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Cardiac resynchronization therapy-defibrillator improves long-term survival compared with cardiac resynchronization therapy-pacemaker in patients with a class IA indication for cardiac resynchronization therapy: data from the Contak Italian Registry

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Aims In candidates for cardiac resynchronization therapy (CRT), the choice between pacemaker (CRT-P) and defibrillator (CRT-D) implantation is still debated. We compared the long-term prognosis of patients who received CRT-D or CRT-P according to class IA recommendations of the European Society of Cardiology (ESC) and who were enrolled in a multicentre prospective registry.

Methods and results A total of 620 heart failure patients underwent successful implantation of a CRT device and were enrolled in the Contak Italian Registry. This analysis included 266 patients who received a CRT-D and 108 who received a CRT-P according to class IA ESC indications. Their survival status was verified after a median follow-up of 55 months. During follow-up, 73 CRT-D and 44 CRT-P patients died (rate 6.6 vs. 10.4%/year; log-rank test, $P = 0.020$). Patients receiving CRT-P were predominantly older, female, had no history of life-threatening ventricular arrhythmias, and more frequently presented non-ischaemic aetiology of heart failure, longer QRS durations, and worse renal function. However, the only independent predictor of death from any cause was the use of CRT-P (hazard ratio, 1.97; 95% confidence interval, 1.21–3.16; $P = 0.007$).

Conclusion The implantation of CRT-D, rather than CRT-P, may be preferable in patients presenting with current class IA ESC indications for CRT. Indeed, CRT-D resulted in greater long-term survival and was independently associated with a better prognosis.

Keywords Cardiac resynchronization therapy • ICD • Pacemaker • Heart Failure • Mortality

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What's new?

- In patients presenting with current class IA European Society of Cardiology indication for cardiac resynchronization therapy (CRT), long-term survival is better in CRT-defibrillator (CRT-D) patients than in CRT-pacemaker patients.
- In current clinical practice CRT-D patients are younger and more frequently present ischaemic heart disease.
- The lack of defibrillator capability represents an independent predictor of mortality.

Introduction

Cardiac resynchronization therapy (CRT), alone (CRT-P) or in combination with an implantable cardioverter defibrillator (CRT-D), effectively reduces morbidity and mortality in advanced heart failure (HF).[1–3] The choice between CRT-P and CRT-D is still debated,[4,5] although the latter appears to be preferred, given the potentially greater survival benefit associated with the defibrillator capability.[6,7] Indeed, patients with an indication for CRT often have a concomitant indication for defibrillator implantation for the primary prevention of sudden cardiac death.[8] In current medical practice, CRT-D account for about 73% of all CRT devices implanted in Europe,[9] and more than 85% in the USA.[10] Cardiac resynchronization therapy-defibrillator is preferentially recommended for less symptomatic patients, i.e. New York Heart Association (NYHA) class II, mainly because most patients included in randomized trials have received this type of device,[11,12] and in general for patients with a reasonable expectation of survival or with an indication for a defibrillator for secondary prevention.[13]

As no randomized clinical trials have specifically compared the long-term outcome of patients on CRT-D with that of those on CRT-P, only observational studies and registries collecting long-term data on CRT patients in current clinical practice can provide a valuable insight into the outcome of therapy and support the treating physician in the final choice of the device. In this perspective, we evaluated the long-term survival of CRT patients enrolled in a multicentre Italian registry. Specifically, we analysed patients in whom CRT-D or CRT-P were implanted in accordance with the class IA indication of current (2010) European Society of Cardiology (ESC) guidelines[13] – i.e. recommended to reduce mortality and prevent disease progression.

Methods

The Contak Italian Registry is a multicentre registry which enrolled all consecutive adult HF patients in whom CRT-P or CRT-D implantation (models Contak Renewal TR/TR 2, Renewal 2/4; Boston Scientific Inc.) had been attempted from 2004 to 2007 at the participating centres. Patients with recent myocardial infarction (<3 months) or with decompensated HF were excluded. The study was approved by the Local Ethics Committees and informed consent was obtained from all patients.

Devices and pacing leads were implanted by means of standard techniques. Baseline evaluation included demographics and medical history, clinical examination, 12-lead electrocardiogram, estimation of NYHA functional class, and echocardiographic evaluation. Specifically, the following parameters were recorded: left ventricular (LV) end-diastolic and end-systolic volumes , LV end-diastolic and end-systolic diameters, and ejection fraction (LVEF), assessed by means of Simpson's equation. The severity of mitral regurgitation was measured by means of colour Doppler in the apical four-chamber view, and classified as mild, moderate, and severe. To optimize haemodynamic function, echo-directed adjustment of the atrio-ventricular pacing interval was performed before patients were discharged and during follow-up, when necessary. Pharmacological treatment was based on clinical evaluation by the attending physicians. During follow-up, patients returned for regular clinical visits according to the standard practice of each study centre.

To investigate the long-term survival of patients presenting with current class IA recommendation for CRT-D or CRT-P,[13] we included, in the analysis, only patients with mild or severe symptomatic chronic HF (NYHA class II–IV) despite pharmacological therapy, LVEF $\leq$ 35%, sinus rhythm, and a wide QRS complex ($\geq$120 ms in NYHA III–IV patients, $\geq$150 ms in NYHA II) on baseline evaluation. Survival status was verified in January 2011. Mortality data were obtained by means of hospital file review or direct telephone contact.

Statistical analysis

Continuous data were expressed as mean $\pm$ standard deviation. Categorical data were expressed as percentages. Differences between mean data were compared by means of a *t*-test for Gaussian variables, and by the Mann–Whitney non-parametric test for non-Gaussian variables. Differences in proportions were compared by means of χ^2 analysis or Fisher's exact test, as appropriate. Mortality rates were summarized by constructing Kaplan–Meier curves, and the distributions of the groups were compared by means of a log-rank test. Cox regression was used to analyse possible predictors of death. All variables associated to a *P* value of <0.20 on univariate analysis were entered into the multivariate regression analysis. A *P* value of <0.05 was considered significant for all tests. All statistical analyses were performed by means of SPSS software (SPSS Inc.).

Results

Study population

From 2004 to 2007, a total of 658 consecutive HF patients with an indication for CRT were scheduled for CRT-P or CRT-D implantation, and were enrolled in the present registry. Implantation was successful in 620 (94%) patients. The reasons for implantation failure were inability to position the coronary sinus lead ($n = 26$) and lack of satisfactory pacing parameters ($n = 12$). Twelve patients were excluded from the analysis owing to permanent loss of CRT within 2 months of implantation. The causes of CRT interruption were dislodgement of the LV lead in eight patients

and phrenic nerve stimulation that could not be corrected by means of device reprogramming in four patients. In the early post-operative period, nine additional patients underwent system revision following lead dislodgement; as effective cardiac resynchronization was successfully restored, they were included in the present analysis. Of the remaining 608 patients, 223 (37%) did not meet the current class IA ESC recommendation for CRT-D or CRT-P. In detail, 104 patients were in atrial fibrillation at the time of implantation (class of recommendation IIa, level of evidence B or C), and 119 had concomitant class I pacemaker indication (class of recommendation I or II, level of evidence B or C). Moreover, 11 patients were excluded from the analysis because they were lost to follow-up and their survival status could not be verified. Therefore, a total of 374 patients were available for the present analysis, of whom 266 received a CRT-D and 108 a CRT-P device. *Table 1* shows baseline clinical variables, echocardiographic parameters, and pharmacological treatment, stratified according to the type of device implanted.

Table 1 Demographics, baseline clinical parameters, and pharmacological treatment of the study population

Parameter	ALL ($n = 374$)	CRT-D ($n = 266$)	CRT-P ($n = 108$)	*P* value
Male gender, *n* (%)	298 (80)	225 (85)	73 (68)	<0.001
Age, years	69 ± 10	67 ± 9	74 ± 9	<0.001
Ischaemic aetiology, *n* (%)	209 (56)	165 (62)	44 (41)	<0.001
NYHA				0.595
Class II	89 (24)	67 (25)	22 (20)	
Class III	231 (62)	162 (61)	69 (64)	
Class IV	54 (14)	37 (14)	17 (16)	
QRS duration, (ms)	168 ± 31	165 ± 32	175 ± 29	0.008
Secondary prevention, *n* (%)	59 (16)	59 (22)	0 (0)	<0.001
Myocardial infarction, *n* (%)	182 (49)	146 (55)	36 (33)	<0.001
Previous CABG, *n* (%)	72 (19)	59 (22)	13 (12)	0.024
Previous angioplasty, *n* (%)	87 (23)	77 (29)	10 (9)	<0.001
Previous valve surgery, *n* (%)	22 (6)	17 (6)	5 (5)	0.512
Hypertension, *n* (%)	182 (49)	128 (48)	54 (50)	0.742
Diabetes, *n* (%)	113 (30)	80 (30)	33 (31)	0.927
Creatinine, (mg/dL)	1.41 ± 0.80	1.39 ± 0.78	1.47 ± 0.82	0.564
Glomerular filtration rate, (mL/min/1.73 m^2)	58 ± 22	60 ± 23	52 ± 21	<0.001
LV lead in cardiac vein:				0.296
Anterior, *n* (%)	22 (6)	13 (5)	9 (8)	
Antero-lateral, *n* (%)	60 (16)	45 (17)	15 (14)	
Posterior, *n* (%)	18 (5)	16 (6)	2 (2)	
Postero-lateral, *n* (%)	75 (20)	53 (20)	22 (20)	
Lateral, *n* (%)	199 (53)	139 (52)	60 (55)	
LV ejection fraction, (%)	27 ± 5	27 ± 5	27 ± 5	0.473
LVEDV, (mL)	218 ± 74	226 ± 75	199 ± 66	0.008
LVESV, (mL)	160 ± 61	168 ± 62	141 ± 54	0.002
LVEDD, (mm)	69 ± 10	70 ± 10	68 ± 10	0.327
LVESD, (mm)	58 ± 10	59 ± 10	57 ± 11	0.135
Severe mitral regurgitation, *n* (%)	63 (17)	48 (18)	15 (14)	0.330
β-Blocker use, *n* (%)	275 (74)	199 (75)	76 (70)	0.378
ACE-inhibitor use, *n* (%)	268 (72)	203 (76)	65 (60)	0.002
Angiotensin-receptor blocker use, *n* (%)	52 (14)	32 (12)	20 (19)	0.100
Aldosterone antagonist use, *n* (%)	100 (27)	77 (29)	23 (21)	0.130
Diuretic use, *n* (%)	277 (74)	201 (76)	76 (70)	0.299
Class III antiarrhythmic use, *n* (%)	74 (20)	61 (23)	13 (12)	0.017
Digoxin use, *n* (%)	72 (19)	45 (17)	27 (25)	0.072
Nitrate use, *n* (%)	80 (21)	64 (24)	16 (15)	0.048
Anticoagulant use, *n* (%)	135 (36)	98 (37)	37 (34)	0.637

NYHA, New York Heart Association; CABG, coronary artery bypass grafting; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; ACE, angiotensin-converting enzyme.

In the CRT-P group, the prevalence of male gender and ischaemic aetiology was lower than in the CRT-D group. Similarly, CRT-P patients were significantly older and presented a longer QRS duration and lower values of estimated glomerular filtration rate (eGFR). No patients in the CRT-P group presented indications for a defibrillator for secondary prevention of sudden cardiac death. The two groups differed in the use of angiotensin-converting enzyme inhibitors, class III antiarrhythmic drugs and nitrates, which was higher among patients with CRT-D. The remaining characteristics were comparable between groups, as were the sites of LV lead position and the use of other pharmacological therapies.

Long-term survival

The median (25th to 75th percentile) follow-up was 55 (41–64) months in the CRT-D group and 53 (27–67) months in the CRT-P group ($P = 0.342$).

During follow-up, 73 of the 266 CRT-D patients and 44 of the 108 CRT-P patients died (rates: 6.6 and 10.4/100 patient-years, respectively). Cardiac resynchronization therapy-defibrillator was associated with substantially lower mortality. *Figure 1* shows the survival curves for all-cause mortality obtained by means of Kaplan–Meier analysis (log-rank test, $P = 0.020$).

As compared with CRT-P, the addition of defibrillator capability resulted in hazard ratios for survival according to baseline characteristics that were consistently above 1.0, except for the subgroup of male patients (*Figure 2*). Cardiac resynchronization therapy-defibrillator therapy was associated with a greater benefit in women (hazard ratio, 2.63; 95% confidence interval, 1.46–4.74; $P = 0.001$) than in men (hazard ratio, 0.78; 95% confidence interval, 0.55–1.13; $P = 0.191$).

Among the factors included in the univariate and multivariate analyses (*Table 2*), the only independent predictor of mortality was the lack of defibrillator capability, i.e. the use of a CRT-P device (hazard ratio, 1.97; 95% confidence interval, 1.21–3.16; $P = 0.007$), while only a non-significant association was detected with regard to the ischaemic aetiology of HF.

Finally, when the analysis was limited to the CRT-D group, no independent predictors of overall mortality emerged from among the baseline clinical variables investigated. The only factor independently associated with a worse prognosis was the positioning of the LV lead in the anterior or in the posterior cardiac vein (hazard ratio, 2.24; 95% confidence interval, 1.13–4.41; $P = 0.021$; *Table 3*).

Discussion

Our analysis of a multicentre registry showed that in HF patients presenting with current class IA ESC indication for CRT, long-term survival was better in CRT-D patients than in CRT-P patients. Cardiac resynchronization therapy-defibrillator and CRT-P patients presented several differences in baseline characteristics. Nonetheless, CRT-D was associated to substantially lower mortality on both univariate and multivariate analyses.

According to the current ESC guidelines, CRT-P and CRT-D are recommended to reduce morbidity and mortality in NYHA class II–IV HF patients. However, the choice of adding a defibrillator is left to the treating physician, who is mainly called upon to consider the patient's expectation of survival.

In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial,[3] which enrolled both CRT-D and CRT-P patients, only CRT-D was associated with significantly

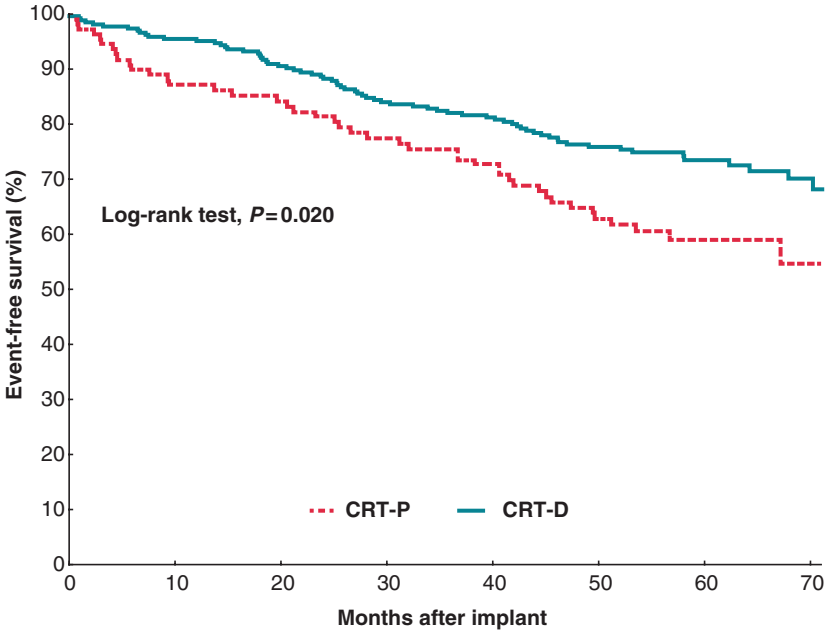

Figure 1 Kaplan–Meier estimates of time to death from any cause, stratified by device type.

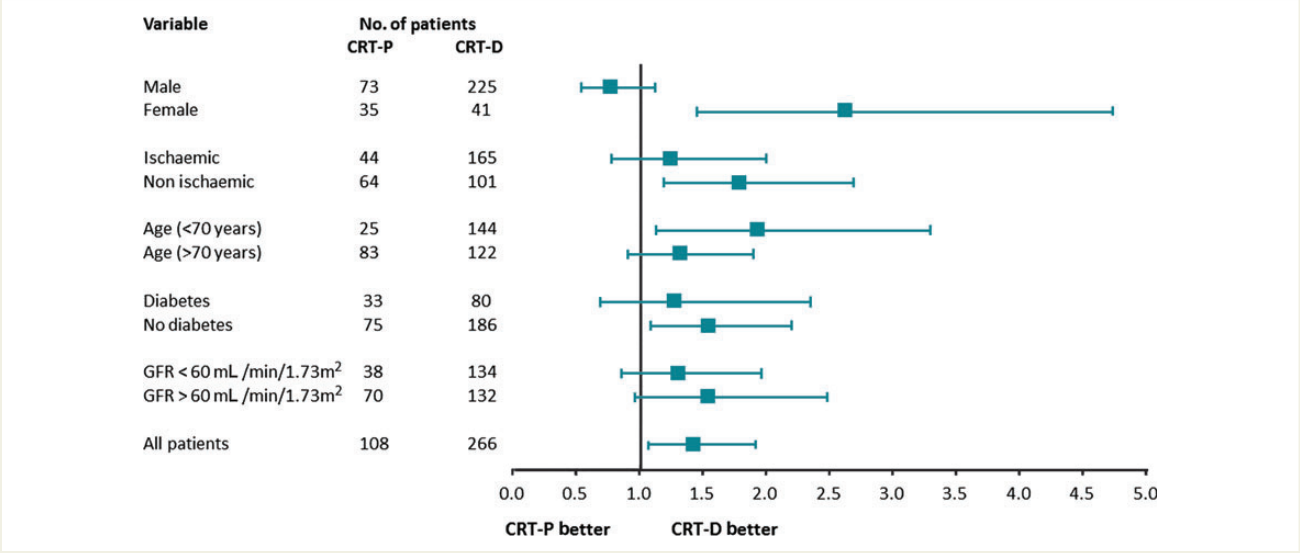

Figure 2 Hazard ratios for survival from all-cause death, according to selected clinical characteristics.

Table 2 Univariate and multivariate analyses of factors predicting all-cause mortality in the study population

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Male gender	1.57	0.96–2.57	0.076	1.74	0.94–3.21	0.078
Age (>70 years)	1.29	0.89–1.87	0.178	0.76	0.47–1.24	0.274
Ischaemic aetiology	1.57	1.07–2.30	0.021	1.59	0.99–2.55	0.051
QRS duration (>160 ms)	0.99	0.69–1.42	0.961	–	–	–
NYHA class III/IV	1.30	0.83–2.03	0.254	–	–	–
LV ejection fraction (<25%)	1.06	0.73–1.54	0.746	–	–	–
Hypertension	0.91	0.62–1.33	0.619	–	–	–
Diabetes	1.42	0.96–2.11	0.080	1.38	0.88–2.17	0.156
Glomerular filtration rate (<60 mL/min/1.73 m^2)	1.45	0.98–2.15	0.066	1.45	0.91–2.32	0.123
CRT-P use	1.57	1.08–2.27	0.019	1.97	1.21–3.16	0.007
LV lead in anterior or posterior cardiac vein	1.71	0.97–2.99	0.064	1.60	0.86–2.95	0.137
β-Blocker use	0.76	0.55–1.06	0.116	0.67	0.40–1.11	0.121
ACE-inhibitor use	1.01	0.72–1.42	0.960	–	–	–
Angiotensin-receptor blocker use	0.89	0.54–1.48	0.658	–	–	–
Aldosterone antagonist use	1.17	0.81–1.58	0.406	–	–	–
Diuretic use	0.97	0.69–1.36	0.855	–	–	–
Class III antiarrhythmic use	0.69	0.42–1.15	0.144	0.78	0.42–1.45	0.439
Digoxin use	1.41	0.95–2.1	0.110	1.63	0.90–2.93	0.107
Nitrate use	1.35	0.89–1.99	0.172	1.03	0.58–1.81	0.932
Anticoagulant use	1.04	0.73–1.48	0.823	–	–	–

CI, confidence interval; HR, hazard ratio; LV, left ventricular.

lower overall mortality in comparison with controls. However, there was no planned head-to-head comparison in the study protocol between the two device arms. In a *post hoc* analysis,[14] CRT-D was seen to reduce the risk of sudden death to a greater extent than CRT-P in the medium term. However, it failed to show a significant incremental survival benefit. Therefore, currently there is no evidence from randomized controlled trials that adding a defibrillator to CRT improves total mortality.

Table 3 Univariate and multivariate analyses of factors predicting all-cause mortality in the CRT-D group

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Male gender	1.07	0.56–2.03	0.840	–	–	–
Age (>70 years)	0.89	0.56–1.41	0.611	–	–	–
Ischaemic aetiology	1.77	1.06–2.97	0.031	1.65	0.96–2.83	0.072
QRS duration (>160 ms)	0.95	0.60–1.50	0.815	–	–	–
NYHA class III/IV	1.10	0.64–1.88	0.743	–	–	–
LV ejection fraction (<25%)	0.98	0.60–1.57	0.918	–	–	–
Hypertension	1.10	0.68–1.79	0.699	–	–	–
Diabetes	1.28	0.77–2.11	0.343	–	–	–
Glomerular filtration rate (<60 mL/min/1.73 m^2)	1.37	0.84–2.22	0.209	–	–	–
LV lead in anterior or posterior cardiac vein	2.24	1.14–4.42	0.020	2.24	1.13–4.41	0.021

CI, confidence interval; HR, hazard ratio; LV, left ventricular.

In recent years, several observational studies have addressed this issue, but their results are controversial. While Pappone *et al.*[15] and Bai *et al.*[16] found that the implantation of a CRT-D device was an independent predictor of improved survival, both Auricchio *et al.*[17] and Stabile *et al.*[18] failed to show that CRT-D was superior to CRT-P in reducing overall mortality, although both authors reported a significant reduction in the rate of sudden cardiac death in patients with a CRT-D device. This discrepancy may be ascribed to the different proportion of NYHA class II patients included in these series. Indeed, it has been shown that the survival benefits conferred by the defibrillator are greater in less advanced HF stages,[7] owing to the fact that sudden cardiac deaths account for a higher proportion of overall mortality in these patients.[19]

Available evidence from randomized and non-randomized studies was summarized in a meta-analysis by Jiang *et al.*,[20] who demonstrated the superiority of CRT-D over CRT-P in terms of reduction of all-cause death. Finally, the recently published results from the 1-year follow-up of the European Survey on CRT seem to confirm that CRT-D confers a greater survival benefit than CRT-P.[21]

Instead of positively impacting total mortality, adding a defibrillator to CRT could merely shift the modality of death from arrhythmic to pump failure, or even increase non-cardiac fatal events. Therefore, only death from any cause constitutes a reliable endpoint when comparing the long-term prognosis of patients receiving CRT-D or CRT-P. Moreover, in the framework of a multicentre observational study, it is very difficult to accurately determine the mechanism leading to death. Thus, in this study, adopting all-cause mortality as the endpoint enabled us to avoid possible misclassification of deaths.

To avoid possible confounding variables, such as atrial fibrillation or concomitant indication for pacemaker implantation, which may result from enrolling unselected subjects at different study centres, we considered only patients who met the more stringent criteria that currently define class IA ESC indication for either CRT-D or CRT-P.[13] Indeed, within these limits, previous trials in patients in NYHA class III/IV[2,3] and in NYHA class II[22] demonstrated a reduction in all-cause mortality among CRT patients.

The all-cause mortality rate after CRT-D in our HF population was 6.6/100 patient-years. Our data compare favourably with recently published data from the Medicare Implantable Cardioverter-Defibrillator Registry.[23] In that real-world registry, which comprised 14 946 patients, the mortality rate was 10.6/100 patient-years. Similarly, the 1-year follow-up results of the recent European CRT Survey of the ESC revealed an all-cause mortality rate of 8.6/100 patient-years in patients receiving CRT-D.[21] However, these two studies enrolled patients with a higher burden of comorbidities, such as atrial fibrillation, than those in our registry, which may justify the higher rate of all-cause mortality.

The present analysis also allowed us to investigate which variables are associated with CRT-P rather than CRT-D implantation in current clinical practice at a large number of Italian centres. In our multicentre registry, patients with CRT-D and CRT-P presented several differences in baseline characteristics: CRT-D patients were younger and more frequently males, and had a higher rate of ischaemic heart disease and more severe LV remodelling. Similar differences in age, gender, aetiology, and degree of LV remodelling between CRT-D and CRT-P patients have been reported in the recent European Survey on CRT.[9,21] Moreover, in our population, CRT-D patients had slightly higher baseline values of eGFR, a parameter which plays a complex role in the subset of HF patients undergoing CRT; indeed, a low eGFR value has been associated with a poorer response to biventricular pacing,[24] a higher incidence of malignant arrhythmias, and reduced efficacy of the defibrillator in preventing sudden cardiac death.[25,26] However, none of these variables proved to be significantly associated with all-cause mortality on multivariate regression analysis, which demonstrated an independent role only for CRT-P.

Finally, we were not able to identify any baseline clinical variable associated with all-cause death in the CRT-D group. Therefore,

our study did not provide evidence of possible predictors of shorter life expectancy, which might be able to refine current indications for CRT-D. Nonetheless, we identified the sub-optimal positioning of the LV lead in an anterior or posterior cardiac vein as a factor independently associated with a worse prognosis among CRT-D patients.

Limitations

The present analysis was performed in a relatively small population and patients were not randomized, this should be considered when interpreting its results. In particular, the small sample size may account for the lack of significance obtained in some of the reported comparisons. Moreover, measuring additional variables usually influencing patient's prognosis would have enhanced the validity of the present findings, as well as recording data on the mode of death and on the occurrence of fatal arrhythmias.

Conclusions

Our data from a multicentre registry confirm that patients receiving CRT-D in current clinical practice differ from patients receiving CRT-P. Moreover, our study provides additional evidence to support the implantation of CRT together with a defibrillator, rather than CRT-P only, in patients presenting with class IA indication, to improve long-term overall survival. However, further randomized trials comparing CRT-P with CRT-D would be desirable to confirm these findings.

Conflict of interest: C.C. is an employee of Boston Scientific, Inc. No other conflicts of interest exist.

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