European Heart Journal (2009) **30**, 2275–2283
doi:10.1093/eurheartj/ehp226

Effectiveness of cardiac resynchronization therapy in heart failure patients with valvular heart disease: comparison with patients affected by ischaemic heart disease or dilated cardiomyopathy. The InSync/InSync ICD Italian Registry

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Received 27 January 2009; revised 5 April 2009; accepted 6 May 2009; online publish-ahead-of-print 10 June 2009

Aims To analyse the effectiveness of cardiac resynchronization therapy (CRT) in patients with valvular heart disease (a subset not specifically investigated in randomized controlled trials) in comparison with ischaemic heart disease or dilated cardiomyopathy patients.

Methods and results Patients enrolled in a national registry were evaluated during a median follow-up of 16 months after CRT implant. Patients with valvular heart disease treated with CRT ($n = 108$) in comparison with ischaemic heart disease ($n = 737$) and dilated cardiomyopathy ($n = 635$) patients presented: (i) a higher prevalence of chronic atrial fibrillation, with atrioventricular node ablation performed in around half of the cases; (ii) a similar clinical and echocardiographic profile at baseline; (iii) a similar improvement of LVEF and a similar reduction in ventricular volumes at 6–12 months; (iv) a favourable clinical response at 12 months with an improvement of the clinical composite score similar to that occurring in patients with dilated cardiomyopathy and more pronounced than that observed in patients with ischaemic heart disease; (v) a long-term outcome, in term of freedom from death or heart transplantation, similar to patients affected by ischaemic heart disease and basically more severe than that of patients affected by dilated cardiomyopathy.

Conclusion In 'real world' clinical practice, CRT appears to be effective also in patients with valvular heart disease. However, in this group of patients the outcome after CRT does not precisely overlap any of the two other groups of patients, for which much more data are currently available.

Keywords Cardiac resynchronization therapy • Heart failure • Valvular heart disease • Remodelling

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Introduction

Heart failure may occur in the presence of a wide range of underlying heart diseases, including valvular heart disease, with or without previous surgery. It is well known that the clinical profile of patients enrolled in randomized clinical trials may be quite different from the profile of patients treated in daily clinical practice[1,2] and these differences may also exist with regard to non-pharmacological treatments such as cardiac resynchronization therapy (CRT). Indeed, in most of the major randomized clinical trials that validated the clinical use of CRT,[3–5] the presence of a clinically significant valvular heart disease or of previous valvular surgery were specific exclusion criteria. Only CARE HF allowed inclusion of patients with valvular heart disease, although excluding those in chronic atrial fibrillation; in this trial, patients with previous valve replacement/repair or with valve-related heart failure accounted for 7% of enrolled patients, but the outcome of this group has never been reported separately from the whole population.[6] Moreover, all the major randomized clinical trials on CRT excluded the enrolment of patients with chronic permanent atrial fibrillation, an arrhythmia which is frequently associated with valvular heart disease, and it is known that atrial fibrillation and its management may affect the efficacy of CRT and patients' prognosis.[7,8] According to these considerations, we do not at present have specific trial-derived information on the impact of CRT in patients with valvular heart disease. Observational registries may provide useful information on the number of patients with valvular heart disease receiving CRT in 'real-world' clinical practice, with or without associated atrial fibrillation, as well as on their outcome. The aim of the present study was to analyse the proportion of patients with valvular heart disease or previous valvular surgery receiving CRT in a large national registry and to compare the outcome of these patients with the outcome of patients with dilated cardiomyopathy or ischaemic heart disease treated with CRT.

Methods

Between 1999 and 2005, patients successfully implanted in Italy with biventricular pacing devices for CRT delivery, with (CRT-D) or without (CRT-P) defibrillator capability (CRT models 8040, 8042; CRT-D models 7272, 7277, 7279, Medtronic Inc., Minneapolis, MN, USA) were enrolled in the InSync/InSync ICD Italian Registry. The Registry enrolled patients with mild or severe symptomatic chronic HF (NYHA class II–IV) despite pharmacological therapy, an ejection fraction (LVEF) $\leq$35% and a wide QRS complex ($>$130 ms). Patients with recent myocardial infarction ($<$3 months) or with decompensated HF were excluded. Informed consent approved by Local Ethics Committees was obtained from all patients.

For the current analysis, patients were classified, according to the underlying heart disease, as being affected by valvular heart disease, ischaemic heart disease, dilated cardiomyopathy, or a combination of previous heart diseases. The assignment to the valvular heart disease group was based on clinical history combined with evidence of clinically significant primary valvular disease (organic alterations of valvular apparatus with at least moderate aortic or mitral regurgitation, the latter not simply due to mitral annulus enlargement with normal leaflets), or previous valve replacement or repair for organic valvular disease, in the absence of other overt causes of left-ventricular dysfunction. The assignment to the ischaemic heart disease group was based on clinical history of prior myocardial infarction, prior percutaneous coronary intervention, or prior coronary bypass surgery, or evidence of clinically significant coronary stenosis (at least 75% narrowing of at least one of the three major coronary arteries), similarly to the assignment used in large CRT trials.[3–6] Patients were classified as affected by dilated cardiomyopathy, in the presence of a typical pattern of this heart disease, without ischaemic or organic valvular heart diseases as identifiable causative factors for heart failure. For the aims of the current analysis, the following groups were considered: (i) patients with valvular heart disease (and no evidence of coronary artery disease); (ii) patients with ischaemic heart disease and no history of primary disease or interventions; (iii) patients with dilated cardiomyopathy. Patients enrolled in the registry but found to be affected by a combination of heart diseases were not included in the present analysis.

The devices and the pacing leads were implanted by means of standard techniques[9] with the transvenous LV lead positioned in a lateral or postero-lateral cardiac vein via the coronary sinus. When a conventional indication for an implantable cardioverter defibrillator existed, a combined device was implanted. The baseline evaluation included demographics and medical history, clinical examination, 12-lead electrocardiogram, estimation of NYHA functional class and 2-dimensional, M-mode, and Doppler echocardiography. Specifically, the following parameters were collected: LV end-systolic and end-diastolic diameters (LVESD and LVEDD, respectively), LV end-diastolic and end-systolic volume (LVEDV and LVESV), LVEF assessed by Simpson's equation using the apical four-chamber view.[10] The severity of mitral regurgitation (from degree 1 to degree 4) was assessed by the percent jet area relative to left atrial size in the apical four-chamber view and, similarly, the severity of aortic regurgitation (from degree 1 to degree 4) was assessed by the area of regurgitant jet relative to left-ventricular chamber.

Echo-directed adjustment of the atrio-ventricular pacing interval was done before patients were discharged and at follow-up to optimize haemodynamic function. Pharmacological treatments were based on clinical evaluation by the attending physicians. Patients returned for regular clinic visits at 1, 3, and 6 months and every 6 months thereafter. Besides the clinical evaluation, 12-lead electrocardiogram, NYHA class, and detailed device checks were performed at each follow-up visit. In addition, standard echocardiography was performed at the 6 and 12 month follow-up visits in all patients.

The impact of CRT on clinical and echocardiography outcome was evaluated comparing the baseline with 6 and 12 month follow-up data. Moreover, at the 12 month follow-up patients were classified according to a clinical composite score, which assigns subjects to one of three response groups—improved, worsened, or unchanged—according to a predefined scheme.[11] A patient was defined as 'improved' in the case of a favourable change in NYHA class and neither hospitalization due to worsening HF nor death during the observation period.

Mortality data were obtained by physicians' or hospitals' files review or by direct telephone contact. Events were classified as cardiac death (defined as sudden or non-sudden cardiac deaths) and non-cardiac death. According to the Hinkle–Thaler classification,[12] sudden cardiac death was defined as abrupt, unexpected death occurring within 1 h from the insurgence of symptoms. Non-sudden cardiac death was mainly represented by progressive HF defined as unstable, clinical progression of deteriorating pump function in the setting of active therapy, most often in an intensive care setting. All deaths not complying with the aforementioned criteria were classified as non-cardiac death.[12]

Statistical analysis

Continuous data were expressed as means ± standard deviation. Categorical data were expressed by percentages. Differences between mean data were compared by a *t*-test for Gaussian variables, and by the Mann–Whitney or Wilcoxon non-parametric test for non-Gaussian variables, respectively, for independent or paired samples. Differences in proportions were compared by a χ^2 analysis or Fisher's exact test, as appropriate. Multiple comparisons were performed with the Bonferroni correction. For the comparison with baseline, 6 and 12 month clinical and echocardiographic values were considered for surviving patients, otherwise the last observation was carried forward. Mortality rate was summarized by construction of Kaplan–Meier curves and the distributions of the groups were compared by a log-rank test. A *P*-value < 0.05 was considered significant for all tests. All statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Patient population

The overall population of 1844 patients enrolled and followed in the InSync/InSync ICD Italian Registry was analysed; after exclusion of cases with a combination of underlying heart diseases, 1480 patients fulfilled the criteria for the present analysis. In particular, 108 presented with dilated cardiomyopathy of valvular aetiology and no evidence of coronary artery disease; in 737 patients the primary cause of heart failure was coronary artery disease and no valvular heart disease was diagnosed, while for the remaining 635 patients the investigators reported a diagnosis of dilated cardiomyopathy.

The median [25–75 percentile] follow-up was 16 [9–26] months, and was comparable in the three groups. The demographics, baseline clinical parameters, and pharmacological therapy are listed in *Table 1*.

In the group of patients with valvular heart disease, 50 had suffered lone aortic insufficiency (previous surgical correction in 22 patients), 38 mitral insufficiency (corrected in 18), and the remaining 20 combined aortic and mitral valvular regurgitation (combined aortic and mitral correction in 12, aortic correction in 2), for a median of 24 [8–50] months. No patient presented a significant (at least moderate) mitral or aortic stenosis at the time of CRT implant. For the 54 patients with a history of valve replacement or repair, the median time from the operation to enrolment was 24 [12–48] months.

A device with defibrillator capability (CRTD) was implanted only in 17 (16%) patients with valvular heart disease, with respect to

Table 1 Demographics, baseline clinical parameters, and pharmacological treatment of the three groups of patients

Parameter	Valvular HD (*n* = 108)	Ischaemic HD (*n* = 737)	Dilated CMP (*n* = 635)
Male gender, *n* (%)	87 (81)	662 (90)*	460 (72)**
Age, years	66 ± 10	69 ± 8*	66 ± 10**
Hospitalizations for HF (prior 12 months), *n*/year	2.0 ± 1.5	1.7 ± 1.6	1.6 ± 1.4
Chronic atrial fibrillation, *n* (%)	40 (37)	88 (12)*	106 (17)*, **
QRS duration, ms	170 ± 33	163 ± 32	165 ± 30
NYHA class			
Class II	16 (15)	140 (19)	121 (19)
Class III	71 (66)	494 (67)	419 (66)
Class IV	21 (19)	103 (14)	95 (15)
LVEF, %	27 ± 7	26 ± 7	26 ± 7
LVEDD, mm	70 ± 8	69 ± 9	69 ± 10
LVESD, mm	60 ± 11	57 ± 10	59 ± 11
LVEDV, mL	257 ± 61	227 ± 85	223 ± 118
LVESV, mL	172 ± 60	155 ± 79	147 ± 93
Mitral regurgitation, degree	2.2 ± 1.2	2.1 ± 0.9	2.1 ± 1.0
CRT-D use, *n* (%)	17 (16)	447 (61)*	212 (33)*, **
Secondary prevention, *n* (%)	12 (11)	229 (31)*	125 (20)**
Diuretic use, *n* (%)	94 (87)	635 (86)	565 (89)
ACE-inhibitors or ARB use, *n* (%)	82 (76)	517 (70)	473 (74)
β-Blockers use, *n* (%)	45 (42)	345 (47)	334 (53)
Class III antiarrhythmics use, *n* (%)	38 (35)	287 (39)	208 (33)**
Nitrates use, *n* (%)	8 (7)	221 (30)*	92 (14)**

CMP, cardiomyopathy; HD, heart disease; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; ACE, angiotensin-converting-enzyme; ARB, angiotensin-receptor blockers.
**P*-value < 0.05 vs. valvular HD.
***P*-value < 0.05 vs. ischaemic HD (Bonferroni-corrected).

447 patients (61%) in the group with ischaemic heart disease and 212 (33%) in the group affected by dilated cardiomyopathy ($P <$ 0.001 for all comparisons). The proportion of patients implanted with a CRTD device increased over time in all three groups of patients (in 1998–2001 CRTD accounted for 13, 38, and 24% of the implants performed in patients with valvular heart disease, ischaemic heart disease and dilated cardiomyopathy, respectively, while the same figures in 2004–2005 increased to 43, 75, and 39%, respectively).

As shown in *Table 1*, a series of clinical and echocardiographic characteristics were comparable among the three groups. A higher prevalence of males and a higher mean age was observed in the group with ischaemic heart disease with respect to the other two groups, whereas a significantly higher proportion of patients with valvular heart disease were in chronic atrial fibrillation at the time of device implant. Among the patients with chronic atrial fibrillation, atrioventricular junction ablation was performed at the time of implant, or within 2 months, in 18 out of 40 patients (45%) with valvular heart disease, 46 out of 88 patients (52%) with ischaemic heart disease, and 49 out of 106 patients (46%) with dilated cardiomyopathy.

Effects on clinical outcomes and on echocardiographic parameters

The comparison of clinical and echocardiographic parameters recorded at baseline and during CRT, at the 6 and 12 month follow-up visits is reported in *Table 2* for the three groups of patients. At the 6 month follow-up, a significant improvement in NYHA functional class was observed in all groups. In all patients, the mean QRS duration during pacing was significantly decreased in comparison with baseline spontaneous QRS, and an increase of LVEF occurred with significant reductions of LVEDD and LVESD. Left-ventricular end-diastolic volume appeared significantly decreased only for patients with dilated cardiomyopathy, whereas a reduction of LVESV was apparent for both the group of patients with valvular heart disease and the group with dilated cardiomyopathy, but not for patients with ischaemic heart disease. All these changes persisted at the 12 month follow-up visit.

The effects of CRT on clinical and echocardiographic variables was also analysed within the group of patients with valvular HD, by stratifying the patients according to the severity of mitral regurgitation at baseline ($<$ or $\geq$3 at baseline, respectively). As shown in *Table 3*, both subgroups showed improvement in NYHA class and LVEF, but with a different effect on mitral regurgitation (a significant reduction was observed in patients with more severe mitral regurgitation at baseline).

The response to CRT at the 12 month follow-up, measured according to the aforementioned clinical composite score, is reported in *Figure 1* for the three study groups, taking into account the overall population (*Figure 1A*) and only patients in NYHA class III and IV (*Figure 1B*), respectively. Specifically, in the whole population 74 patients in the group with valvular heart disease (69%) were defined as 'improved', with respect to 399 patients with dilated cardiomyopathy (63%, P=NS vs. valvular heart disease) and 419 patients with ischaemic heart disease (57%, $P = 0.022$ vs. valvular and $P = 0.024$ vs. dilated

Table 2 Clinical and echocardiographic parameters at baseline, 6 month, and 12 month follow-up

Parameter	Baseline			6 month follow-up			12 month follow-up		
	Valvular HD	Ischaemic HD	Dilated CMP	Valvular HD	Ischaemic HD	Dilated CMP	Valvular HD	Ischaemic HD	Dilated CMP
QRS duration, ms	170 ± 33	163 ± 32	165 ± 30	149 ± 28*	145 ± 28*	143 ± 27*	148 ± 26*	145 ± 27*	143 ± 26*
NYHA class	3.0 ± 0.6	2.9 ± 0.6	3.0 ± 0.6	2.0 ± 0.7*	2.0 ± 0.9*	2.0 ± 0.8*	2.0 ± 0.7*	2.2 ± 0.7*	2.1 ± 0.7*
LVEF, %	27 ± 7	26 ± 7	26 ± 7	35 ± 10*	33 ± 10*	35 ± 11*	35 ± 11*	33 ± 11*	36 ± 12*
LVEDD, mm	70 ± 8	69 ± 9	69 ± 10	66 ± 11*	66 ± 10*	66 ± 12*	66 ± 12*	66 ± 10*	65 ± 12*
LVESD, mm	60 ± 11	57 ± 10	59 ± 11	54 ± 14*	54 ± 12*	53 ± 13*	54 ± 14*	54 ± 12*	52 ± 14*
LVEDV, mL	257 ± 61	227 ± 85	223 ± 118	220 ± 98	185 ± 72	179 ± 94*	220 ± 98	186 ± 73	176 ± 91*
LVESV, mL	172 ± 60	155 ± 79	147 ± 93	146 ± 81*	135 ± 61	118 ± 82*	145 ± 81*	137 ± 62	117 ± 81*
Mitral regurgitation, degree	2.2 ± 1.2	2.1 ± 0.9	2.1 ± 1.0	2.0 ± 1.0	1.7 ± 0.8*	1.7 ± 0.9*	1.9 ± 1.0	1.7 ± 0.8*	1.7 ± 0.9*

CMP, cardiomyopathy; HD, heart disease; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.
*P-value $<$ 0.05 vs. baseline.

Table 3 Clinical and echocardiographic parameters at baseline and 6 month follow-up for the group of patients with valvular heart disease, stratified according to the degree of mitral regurgitation at baseline, <3 (73 patients of whom 28 with previous mitral surgery) and ≥3 (35 patients of whom two with previous mitral surgery), respectively

Parameter	Patients with valvular heart disease and mitral regurgitation degree <3 at baseline (n = 73)		Patients with valvular heart disease and mitral regurgitation degree ≥3 at baseline (n = 35)	
	Baseline	6 month follow-up	Baseline	6 month follow-up
QRS duration, ms	168 ± 31	147 ± 27***	186 ± 40	159 ± 31***
NYHA class	3.1 ± 0.6	2.1 ± 0.6***	2.9 ± 0.5	1.9 ± 0.5***
LVEF, %	27 ± 7	34 ± 9***	25 ± 7	33 ± 7*
LVEDD, mm	70 ± 8	65 ± 11*	71 ± 8	69 ± 13
LVESD, mm	60 ± 11	53 ± 14*	59 ± 10	57 ± 13
LVEDV, mL	257 ± 62	200 ± 81*	257 ± 63	259 ± 70
LVESV, mL	174 ± 43	125 ± 56**	169 ± 89	160 ± 90
Mitral regurgitation, degree	1.5 ± 0.5	1.7 ± 0.8	3.7 ± 0.5	2.7 ± 0.9*

*P-value <0.05 vs. baseline.
**P-value <0.01 vs. baseline.
***P-value <0.001 vs. baseline.

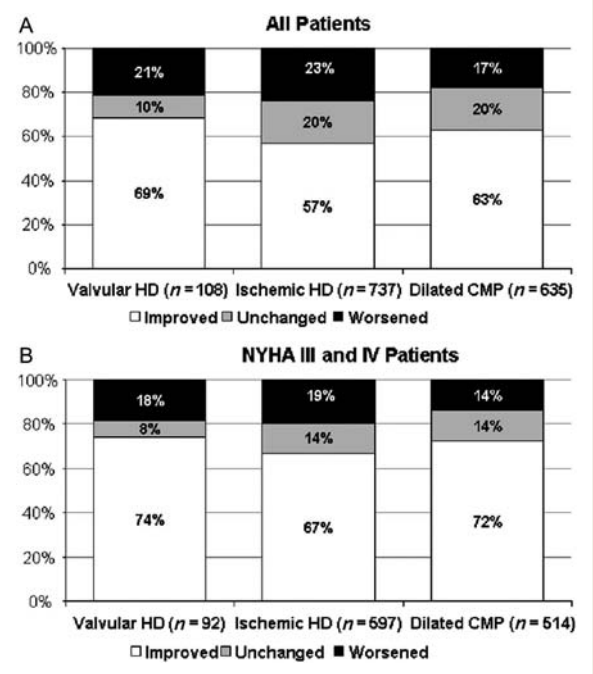

Figure 1 Response to cardiac resynchronization therapy according to the clinical composite score in the whole patient population (*A*) or only in patients with NYHA functional class III–IV at baseline (*B*), according to the underlying heart disease.

cardiomyopathy patients). Specifically, among the components of the clinical composite score, a favourable change in NYHA class was observed, in the whole population, in 82 patients (76%) in the group with valvular heart disease, in 465 patients (63%) with ischaemic heart disease ($P = 0.009$ vs. valvular heart disease), and in 433 patients (68%) with dilated cardiomyopathy ($P = 0.107$ vs. valvular heart disease). The pattern of response in the analysis performed in NYHA class III and IV patients proved to be similar to the previous response pattern, although with slightly higher improvement rates (*Figure 1B*).

In the whole study population, 166 of 1480 patients died or underwent urgent heart transplantation (rate 7.3 per 100 patient-years of follow-up). There were 17 deaths in the group with valvular heart disease (rate 8.8 per 100 patient-years of follow-up), 96 deaths in the group with ischaemic heart disease (rate 8.7 per 100 patient-years of follow-up), and 53 deaths in the group with dilated cardiomyopathy (rate 5.3 per 100 patient-years of follow-up, $P = 0.005$ vs. ischaemic group).

The survival curves for all-cause mortality or heart transplantation obtained by Kaplan–Meier analysis are shown in *Figure 2*, for both the overall population (*Figure 2A*) and the patients with NYHA class III-IV at device implant (*Figure 2B*). In the overall population the survival curve of patients with ischaemic heart disease differed from that of patients with dilated cardiomyopathy (Log-rank test, $P = 0.004$), and the worse prognosis of patients with ischaemic heart disease was confirmed in the analysis of NYHA class III–IV patients.

A series of factors were analysed by univariate and multivariate logistic regression analysis as predictors of death from any cause or urgent heart transplantation: chronic atrial fibrillation, not treated with atrioventricular node ablation, significantly increased the risk, while beta-blocker use proved to have a significant protective role in the whole patient population (*Table 4*). Among patients with valvular heart disease or dilated cardiomyopathy, the only independent predictor of death from any cause or urgent heart transplantation was chronic atrial fibrillation, not treated with atrioventricular node ablation (*Table 5*).

A total of 168 patients had at least one hospitalization for worsening HF, 13 were in the group with valvular heart disease (rate

6.7 per 100 patient-years of follow-up), 96 in the group with ischaemic heart disease (rate 8.7 per 100 patient-years of follow-up), and 59 in the group affected by dilated cardiomyopathy (rate 6.0 per 100 patient-years of follow-up, all P = NS).

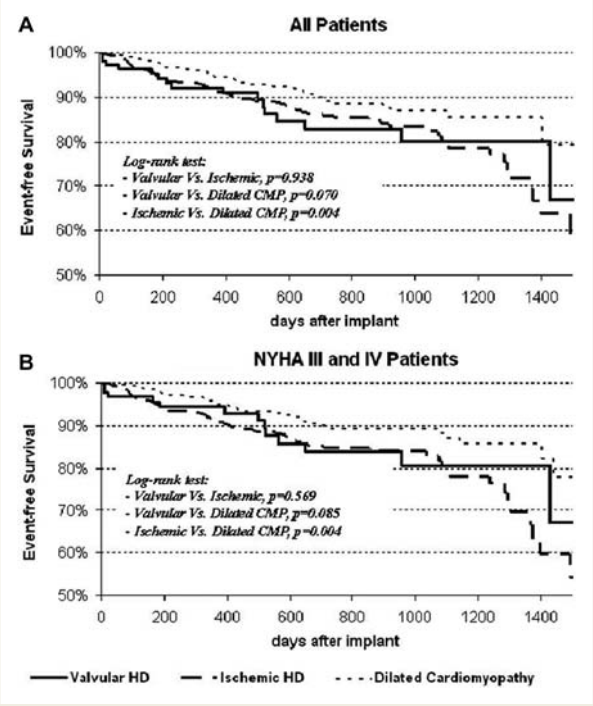

Figure 2 Kaplan–Meier estimates of time to death from any cause in the whole patient population (*A*) or only in patients with NYHA functional class III–IV at baseline (*B*), according to the underlying heart disease.

Discussion

The impact of CRT on symptoms and survival in the specific setting of heart failure patients with underlying valvular heart disease has not been previously investigated. In our registry, 5.9% of the patients treated with CRT had a valvular heart disease as the primary and sole cause of heart failure, as evaluated by attending physicians.

A series of considerations linked to patients' characteristics and pathophysiological issues make it interesting to assess the effectiveness of CRT in this subset of patients in comparison with patients affected by ischaemic heart disease and dilated cardiomyopathy, the two subsets of patients in whom the efficacy of CRT has already been validated by a series of randomized controlled trials.[13] These considerations include: the consequences of a potentially increased prevalence of chronic atrial fibrillation and the unknown effects of biventricular pacing on ventricular volumes in the presence of some degree of volume overload due to aortic valve insufficiency, or mitral regurgitation, with or without surgical correction.

The present study shows that in daily clinical practice, where the strict exclusion criteria of randomized clinical trials are not applied, patients with valvular heart disease represent a relatively small minority of CRT recipients, with both some similarities and some distinct features in comparison to patients with ischaemic heart disease or dilated cardiomyopathy. According to our findings, chronic atrial fibrillation is much more common in patients with valvular heart disease treated with CRT than in the other two groups of underlying heart disease, being present in more than one-third of the cases, with atrioventricular node ablation performed in around half of the cases with chronic atrial fibrillation. It is expected that atrioventricular node ablation will be more widely used in the future, as a way of ensuring constant ventricular pacing during CRT (if the percentage of ventricular pacing is lower

Table 4 Univariate and multivariate analysis of factors predicting death from any cause or urgent heart transplantation in the whole population (n = 1480)

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Ischaemic heart disease	1.5	1.1–2.0	0.012	1.3	0.8–2.1	0.308
Male gender	1.7	1.1–2.7	0.027	1.2	0.7–2.3	0.481
Age	1.1	1.0–1.1	0.004	1.0	1.0–1.0	0.203
Chronic atrial fibrillation (no AVN ablation)	1.6	1.1–2.3	0.021	1.8	1.1–3.2	0.030
Chronic atrial fibrillation (AVN ablation)	1.0	0.5–1.4	0.612	—	—	—
QRS duration	1.0	0.9–1.0	0.711	—	—	—
NYHA class	1.1	0.8–1.4	0.691	—	—	—
LV ejection fraction	0.9	0.8–0.9	0.001	1.0	0.9–1.0	0.073
LVEDD	1.0	0.9–1.1	0.371	—	—	—
LVESD	1.0	0.9–1.1	0.347	—	—	—
Mitral regurgitation	1.2	0.9–1.5	0.069	1.2	1.0–1.6	0.077
CRT-D use	1.0	0.8–1.4	0.810	—	—	—
β-Blockers use	0.4	0.3–0.6	0.001	0.4	0.2–0.6	0.001

AVN, atrioventricular node.

Table 5 Univariate and multivariate analysis of factors predicting death from any cause or urgent heart transplantation in patients with valvular heart disease and dilated cardiomyopathy ($n = 743$)

	Univariate analysis			Multivariate aalysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Valvular heart disease	1.6	0.9–2.8	0.082	1.1	0.4–2.9	0.495
Male gender	2.1	1.1–4.0	0.022	1.2	0.5–2.9	0.617
Age	1.1	1.0–1.1	0.038	1.0	1.0–1.1	0.054
Chronic atrial fibrillation (no AVN ablation)	1.9	1.3–3.0	0.012	3.1	1.2–7.8	0.018
Chronic atrial fibrillation (AVN ablation)	0.9	0.6–1.2	0.515	—	—	—
QRS duration	1.0	0.9–1.0	0.715	—	—	—
NYHA class	0.8	0.5–1.1	0.163	—	—	—
LV ejection fraction	0.9	0.9–1.0	0.055	1.0	0.9–1.0	0.169
LVEDD	1.1	1.0–1.1	0.006	1.1	1.0–1.1	0.221
LVESD	1.1	1.0–1.1	0.026	1.1	1.0–1.1	0.330
Mitral regurgitation	1.4	1.0–2.0	0.040	1.4	1.0–1.9	0.498
CRT-D use	1.4	0.8–2.3	0.219	—	—	—
β-Blockers use	0.5	0.3–0.9	0.010	0.6	0.3–1.1	0.060

AVN, atrioventricular node.

than 85%) and as a way of improving patient outcome after CRT.[7,8] The present observational study stresses the role of atrioventricular node ablation as a factor linked to patient outcome, not only in the usual setting of patients with ischaemic heart disease or dilated cardiomyopathy but also in a less selected setting, taken from daily clinical practice, also including patients with valvular heart disease. In our analysis, the other clinical and echocardiographic characteristics of valvular heart disease patients at baseline do not show marked differences in comparison with the two other groups and this is the basis for comparing the response to CRT, in terms of echocardiographic changes and clinical effectiveness. In our population sample, the response at 6 and 12 months of follow-up appeared to be favourable in patients with valvular heart disease, with a significant improvement in NYHA functional class and LVEF and a reduction in LV volumes, similarly to patients affected by dilated cardiomyopathy or ischaemic heart disease. In an observational, non-comparative study on 40 patients with CRT in the setting of HF after corrective valvular surgery, Macias *et al.*[14] recently reported an improvement of symptoms, functional capacity and echocardiographic indices, on the basis of a 6 month follow-up.

In the literature, various authors[15–17] have reported that the response to CRT is different in ischaemic patients in comparison to patients with dilated cardiomyopathy, but no data are available on the response rate in patients with valvular heart disease. It is noteworthy to consider that while the clinical response to CRT at 12 months in patients with valvular heart disease appears to be similar to the response rate of dilated cardiomyopathy patients, the long-term outcome in terms of freedom from all-cause death or heart transplantation is more similar to that of ischaemic heart disease patients, with a trend towards a worse outcome in comparison with dilated cardiomyopathy patients. It can be argued that the worse long-term outcome in comparison with dilated cardiomyopathy may be due to progression of the underlying disease with evolution of the haemodynamic load due to uncorrected or lately corrected valvular dysfunction. Larger population samples should further address this topic, also considering the specific outcome of various subgroups of patients with valvular heart disease (i.e. mitral regurgitation, previous mitral repair, mitral valve prosthesis, aortic insufficiency, aortic prosthesis, combined valvular, and aortic diseases, etc.).

No randomized controlled trial has specifically evaluated the effects of CRT in patients affected by a valvular heart disease, but on the basis of the present observational study, where the effectiveness of CRT in this particular subset of patients was compared with the effectiveness of CRT in two settings (ischaemic heart disease and dilated cardioyopathy) with a full validation of CRT by randomized controlled trials, it appears worth to apply CRT to similar patients with valvular heart disease. It should in any case be stressed that patients with valvular heart disease treated with CRT in daily clinical practice appear to have some distinct clinical features, as well as an overall response rate, by combining clinical and structural changes (reverse remodelling) and outcome that do not precisely overlap any of the two other groups of patients, for which much more data are currently available.

The data of the present study derive from an observational registry, with prospective collection of data according to a predefined scheme, including clinical and laboratory evaluations performed before and after device implant, as well as periodic follow-up visits and checks of the device system. This study therefore has all the limitations of multicentre observational studies, such as potential bias in patient selection and the lack of a control group. The study also included patients in NYHA class II, who were implanted on the basis of preliminary evidence in favour of the beneficial effect of CRT in subjects with mild heart failure

symptoms[18,19] often combined with the indication for a defibrillator for secondary prevention. The pharmacological therapy at enrolment was not optimal, in comparison to prescription rates of β-blockers and angiotensin-converting enzyme inhibitors or ARB in randomized controlled trials. This observation is in line with 'real-world' surveys and indicates that some gaps still exist between trials and 'real-world' practice, with relatively slow adoption of guidelines for the management of heart failure.[1,2] However, pharmacological treatment did not present great differences between the three groups of patients we examined, with regard to prescription of diuretics, β-blockers, angiotensin-converting enzyme inhibitors, or ARBs, respectively.

In summary, in a 'real-world' registry of patients treated with CRT, with or without defibrillation capabilities, around 6% of patients are found to have a valvular heart disease as the primary and sole cause of heart failure. The analysis of our registry, where data were prospectively collected, shows that CRT is effective also in this group of patients, not evaluated by randomized controlled trials. However, patients with valvular heart disease treated with CRT present a series of features, in comparison to patients affected by ischaemic heart disease and dilated cardiomyopathy: (i) a higher prevalence of chronic atrial fibrillation, with atrioventricular node ablation performed in around half of the cases; (ii) a similar clinical and echocardiographic profile at baseline; (iii) a similar improvement of LVEF and a similar reduction in ventricular volumes at 6–12 months; (iv) a favourable clinical response with an improvement of the clinical composite score at 12 months similar to that occurring in patients with dilated cardiomyopathy and more pronounced than that observed in patients with ischaemic heart disease; (v) a long-term outcome, in terms of freedom from death or heart transplantation, similar to patients affected by ischaemic heart disease and basically more severe than that of patients affected by dilated cardiomyopathy. Thus, patients with valvular heart disease treated with CRT appear to present a clinical benefit, but with some distinct clinical features, as well as an outcome, that do not precisely overlap any of the two other groups of patients, for which much more data are currently available.

Funding

Funding to pay the Open Access publication charges for this article was provided by Medtronic Italia.

Conflict of interest: T.D.S. and S.V. are employees of Medtronic, Inc. No other conflicts of interest exist.

Appendix

Centres and investigators participating in the InSync/InSync ICD Italian Registry are listed below.

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