with mild heart failure treated with CRT.[15]

Atrial fibrillation

The poor prognosis in patients with advanced heart failure and AF has been described in large studies.[16–18] Although many studies describe the positive effects of CRT in patients with AF,[19–21] it

Table 2 Predictors of all-cause mortality risk, uni- and multivariate Cox proportional hazards models

	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age ≥ 70 years	1.58 (1.17–2.15)	<0.01	1.44 (1.04–2.00)	<0.02
Sex (male)	1.36 (0.93–1.98)	0.114		
Ischaemic aetiology	1.38 (1.01–1.84)	0.039		
LBBB morphology	0.96 (0.70–1.32)	0.799		
GFR ≥60 mL/min/1.73 m^2	2.12 (1.52–2.97)	<0.001	1.69 (1.20–2.35)	0.013
Atrial fibrillation	1.99 (1.45–2.74)	<0.001	1.68 (1.20–2.35)	<0.001
QRS duration (per 10 ms increase)	0.95 (0.90–1.01)	0.065		
NYHA functional class IV	3.42 (2.36–4.95)	<0.001	2.42 (1.62–3.60)	<0.001
6MWT (m) (per 50 m increase)	0.93 (0.89–0.99)	0.013		
QoL (per 10 points increase)	1.15 (1.09–1.20)	<0.001		
LVEF <22%	1.94 (1.42–2.64)	<0.001	1.83 (1.33–2.52)	<0.001
LVEDV (per 10 mL increase)	1.01 (0.99–1.03)	0.181		
LVESV (per 10 mL increase)	1.02 (0.99–1.04)	0.083		
MR, severe	1.67 (1.06–2.63)	0.028		
Type of device (CRT-P)	1.71 (1.27–2.29)	<0.001		

CRT-P, cardiac resynchronization therapy-pacemaker; GFR, glomerular filtration rate; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; 6MWT, 6 min walk test; QoL, quality of life test.

should be highlighted that mortality remains high in these patients despite the benefits of the therapy.[3,19–21]

New York Heart Association functional class IV

A worse NYHA functional class was associated with poorer survival.[3,4,22,23] Although it seems that CRT and CRT-D significantly improve the combined endpoint of time to all-cause mortality and hospitalizations in NYHA class IV patients, improvement in mortality reduction has not been clearly established in these patients.[14,22]. From 8% to 12% of patients who received a CRT device were in ambulatory NYHA class IV.[4] As in previous published studies,[3,4,22,23] our study demonstrated the poor prognosis and high mortality in this subgroup of patients. This supports the need to start therapy at early stages of the disease, avoiding as much as possible the implant of devices in this advanced stage of heart failure.

Baseline left ventricular ejection fraction

This finding is supported by the largest multicentre studies.[14,24] The guidelines state clearly that patients with LVEF ≤35% will benefit from CRT,[2] but we also should be aware that patients with very low LVEF at implantation have an increased all-cause and cardiovascular mortality.

Age

Age was associated with increased mortality in our population. In contrast, other studies have not reported higher mortality in elderly patients.[2,3] The long follow-up of our series may explain the high mortality of elderly patients despite the benefits of the therapy. Older people have many more co-morbidities, which worsen the long-term survival outcomes.

EAARN score

Previous reports[2,3,14,25,26] have described the various predictors of mortality in patients treated with CRT. This study evaluated the add-on effects of these factors and designed a simple prognostic risk score to assess the prognosis of these patients.

It is common that CRT candidates had several predictors of mortality. In fact, in our series >50% had at least 2 predictors and ~20% of the patients had ≥3 predictors. Each addition of a risk factor, from one to four or more, significantly increased mortality, by 3, 5, 9, and 14 times, respectively.

Most of the variables included in our score were defined at the MADIT-II long-term risk score in patients with primary prevention implantable cardioverter defibrillators (ICDs).[27] Our results demonstrated that despite the effects of CRT, the long-term mortality remained high in patients with a high risk score.

The Seattle Heart Failure Model (SHFM) is a multifactor risk assessment score for patients with heart failure, which has been validated in several cohorts derived both from randomized controlled trials and from outpatient community practice settings in the USA and Europe.[28] A recent study has described modest success using the SHFM to predict outcomes of a 'real-life' CRT patient cohort; the mortality risk in a specific population of patients with heart failure treated with CRT was underestimated.[29] In contrast to the SHFM, our score is based on different predictors of mortality identified in the specific group of patients with HF treated with CRT. Our score allowed simple stratification of CRT patients, and identified patients with poor prognosis and high mortality as well as patients with an excellent prognosis and long-term survival.

Current guidelines recommend CRT implantation in a broad spectrum of patients with advanced heart failure, systolic dysfunction, and wide QRS duration. However, the benefits of CRT are

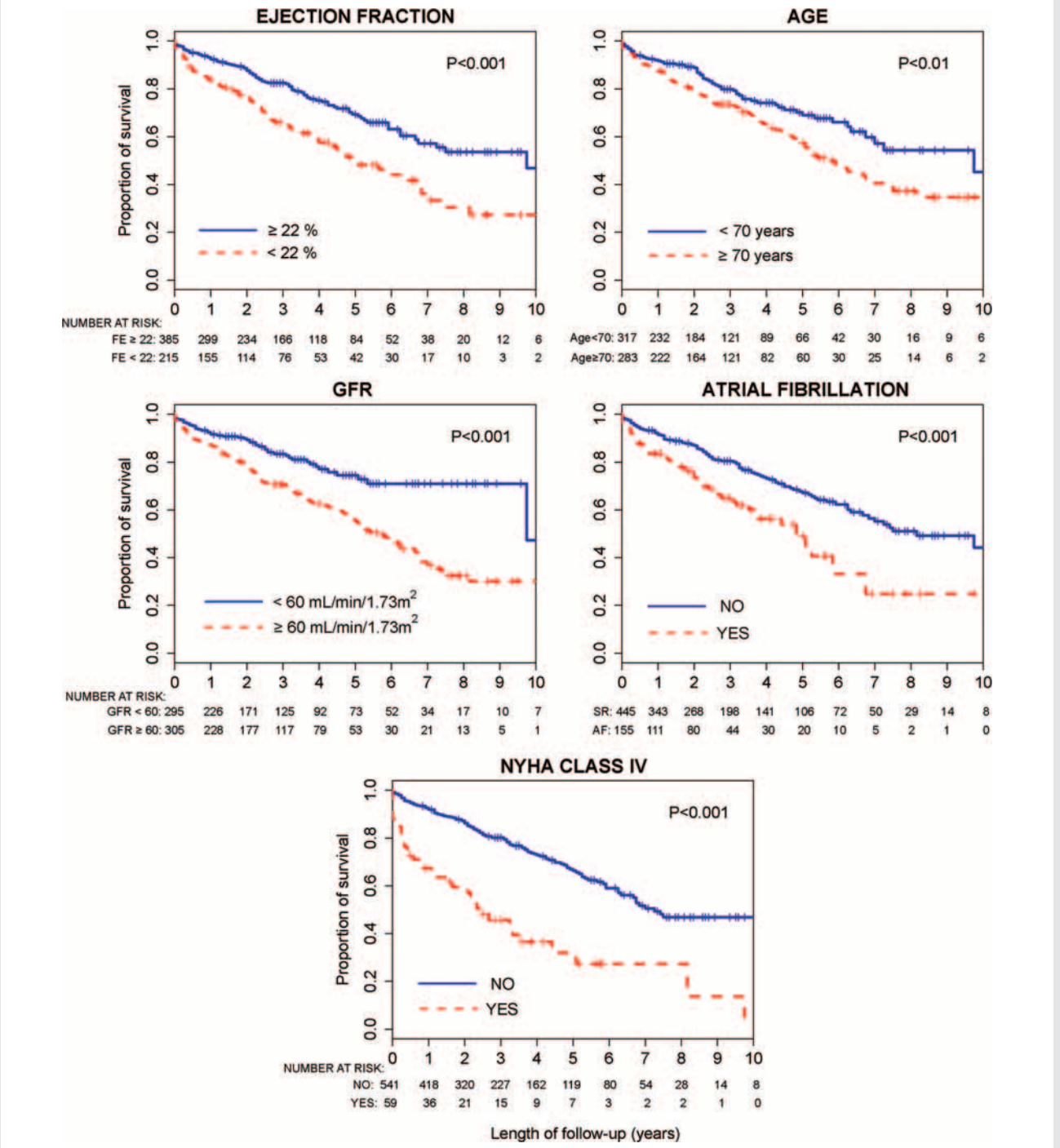

Figure 1 Kaplan–Meier survival curves for time to all-cause mortality for each EAARN risk factor. GFR, glomerular filtration rate.

not uniform, and about one-third of CRT-treated patients receive no benefit from the therapy and have poor outcomes. A more appropriate selection of patients for treatment with CRT is possible and needed. Improved patient selection may improve the cost-effectiveness of this treatment.

EAARN scores identified a subgroup of patients with excellent prognosis and low mortality (EAARN 0–1) and a subgroup of patients with high mortality and poor prognosis (EAARN ≥3). The high mortality observed in these patients suggests only a small benefit from CRT. Patients with ≥3 risk factors may possibly have reached a point of no return, and CRT came too late to reverse such an advanced phase. Nevertheless, any potential and transient beneficial effect that may have occurred cannot be derived from the score.

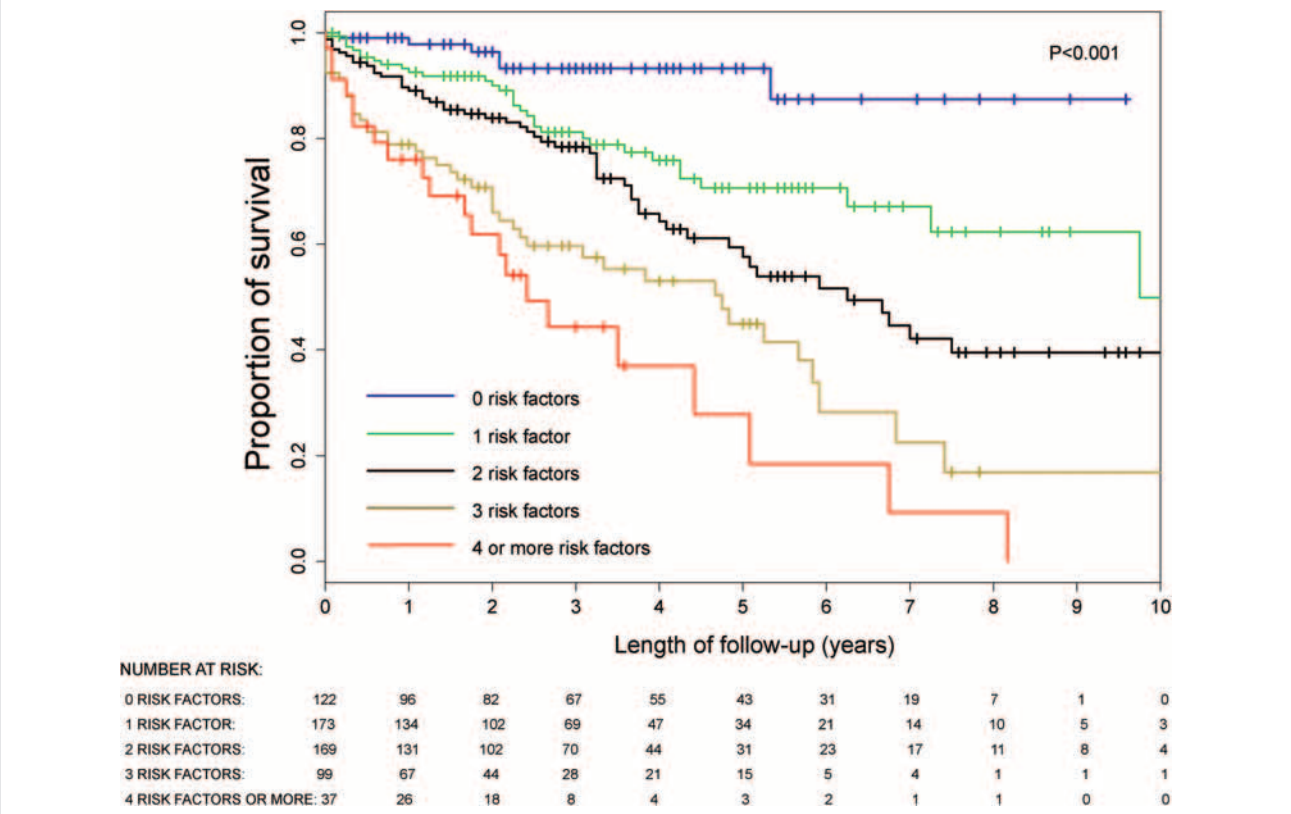

Figure 2 Survival based on number of risk factors before cadiac resynchronization therapy device implantation.

In our view, an EAARN score ≥3 should not be an absolute contraindication, because the score does not include symptomatic benefits of CRT. It may, however, help physicians to individualize CRT therapy. Furthermore, it highlights the need to start the therapy at the earliest stages of disease, avoiding if possible the implant of CRT devices in patients with very advanced heart disease and systemic involvement

Although CRT is a costly technology, in view of these results it should not considered a therapy of last resort. On the other hand, once the advanced stage of heart failure is reached, with a very high expected mortality, careful risk–benefit and cost-effectiveness analyses are indicated.

Limitations

This is an observational single-centre study with a limited number of patients. Although the EAARN score was internally validated by bootstrap analysis,[10] larger and multicentre studies are needed to validate the generalized use of this score in patients treated with CRT.

Our population was not homogeneous and included patients who received CRT-D and CRT-P devices. The percentage of CRT-D implants was lower in patients with an EAARN score ≥3 compared with an EAARN score ≤1, which may have influenced mortality. Nevertheless, most deaths were due to progressive heart failure and not to sudden death, suggesting that a defibrillator

Table 3 Comparison of EAARN score 0–1 vs. 3–5

	0–1 risk factors (*n* = 295)	3–5 risk factors (*n* = 136)	*P*-value
Age (years)	62 ± 10	72 ± 7	<0.001
Sex (male)	62 (21%)	29 (21%)	0.71
Ischaemic	124 (42%)	63 (46%)	0.68
QRS (ms)	166 ± 30	175 ± 31	0.02
LBBB	198 (67%)	73 (54%)	0.01
AF	25 (8%)	86 (63%)	<0.001
CRT-D	230 (78%)	61 (45%)	<0.001
NYHA class			<0.001
II	89 (30%)	11 (8%)	
III	200 (68%)	79 (58%)	
IV	6 (2%)	46 (34%)	
6 MWT (m)	310 ± 138	188 ± 133	<0.001
QoL test (points)	43 ± 21	54 ± 29	<0.001
GFR	78.1 ± 23.7	46.2 ± 16.2	<0.001
LVEDV	238 ± 83	244 ± 89	0.42
LVESV	175 ± 70	191 ± 79	0.12
LVEF (%)	27 ± 6	21 ± 6	<0.001

CRT-D, cardiac resynchronization therapy-defibrillator; GFR, glomerular filtration rate; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; 6MWT, 6 min walk test; QoL, quality of life test.

had little impact in the population with a high prevalence of co-morbidities.[27]

The number of hospitalizations during follow-up was not recorded prospectively in the study cohort, making it impossible to detect any reduction in hospital admissions. Therefore, the EAARN score estimates the probability of death of a patient treated with CRT, but is not useful to predict symptomatic response based on parameters such as hospital admissions.

The study design may have precluded a precise determination of the aetiology of death in some cases. Nevertheless, because the EAARN score was based on overall mortality, the specific cause of death did not affect the score.

Conclusions

The predictors of mortality have a significant add-on predictive effect on mortality. The EAARN score could be useful to stratify the prognosis of CRT patients.

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Conflict of interest: L.M. is currently consultant to St Jude, Boston, Medtronic, Biotronik, and Sorin, and is a member of advisory boards to Sanofi, Merck, and St Jude Medical. J.T. is currently conducting research sponsored by Medtronic, St Jude, and Biotronik, and is a member of the European Advisory Board for Medtronic. All other authors have no conflicts to declare.

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