

# Cardiac resynchronization therapy: implant rates, temporal trends and relationships with heart failure epidemiology

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**Background** Consensus guidelines define indications for cardiac resynchronization therapy (CRT), but the variability in implant rates in 'real world' clinical practice, as well as the relationship with the epidemiology of heart failure are not defined.

**Methods and results** In Emilia-Romagna, an Italian region with around 4.4 million inhabitants, a registry was instituted to collect data on implanted devices for CRT, with (CRT-D) or without defibrillation (CRT-P) capabilities. Data from all consecutive patients resident in this region who underwent a first implant of a CRT device in years 2006–2010 were collected and standardized (considering each of the nine provinces of the region). The number of CRT implants increased progressively, with a 71% increase in 2010 compared to 2006. Between 84 and 90% of implants were with CRT-D devices. The variability in standardized implant rates among the provinces was substantial and the ratio between the provinces with the highest and the lowest implant rates was always greater than 2. Considering prevalent cases of heart failure in the period 2006–2010, the proportion of patients implanted with CRT per year ranged between 0.23 and 0.30%.

**Conclusions** The application in 'real world' clinical practice of CRT in heart failure is quite heterogeneous, with

substantial variability even among areas belonging to the same region, with the need to make the access to this treatment more equitable. Despite the increased use of CRT, its overall rate of adoption is low, if a population of prevalent heart failure patients is selected on the basis of administrative data on hospitalizations.

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## Introduction

Cardiac resynchronization therapy (CRT) is a valuable treatment for appropriately selected patients with left-ventricular dysfunction, wide QRS complex and moderate to severe heart failure, with NYHA (New York Heart Association) class III–IV.<sup>1</sup> More recently, it also proved effective in patients with less advanced heart failure (NYHA class II).<sup>2,3</sup>

Despite the efficacy proven in randomized controlled trials (RCTs), the implementation of CRT in clinical practice is still the subject of debate. Specifically, it is not clear how much the indications for device implant, validated by RCTs and implemented in

recommendations of consensus guidelines, are applied in daily clinical practice, and what the relationship is with the epidemiology of heart failure.<sup>3–7</sup> Moreover, it is not well known to what proportion of patients CRT is currently applied by using a pacemaker (CRT-P device) or, rather, a biventricular defibrillator (CRT-D).<sup>8</sup>

The aim of the present study was to analyse implant rates of devices for CRT, taking into consideration both CRT-D and CRT-P devices in the context of a single Italian region (Emilia-Romagna), in order to assess the degree of implementation, in different areas, of current guidelines, as well as the relationship with the

epidemiology of heart failure (prevalent cases) and with the population burden of heart failure hospitalizations.

## Methods

In July 2005, the Regional Healthcare and Social Agency of Emilia-Romagna, an Italian region with around 4.4 million inhabitants, launched a prospective Web-based registry called Registro Regionale di Aritmologia Interventistica (RERAI), aimed at collecting clinical and implant data for all cardiac devices implanted in the Emilia-Romagna region.<sup>9</sup> All 21 public and three private cardiology centres implanting cardioverter-defibrillators and CRT devices in this region participated in the data collection.

In the present study (conceived in accordance with the principles of the most recent revision of the Declaration of Helsinki), we analysed data from all consecutive patients resident in the Emilia-Romagna region who underwent a first implant of a biventricular pacemaker (CRT-P device) or a biventricular defibrillator (CRT-D device) for delivery of cardiac resynchronization therapy for heart failure between January 2006 and December 2010. Device replacements and upgrades of a previous implant were excluded. Since the RERAI registry was designed to observe current clinical practice, the ethics committees of each participating hospital required only ordinary written informed consent for implant (in line with national regulations) and anonymous publication of scientific data. Written informed consent was obtained from all patients. National and international consensus guidelines for indication to implant a CRT device were followed in all the centres.

Implant of a CRT-D device was classified as primary prevention if performed in a patient identified at increased risk of sudden cardiac death, according to current guidelines, in the absence of previously documented sustained ventricular tachyarrhythmias or cardiac arrest.

On the basis of actual implants performed in the resident population (independently of the hospital where implants had been performed), the implantation rates for 1 000 000 inhabitants aged at least 18 years were calculated annually for each of the nine provinces of residence. Crude rates of implantations for each province were adjusted for differences in age and sex, using the regional population during the year 2006 as the standard population (Emilia-Romagna Region Statistics. [http://sasweb.regione.emilia-romagna.it/cgi-bin/broker.exe?\\_service=stat&\\_program=prog.selezione.sas&\\_ds=resident](http://sasweb.regione.emilia-romagna.it/cgi-bin/broker.exe?_service=stat&_program=prog.selezione.sas&_ds=resident)). The standardization was performed in order to compare implant rates in provinces with different distributions of age and sex.

The information on heart failure hospitalizations was retrieved from the regional database of hospital discharge forms (SDO). This database was linked to the regional

mortality registry to evaluate survival. We extracted all hospitalizations for heart failure that occurred, in private or public structures, from 1 January 1997 to 31 December 2010, in the Emilia-Romagna region. The following International Classification of Diseases 9-CM codes were searched for in primary and secondary diagnoses: 428.0, 428.1, 428.2x, 428.3x, 428.4x, 428.9x, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 and 398.91. Patients under the age of 18 years and those not resident in Emilia-Romagna were excluded from the analysis.

For each year of discharge, we estimated the incidence and the prevalence of heart failure. The incidence cases were defined as all patients with a first hospital admission for heart failure, without any hospitalizations for heart failure since 1997. The prevalence cases included patients aged at least 18 years newly hospitalized for heart failure and previous incident patients, surviving at 1 January.<sup>10</sup>

Histograms, maps and box-plots were used to represent results graphically. Spearman's rank correlation indices were calculated to evaluate the correlation between implantation rates in every year of the 5-year period we analysed and the number of implanting centres per province. Statistical analyses were conducted using SAS Software version 9.1.3 (SAS Institute Inc., Cary, North Carolina, USA).

The authors of this manuscript declare that they comply with the Principles of Ethical Publishing.<sup>11</sup>

## Results

In this analysis of CRT implants in the Emilia-Romagna region, we found that 1100 patients received a first implant of a CRT-D or CRT-P device between 2006 and 2010 for heart failure. The demographic characteristics of implanted patients, and the number and type of implanted devices are shown in Table 1. The number of CRT implants increased progressively in the 2006–2010 period, with a 71% increase in 2010 compared to 2006. The large majority of CRT implants were with CRT-D devices, but the CRT-D/CRT-P ratio peaked in 2008 at 9.3:1, decreasing in 2010 to 5.2:1, the same ratio as 2006.

With regard to clinical characteristics (Table 2), around 40% of the patients had an underlying ischaemic heart disease, although with a lower prevalence among CRT-P recipients. In more recent years, the presence of moderate-to-severe functional impairment, expressed by an advanced NYHA class, decreased up to values around 60%. A left-ventricular dysfunction [left-ventricular ejection fraction (LVEF)  $\leq 35\%$ ] was present in around 90% of CRT-D patients, but was lower in patients implanted with a CRT-P device. Around 20% of patients were in atrial fibrillation (AF) at the time of implant. Among AF patients atrio-ventricular node ablation was

**Table 1 Demographic characteristics of implanted patients and number and type of implanted devices**

Characteristics of patients	Type	2006	2007	2008	2009	2010
Patients implanted with a CRT (n, %)	CRT	163 (100)	181 (100)	248 (100)	229 (100)	279 (100)
	CRT-D	137 (84)	157 (87)	224 (90)	204 (89)	234 (84)
	CRT-P	26 (16)	24 (13)	24 (10)	25 (11)	45 (16)
CRT-D/CRT-P ratio		5.3 : 1	6.5 : 1	9.3 : 1	8.2 : 1	5.2 : 1
Male sex (%)	CRT	78	74	74	75	75
	CRT-D	82	76	74	76	79
	CRT-P	58	58	71	68	53
Patient age (median)	CRT	68	70	71	70	72
	CRT-D	67	70	70	69	71
	CRT-P	74	75	78	79	77
Patient age ≥65 years (%)	CRT	63	66	77	72	70
	CRT-D	59	64	76	69	65
	CRT-P	85	79	88	96	93
Patient age ≥75 years (%)	CRT	23	25	28	30	34
	CRT-D	19	22	24	26	28
	CRT-P	42	46	63	64	64

CRT, cardiac resynchronization therapy.

performed in all the patients in whom a high rate of biventricular pacing (at least 95%) was not obtained or predicted, as a consequence of competition between the ventricular rate of spontaneous atrio-ventricular conduction and biventricular stimulation. Overall atrio-ventricular node ablation was performed in 41% of CRT implants performed in patients with AF. For CRT-D implants, the indication was classified as primary prevention in 94% of implants, overall.

Standardized implant rates of CRT devices (CRT-P + CRT-D) per 1 000 000 inhabitants are shown for the entire region and for each province in Fig. 1. The extent of variability in implant rates among the provinces, for CRT-P and CRT-D, respectively, and its temporal changes, can be better assessed by box-plots showing median and interquartile ranges of standardized implant rates (Fig. 2). It is clear that the widest variability in implant rates was observed in 2008.

As previously shown (Table 1), a CRT-D device was implanted in 84–90% of CRT implants, and implant rates for this type of device are shown in Table 3 for each province. The variability in standardized implant rates among the provinces was substantial and the ratio

between the provinces with the highest and the lowest implant rates for CRT-D devices per year was around 3 for years 2006 and 2007, peaking at 3.7 in 2008 and then falling to around 2 in 2009 and 2010.

No significant correlation was found between the number of implanting centres per province (ranging from 1 to 6) and standardized implant rates of CRT devices for each province (including all the data of the 5 years in the same analysis) ( $r = 0.266$  at Spearman's test;  $P = 0.487$ ). Similar results were found in the analysis considering every single year.

Among CRT recipients (overall 1100 patients in the period between 2006 and 2010), we assessed what proportion of implanted patients had a history of at least two hospital admissions for heart failure in the two calendar years preceding device implant (117 patients corresponding to 10.6% of the total). This rate was 17.2% in 2006 and progressively declined over time (10.5% in 2007, 9.7% in 2008, 9.6% in 2009 and 8.6% in 2010, respectively) (Fig. 3).

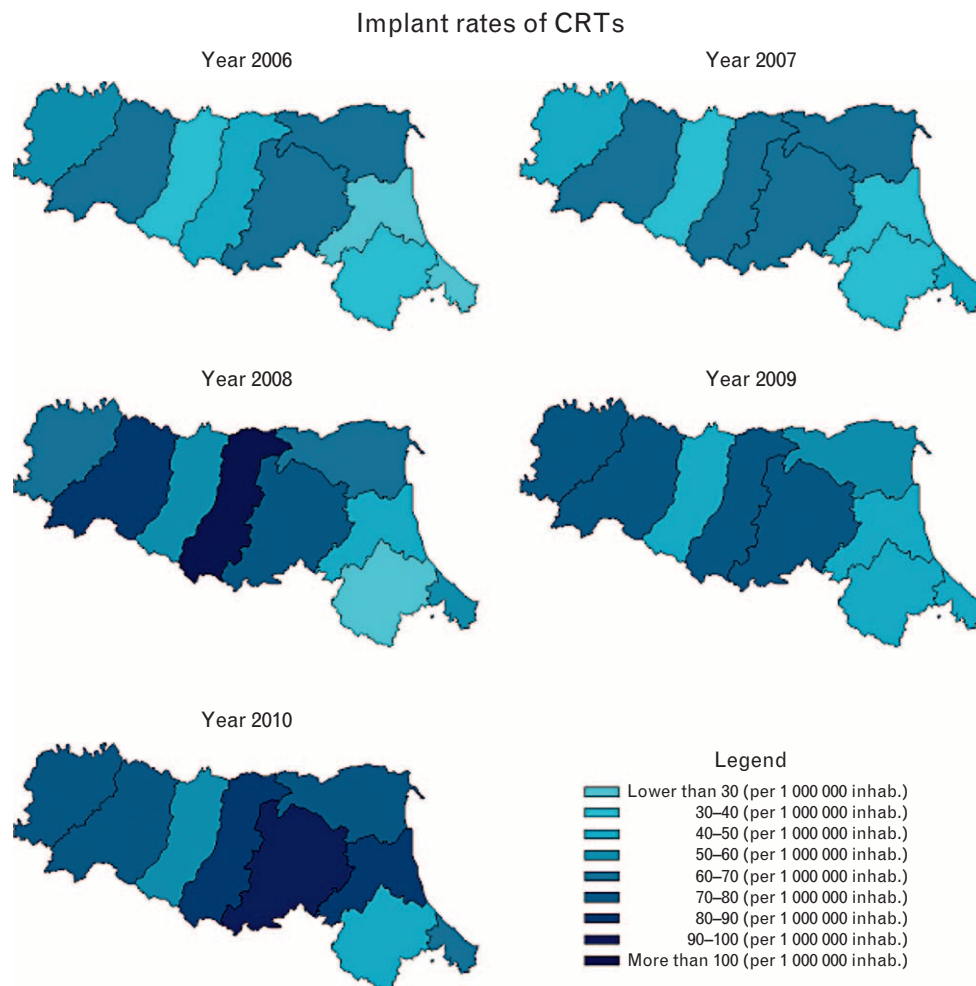
We analysed implant rates of CRT devices with regard to prevalent cases of heart failure in the Emilia-Romagna

**Table 2 Clinical characteristics of implanted patients**

Characteristics of patients	Type	2006	2007	2008	2009	2010
Underlying ischaemic HD (%)	CRT	40	30	37	38	37
	CRT-D	42	30	37	38	39
	CRT-P	27	29	33	39	22
NYHA class III–IV (%)	CRT	79	62	75	63	61
	CRT-D	81	63	75	64	64
	CRT-P	71	55	74	56	43
LVEF ≤ 35 (%)	CRT	90	88	85	91	77
	CRT-D	94	93	86	93	82
	CRT-P	64	57	79	77	51
QRS ≥ 120 ms at implant (%)	CRT	93	85	93	89	86
	CRT-D	92	86	95	89	90
	CRT-P	96	79	79	84	70
AF at implant (%)	CRT	15	17	15	13	18
	CRT-D	16	16	14	13	17
	CRT-P	4	18	27	15	28

AF, atrial fibrillation; CRT, cardiac resynchronization therapy; HD, heart disease; LVEF, left-ventricular ejection fraction; NYHA, New York Heart Association.

Fig. 1



Implant rates of CRT devices (CRT-D + CRT-P) among the nine provinces of Emilia-Romagna region, standardized per age and sex. CRT, cardiac resynchronization therapy.

region for every year in the period 2006–2010 (Table 4). As shown, the proportion of patients implanted with CRT ranged between 0.23 and 0.3% of prevalent cases.

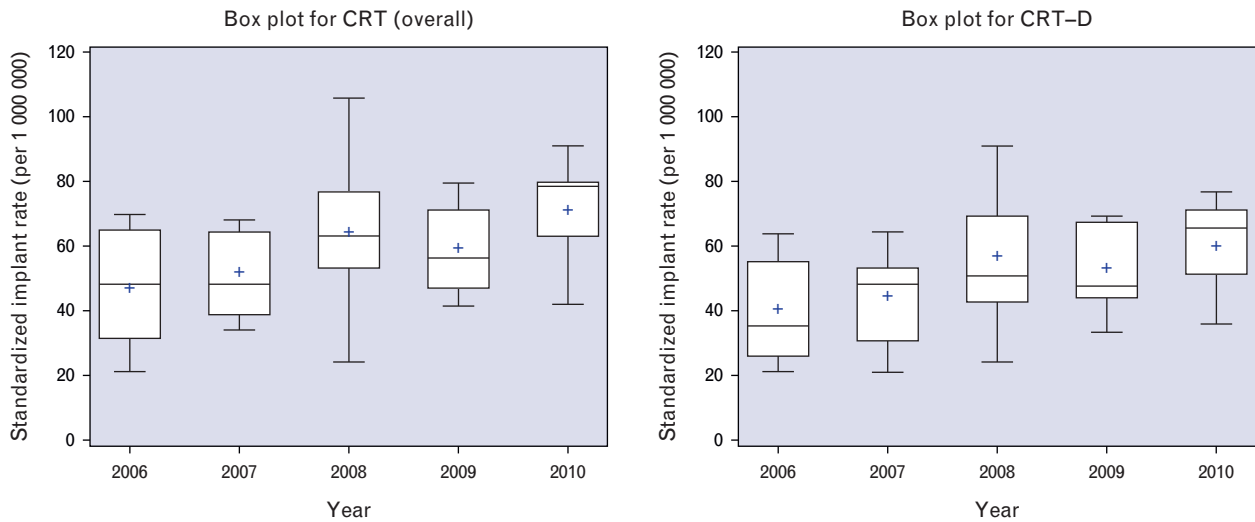
### Discussion

Cardiac resynchronization therapy is an effective treatment for selected patients with heart failure, and is increasingly used in selected patients with heart failure, according to consensus guidelines.<sup>12–14</sup> In our Italian region, we found a 71% increase in CRT implants in 2010 versus 2006, which is similar to the 75% increment in 2008 versus 2004 reported by van Veldhuisen *et al.*<sup>12</sup> on the basis of Eucomed data. However, implementation of CRT requires a series of actions, such as identification of the potential candidate fulfilling current criteria for implant, optimization of pharmacological treatment, referral to a centre specialized in interventional electrophysiology and, last but not least, a successful implant procedure. In view of the chain of processes required for a

CRT implant, it is not surprising that only a very small proportion of heart failure patients are treated with a CRT device. In the present study, we considered 1100 CRT devices implanted in our region in the years 2006–2010, and we calculated that the implant rate referred to a population of patients with prevalent heart failure, with the result that only around 0.3% of patients received CRT during the observation period. Our selection of prevalent heart failure was based on administrative data, which is a validated method<sup>10</sup> and led to a calculation of heart failure prevalence in line with the literature;<sup>15,16</sup> however, this method did not make it possible to assess what proportion of patients could be eligible for CRT according to guidelines, since clinical, electrocardiographic and echocardiographic data were not available.

Most of the available studies assessing CRT in relationship with heart failure epidemiology evaluated the

Fig. 2



Box-plots showing mean (symbol plus), median and interquartile ranges of standardized implant rates (per 1 000 000 inhabitants) for all the provinces. Data on overall implants and on CRT-D implants (on the left side and on the right side, respectively) are shown.

eligibility for CRT or the actual rate of CRT implants related to incident heart failure, in more or less selected settings.<sup>4,6,17,18</sup> In the study by McAlister *et al.*,<sup>17</sup> evaluating the number of patients with incident heart failure in a group of 103 Canadian hospitals, only 34 patients out of 9943 unselected patients admitted with a confirmed diagnosis of heart failure (0.3%) fulfilled strict criteria for eligibility for CRT. By analysing patients discharged after hospitalization for heart failure or followed in specialized cardiology clinics, it has been estimated that around 10% of patients have the indication for implanting a CRT device.<sup>4,6</sup> However, as a matter of fact, we do not yet know the optimal rate of CRT implants.<sup>3</sup> Considering that the overall prevalence of heart failure is increasing, because of the ageing of the population, planning of health services and policy making suggests the opportunity for further studies assessing CRT needs in relationship with prevalent heart failure.

The present study shows that an important variability in implant rates of CRT devices exists even within a region with a relatively high standard for delivery of healthcare services. The extent of variation in implant rates among the provinces of the Emilia-Romagna for CRT devices tends to be higher than that previously found for implantable cardiac defibrillators (ICDs) in the same region for years 2006–2008.<sup>9</sup> This may be related to a series of differences that exist between the two types of electrical therapy: implant of a CRT device is more technically challenging and with potential complications that make it less attractive for centres with a low volume of implants<sup>19,20</sup>; referral of candidates to CRT requires a strict connection between heart failure specialists and electrophysiologists and functional networks need organizational planning<sup>8,21</sup>; the cost of CRT-D devices is much higher than for conventional ICD devices (single and dual chamber) and in the setting of budget

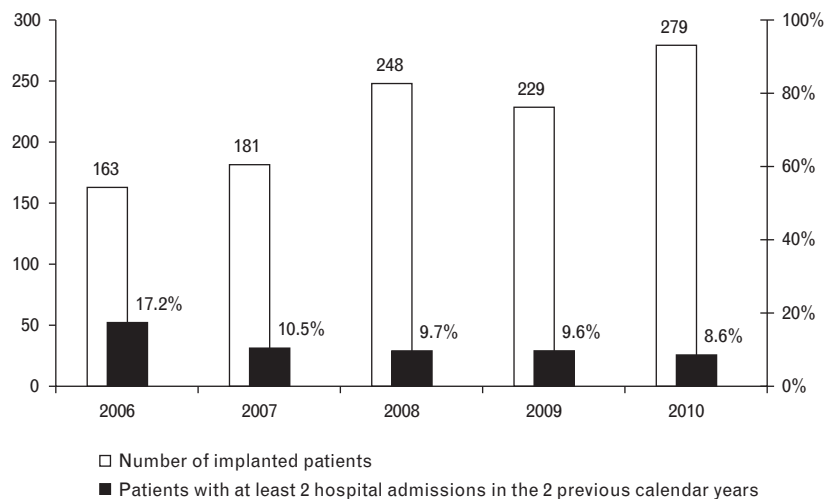
Table 3 Implant rates for CRT-D devices, standardized according to age and sex (per 1 000 000 inhabitants)

Province	Standardized implant rates for CRT-D devices				
	Year 2006	Year 2007	Year 2008	Year 2009	Year 2010
Piacenza	52.1	30.7	38.6	68.6	55.2
Parma	56.4	53.2	86.1	67.5	76.6
Reggio Emilia	26.4	20.9	48.0	33.6	51.3
Modena	35.0	53.6	91.2	69.3	71.0
Bologna	55.0	63.2	69.5	65.5	69.9
Ferrara	63.9	64.4	63.3	47.6	73.4
Ravenna	26.3	30.4	42.6	38.9	65.5
Forlì-Cesena	31.6	37.2	24.4	45.6	35.7
Rimini	21.2	48.2	50.8	44.1	44.3
Max/min implant rate ratio	3.0	3.1	3.7	2.1	2.1
Entire Emilia Romagna region	42.6	47.5	61.4	55.7	62.8

CRT, cardiac resynchronization therapy.



Fig. 3



Number of CRT devices implanted per year (white columns) and proportion of implants performed in patients with at least two hospitalizations for heart failure in the two previous calendar years (black columns). The number of patients corresponding to each percentage is also shown. CRT, cardiac resynchronization therapy.

limitations some rationing may occur, even despite the favourable cost-effectiveness profile.<sup>22–24</sup>

It is well known that several barriers (cultural, organizational, financial, technical, etc.) may affect implementation of guidelines for device therapy<sup>22,25</sup>; what emerges from this study is that implementation of CRT may show some differences from implementation of single or dual-chamber ICDs and that a detailed analysis of a real world practice should keep these two types of device therapies separate. In this perspective, analysis of registries may be the basis for proposing clinical audits and, when necessary, to promote organizational changes and more appropriately defined clinical pathways for patient management and referral, as suggested by the important financial burden linked to heart failure.<sup>26</sup> Appropriate implementation of guidelines in clinical practice is a topical issue and several regulatory institutions are evaluating the appropriateness of indications in the ‘real world’. In our region a clinical audit on a sample of cardiac device implants (385 implants) was promoted by the regional health authority in 2010 and carried out in every regional electrophysiology laboratory. The audit results did not reveal cases of inappropriate procedures, according to consensus guidelines recommendations, and showed a high number of procedures (86%) performed

according to class I recommendations together with a small minority (14%) according to class II.

The regional authorities of our Region launched the present Registry to monitor the activity of interventional electrophysiology, practised according to National and International guidelines. Adoption of CRT in the real world has been the subject of surveys and analysis of registry data, both in the US and in Europe,<sup>4–6,27</sup> in line with a general interest in outcome research, quality of care and comparative effectiveness.<sup>28,29</sup> In several reports on CRT, an important variability in implant rates was described, by comparing different regional areas or different hospitals,<sup>4–6,18</sup> but data are lacking on implantation rates of CRT devices per resident population, an important source of information for resource allocation and policy making. However, even if the global picture is not fully clear, it appears that there is a need to make the access to CRT more equitable for those patients who can obtain clinical benefit in terms of symptoms and outcome. On the basis of the efficacy shown by RCT, a substantial improvement in the outcome of heart failure patients has been predicted by using evidence-based therapies, including CRT for appropriate patients.<sup>30</sup> It is noteworthy to consider that, in an analysis of ‘real world’ Medicare beneficiaries, Epstein *et al.*<sup>31</sup>

Table 4 Prevalent cases of HF in the Emilia Romagna region and implant rate of CRT devices

	2006	2007	2008	2009	2010
Overall population ≥18 years	3 589 860	3 625 798	3 670 044	3 711 375	3 737 396
Prevalent cases of HF	77 912	82 709	86 551	89 915	93 492
Prevalent cases of HF per 100 inhabitants	2.2	2.3	2.4	2.4	2.5
CRT implants rate on prevalent cases of HF per 100 inhabitants	0.23	0.24	0.29	0.26	0.30

CRT, cardiac resynchronization therapy; HF, heart failure.

recently reported that geographic areas with greater increases in ICD/CRT-D utilization from 2002 to 2007 showed greater reductions in heart failure mortality rates.

The indications for CRT have expanded in recent years, extending to mild heart failure,<sup>3,16</sup> but European registries showed how this indication was, in part, already applied.<sup>20,27</sup> This evolution of CRT corresponds to a different perspective, linked to improvement of patient outcome through prevention of heart failure progression rather than through improvement in functional status and reducing the hospitalization burden. In our registry, the use of CRT increased along with time during the 5-year observation period. However, the proportion of patients with repeated hospitalization for heart failure (around 17% of implanted patients in year 2006) progressively decreased. This is in line with the changing trend in clinical use of CRT, extending from advanced heart failure (NYHA III–IV, consequently with a relatively high chance of previous hospitalizations for heart failure) to mild heart failure (NYHA II).<sup>3</sup> Similarly to other registries,<sup>21</sup> the present study shows how implant of CRT devices in NYHA II patients was applied in clinical practice even before the publication of REVERSE (REsynchronization reVERSe Remodeling in Systolic left vEntricular dysfunction) and MADIT CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trials.<sup>3</sup>

Cardiac resynchronization therapy can be delivered by using devices with or without defibrillation capabilities. In our analysis of 1100 CRT devices implanted in a 5-year period, we found that the ratio of CRT-D versus CRT-P was markedly in favour of the former type of device, a constant finding when comparing Italy to other European countries such as Sweden and Belgium, where an inverse relationship between CRT-D and CRT-P is found.<sup>8,14</sup> Both the EHRA (European Heart Rhythm Association) White Book<sup>14</sup> and the specific analysis reported by Merkely *et al.*<sup>13</sup> show important differences in implant rates of both CRT-P and CRT-D devices across Europe, and in CRT-D/CRT-P implants ratio, without a strict relationship with indices reflecting national financial status. Although financial and reimbursement issues may play an important role in analysis based on comparison between different countries, their role is probably less important for areas belonging to the same region.<sup>24</sup> In our analysis, we found a change in the trend in year 2010 (relative increase in CRT-P implants) that needs to be confirmed in subsequent years and that may be explained by increasing financial pressures on cost control. As a matter of fact the cost of a CRT-D device is usually between two and three times that of a CRT-P device and no direct comparison of the cost-effectiveness estimates for CRT-P and CRT-D in NYHA class III-IV patients is available.<sup>32</sup> The choice between CRT-P and CRT-D should be based on a tailored judgment regarding the patient's clinical profile, in conjunction

with current evidence on the added benefit of defibrillator treatment, together with cost-effectiveness considerations coupled with appropriate discussion between the patient, implanting electrophysiologist, heart failure specialist and referring physician, with the aim of a tailored decision-making.<sup>32</sup>

The present study has a series of obvious limitations, related to its observational nature and the limited clinical data available for the population with prevalent heart failure taken into consideration. The methods used to calculate heart failure prevalence, even if validated,<sup>10</sup> may lead to overestimation of prevalent cases, since we included both primary and secondary discharge diagnosis of heart failure in order to achieve a high sensitivity.<sup>33</sup> Another limitation is that administrative data based on hospital discharge may lack the clinical accuracy needed for surveillance of certain disease states, particularly chronic diseases such as heart failure which are also managed on an outpatient basis.

In conclusion, cardiac resynchronization therapy is a treatment for selected patients affected by heart failure whose application in 'real world' clinical practice is quite heterogeneous, with substantial variability even among areas belonging to the same region. There is a need to make the access to this treatment more equitable for those patients who can obtain clinical benefit in terms of symptoms and outcome. Despite the increased use of CRT over time in the years between 2006 and 2010, its overall rate of adoption is low, if a population of prevalent heart failure is selected on the basis of administrative data on hospitalizations.

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