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Original article

Cross-sectional Study of Cardiac Resynchronization Therapy in Spain. Indications, Implant Techniques, Optimization and Follow-up

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ABSTRACT

Introduction and objectives: A cross-sectional study of cardiac resynchronization therapy use in Spain was performed to analyze problems with indications, implantation, and patient follow-up.
Methods: Spanish cardiac resynchronization therapy implanter centers were identified, then the department members were surveyed and the data were recorded by each implantation team.
Results: Eighty-eight implanter centers were identified; of these, 85 (96.6%) answered the survey. A total of 2147 device implantations were reported, comprising 85.6% of the overall number of 2518 implantations estimated by the European Confederation of Medical Suppliers Associations for the same period. The reported implantation rate was 46 per million inhabitants versus an estimated implantation rate of 51 per million (European average, 131). Cardiac resynchronization therapy devices accounted for 84% of implantations, and upgrades to previously implanted devices, 16%. The majority of cardiac resynchronization therapy devices were implanted in men (70.7%). The mean age was 68 (12) years, and the mean left ventricular ejection fraction was 26.4% (5%). Most patients (67%) were in New York Heart Association functional class III. The group of patients for whom cardiac resynchronization therapy was indicated according to the latest update of the guidelines was significant: 17.3% among New York Heart Association class II patients and more than 21.6% among patients with atrial fibrillation. In all, electrophysiologists accounted for 73.8% of implanters, followed by surgeons, accounting for 21.4%.
Conclusions: The latest update of the guidelines is being progressively implemented in Spain, according to data obtained in patients in New York Heart Association class II or with atrial fibrillation. Nevertheless, the number of cardiac resynchronization therapy device implants is still well below the European average.
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Análisis transversal de la resincronización cardiaca en España. Indicaciones, técnicas de implante, optimización y seguimiento

Palabras clave:
Insuficiencia cardiaca
Marcapasos
Desfibrilador

RESUMEN

Introducción y objetivos: Realizar un estudio transversal de la terapia de resincronización cardiaca en España, analizando los problemas en las indicaciones, el implante y el seguimiento del paciente.
Métodos: Identificar los centros españoles que realizan implantes de resincronización solicitando un cuestionario (septiembre de 2010 a septiembre de 2011) a cada equipo.
Resultados: Se identificó un total de 88 centros, de los que 85 (96,6%) cumplimentaron la hoja de recogida de datos. El número de implantes de resincronizador (marcapasos o desfibriladores) fue de 2.147 (el 85,6% del total estimado de 2.518 por la *European Confederation of Medical Suppliers Associations* en ese periodo). El número de implantes/millón de habitantes comunicados fue 46 y el estimado, 54 (media en Europa, 131). Los implantes/recambios de resincronizador suponen el 84% y las mejoras del modo de estimulación *upgrade* de dispositivos previos, un 16%. La mayor parte de los resincronizadores se implantaron en varones (70,7%), con medias de edad de 68 ± 12 años y de fracción de eyección ventricular izquierda del 26,4 ± 5%. La mayoría de los pacientes (67%) estaban en clase funcional III de la *New York Heart Association.* El grupo de pacientes con nueva indicación según la última actualización de guías es ya significativo, con el 17,3% entre los pacientes en clase II y el 21,6% de los pacientes con fibrilación auricular. El 73,8% de los implantadores son electrofisiólogos, seguidos por los cirujanos (21,4%).

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Conclusiones: Las nuevas indicaciones recomendadas se están implantando progresivamente según los datos obtenidos en pacientes en clase II o fibrilación auricular. Sin embargo, el número de implantes de resincronizador en España aún está lejos de la media europea.
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Abbreviations

CRT: cardiac resynchronization therapy
ICD: implantable cardioverter-defibrillator

INTRODUCTION

Cardiac resynchronization therapy (CRT) has proven to be effective for the treatment of patients with acute heart failure and wide QRS complex.[1–4] This article analyzes various aspects such as activity, as well as variables such as adherence to the latest update of the clinical guidelines, problems with their implementation, patient selection, CRT implantation and techniques, optimization, and follow-up data on patients with CRT therapy. We also report on CRT implants carried out between September 2010 (date of the latest guidelines) and September 2011. Most hospitals performing CRT implantation in Spain (appendix) participated in the survey. These data allowed us to compare and analyze differences between Spain and other European countries and to identify differences among the autonomous communities.

METHODS

All data were obtained using a 59-question survey. Fieldwork was undertaken to identify all hospitals in each autonomous community that performed CRT device implantation. The fieldwork included all public and private hospitals that volunteered to participate and had an organized system for CRT implantation; hospitals with only sporadic activity were not included. A member from each implanter team voluntarily completed the survey, and the information was introduced into a specially created database. A contract statistician handled the anonymous statistical analysis of the data. The authors of this article were responsible for analyzing the data or reviewing the article and are responsible for its publication.

The population data used to calculate rates per million inhabitants for both Spain and the Spanish autonomous communities were obtained from estimations at 1 January 2011 by the Spanish National Institute of Statistics *(Instituto Nacional de Estadística)*.[5] For European populations, the US Census Bureau[6] was used. To estimate data representativity, we calculated the percentage of CRT devices shipped compared with the total number of devices implanted in Spain during the same time period. This number is based on data reported by CRT marketers to the European Confederation of Medical Suppliers Associations (EUCOMED),[7] with small variations due to the different methods and times of quantitation. The percentages for each of the variables analyzed were calculated from the total number of implanters reporting information on the variable.

Statistical Analysis

The continuous variables are expressed as no., mean (SD) (minimum-maximum), and median 25th percentile- 75th percentile. The categorical variables are expressed as frequency and percentage. IBM® SPSS® v. 20 was used for the statistical analysis.

RESULTS

Implanter Centers

A total of 88 CRT implanter hospitals/teams were identified; 85 (96.6%) answered the survey. Of these, 78 were public hospitals and 7 were private. The Table lists the number of implanter hospitals and the number of implants according to autonomous community, as well as the rate per million inhabitants. The results described correspond to the analysis of this sample, which we believe is closely representative of all current CRT therapy in Spain.

Sample Analyzed

The total number of CRT device implants (first-time implants, replacements, CRT with/without implantable cardioverter-defibrillator [ICD]) reported was 2147 (621 pacemakers and 1486 ICD). According to EUCOMED data, 2518 devices (1833 ICDs and 685 pacemakers-CRT) were implanted during the same period (October 2010-September 2011), accounting for 85.6% of all implants in Spain. Therefore, based on the National Statistics Institute population census of 46 162 024 inhabitants for 2011, the total number of implants per million inhabitants reported was 46. According to EUCOMED, the total number of implants per million

Table
Autonomous Community Where the Cardiac Resynchronization Therapy Devices Reported Were Implanted, Number of Implanter Centers, Number of Implants, and Units per Million Inhabitants

	Implant centers, No. (no./million inhabitants	Units	Units/ million inhabitants
Total for Spain	87 (1.88)	2147	46
Andalusia	14 (1.69)	373	45
Aragon	2 (1.52)	21	15
Principality of Asturias	1 (0.94)	29	27
Balearic Islands	3 (2.73)	43	39
Canary Islands	4 (1.89)	87	41
Cantabria	1 (1.73)	51	88
Castile and León	6 (2.42)	130	52
Castile-La-Mancha	5 (2.44)	65	31
Catalonia	9 (1.23)	265	36
Valencian Community	10 (1.99)	289	57
Extremadura	2 (1.85)	64	59
Galicia	4 (2.73)	58	21
Community of Madrid	18 (2.82)	414	64
Region of Murcia	2 (1.36)	52	35
Chartered Community of Navarre	2 (3.21)	72	115
Basque Country	5 (2.35)	131	61
La Rioja	1 (3.2)	8	26

Some of the differences among various autonomous communities are explained by patient referrals between the communities, rather than underusage of the therapy.

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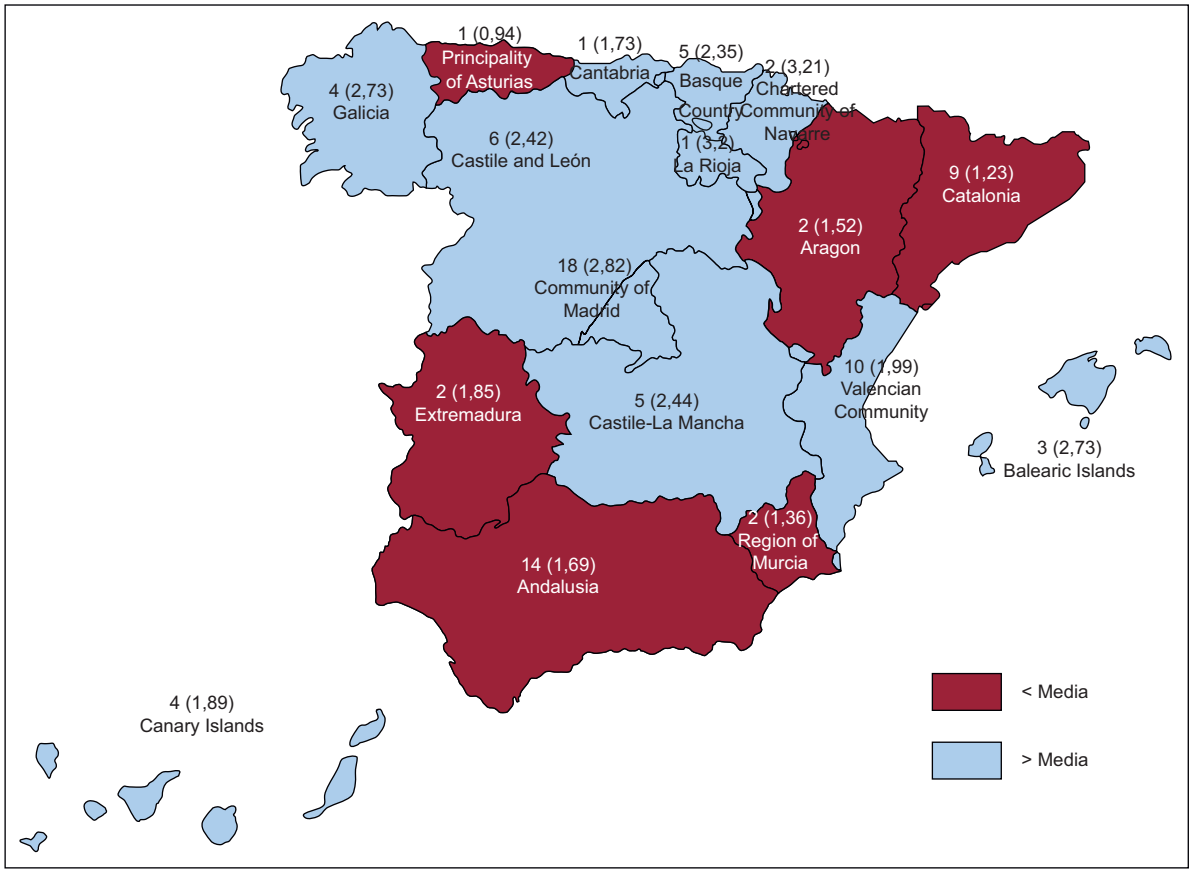

Figure 1. Number of implanter centers (centers per million inhabitants) according to autonomous community.

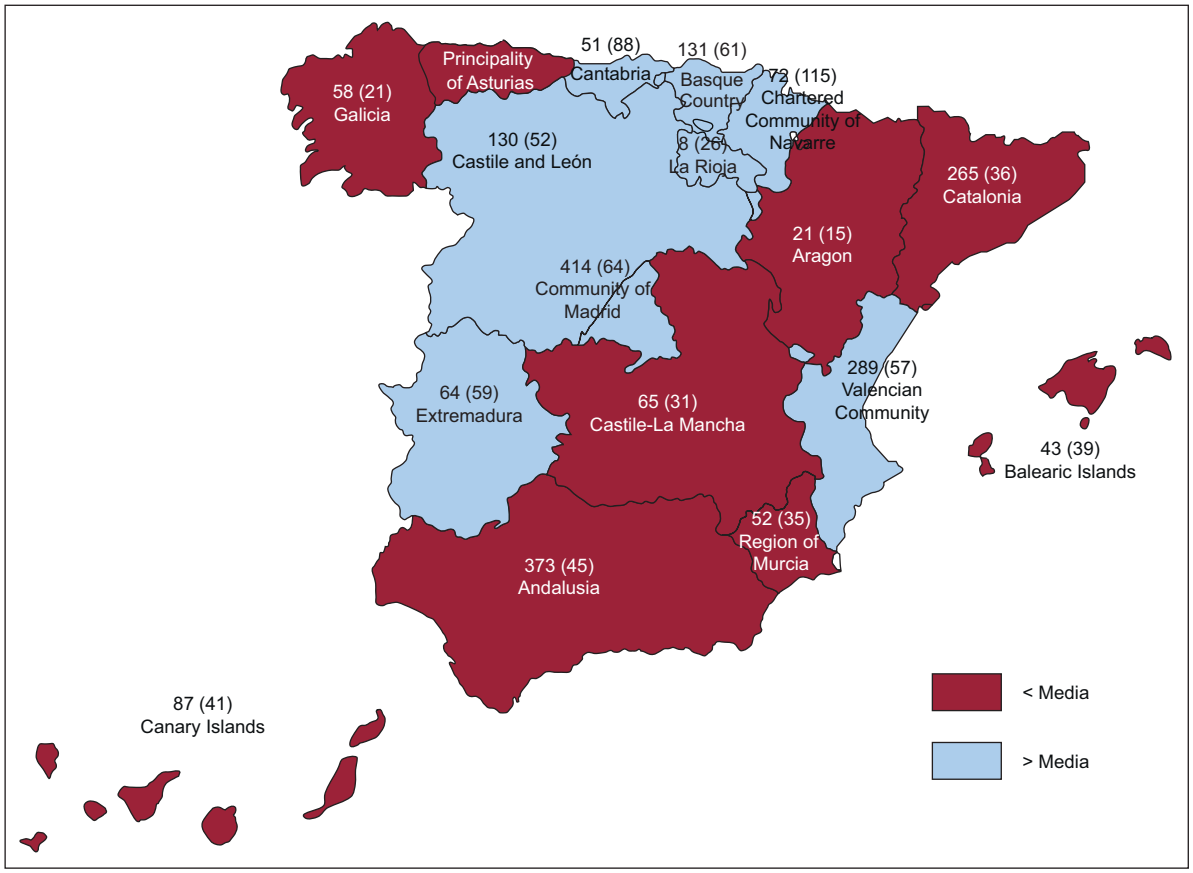

Figure 2. Number of implants (rate of implants per million inhabitants) according to autonomous community.

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inhabitants was 54. Figures 1 and 2 show the number of implanter centers and the number of implants according to autonomous community and the number of implants per million inhabitants. Most implants reported were carried out in public hospitals (2028, 94.4%), and the mean number per hospital in Spain was 27 (21) implants. In the series, upgrades to an improved pacing mode accounted for 16.3% (10.6%), representing a substantial percentage of the total number of devices.

The main reason for the low rate of inclusion in Spain was improper referral of patients (94% of hospitals reported that patients are not referred), and other hospitals report budgetary restraints. A lack of confidence in the usefulness of CRT was reported by fewer than 12% of hospitals. Less than half the hospitals receive patients from other health areas, and 71% (21%) of patients are from the same health area. To increase the number of implants, most hospitals have proposed that the bulk of continuous training funds be used for courses that target the referring physicians (consistent with answers to similar questions) who acknowledge that CRT is not sufficiently recognized, a fact they believe explains the low rate of implants per million inhabitants.

Patient Selection

CRT device implants continue to be indicated primarily in men (70.7%), possibly consistent with the higher incidence of ischemic heart disease and systolic dysfunction in this group. The mean left ventricular ejection fraction was 26.4% (5%), being 28.2% (5%) in patients with pacemakers and 24.7% (6%) in patients with ICDs. The mean patient age was 68 (12) years. Because of the age distribution of the Spanish population, a large majority (63.96%) of patients were between 60 and 80 years of age and very few implantations (5.3%) were performed in patients younger than 40 years of age (Fig. 3). Implantation in patients older than 80 years of age is widely accepted by most hospitals in Spain (n=59); however, little more than 6% of these patients undergo this procedure, perhaps due to more numerous comorbidities and lower life expectancy. In this population group, a higher rate (76.6 [30.4]) of pacemaker implants was observed, which practically reverses the pacemaker/defibrillator ratio observed in the group as a whole.

Most patients had an ischemic (48%) or idiopathic (46%) etiology, and CRT was indicated for valve disease or congenital heart disease in only a few patients. The majority of patients (67%) were in sinus rhythm (Fig. 4), and the indication of atrial fibrillation accounted for 19%. Likewise, most patients (76.5%) had left bundle-branch block, followed by right bundle-branch block in 4.3% of patients and abnormal intraventricular conduction in 6.7%; all others were paced (Figs. 5–7).

A total of 18 hospitals reported that they currently consider CRT to be indicated in patients with narrow QRS and mechanical asynchrony, an indication not within the latest clinical guidelines; these 18 centers account for almost 20% of hospitals, but for a much lower percentage of patients. The same observation was made regarding the number of hospitals (n=27) that perform CRT in patients with a standard indication for cardiac pacing, which means, among other things, a greater acceptance of CRT in these patients. In terms of QRS complex duration, although a significant number of hospitals acknowledged in previous questions that they consider CRT to be indicated in narrow QRS with mechanical asynchrony, in reality this indication accounted for a very low percentage of patients (2.1%). The largest (48.2%) group had a QRS complex duration of 150 ms-200 ms; 30.6% had QRS 120 ms-150 ms, and only 5.7% had QRS >200 ms (Fig. 8).

Implantation Tools and Techniques

In Spain, CRT devices are most commonly implanted by electrophysiologists (73.8%), followed by cardiac surgeons (21.4%) and pacemaker specialists (8.3%); other specializations (interventional cardiologists, catherization specialists, and vascular surgeons) account for a lower percentage. The total sum exceeds 100% because various specializations perform the procedure in some hospitals.

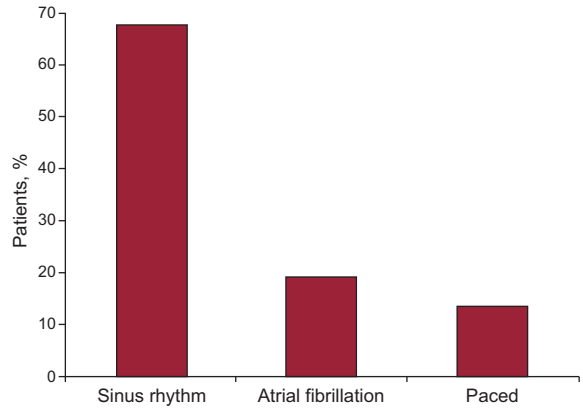

Figure 4. Rhythm of patient receiving cardiac resynchronization therapy.

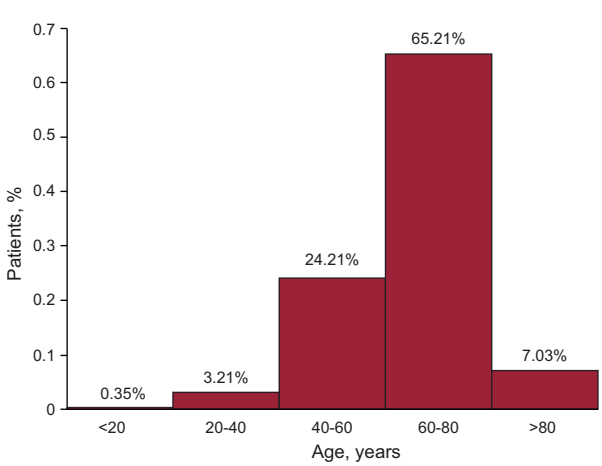

Figure 3. Histogram of the number of cardiac resynchronization therapy implants according to age bracket.

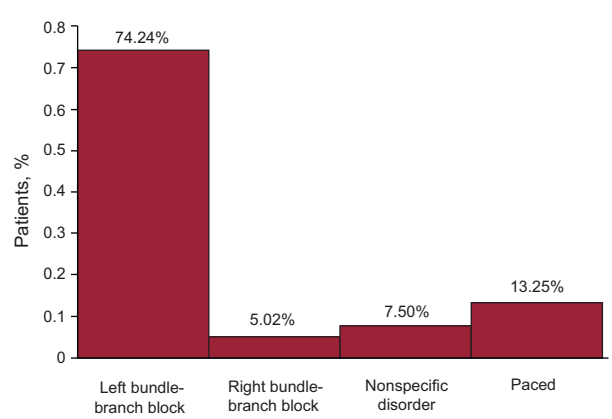

Figure 5. Distribution of patients (n=2069) and electrocardiographic disorder.

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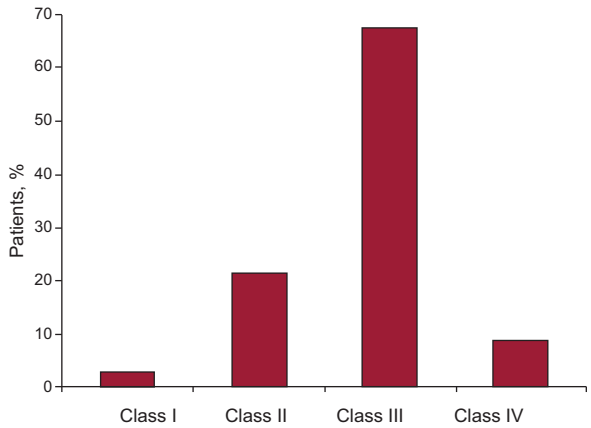

Figure 6. Distribution of patients and New York Heart Association functional class.

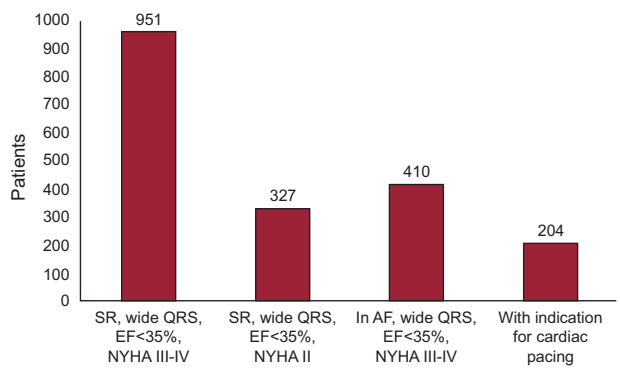

Figure 7. Histogram of the clinical profile of patients receiving cardiac resynchronization therapy (n=1892) as per guidelines. AF, atrial fibrillation; EF, ejection fraction; NYHA, New York Heart Association; SR, sinus rhythm.

The duration of implantation was considerably shortened from the initial times for the techniques, and the mean procedure time in Spain is currently 121.9 (38.7; range, 55-240) min. Epicardial (surgical) implants are used in many hospitals (32%), and the transseptal route is used in only a few (4.7%). The mean percentages of pacemakers and ICDs implanted in each hospital were 33.3% and 66.6%, respectively.

In terms of the implant system, 51.1% of hospitals stated that the main technical obstacle for an initial implant was lead introduction in the selected vein, followed by stability (26% of hospitals), and lastly, coronary sinus canalization and catheter guide withdrawal. For coronary sinus cannulation, 45.2% of hospitals use a catheter guidewire with an electrophysiology catheter support and 42.8% use only a catheter guidewire.

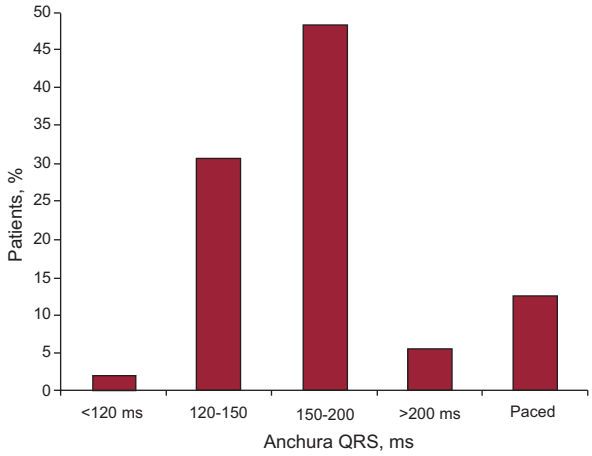

Figure 8. QRS complex width in patients who received a cardiac resynchronization therapy device.

Most hospitals (82%) do not routinely use specific subselectors for vein selection, but only when the vein is not directly cannulated. Only 13% of hospitals use them in their usual procedure. Venoplasty of a vein that does not allow the lead to be initially advanced is also nonroutine: 82% of hospitals never perform venoplasty and select another, technically more favorable vein, and 13% reported that they perform this procedure only occasionally. Regarding the lead cables, 70.2% of hospitals initially use a bipolar lead for introduction in the selected coronary vein, 32.1% use a quatripolar lead, and 5.9% use an "active fixation" lead. The right ventricular lead is also placed differently in the various hospitals. The final site of the right electrode was high septal in 7.3% of hospitals, medioseptal in 20.1%, and the classic apical site in 72.7%. Thus, 38% of hospitals reported the use of alternative implant sites for the right ventricle and 62% did not.

Most hospitals (72.6%) do not use any method to enhance siting for left pacing before implantation, for example, to assess viability or scarring. Echocardiography is used for this purpose by 14.2% of hospitals, computed tomography by 4.7%, and magnetic resonance imaging by 9.5%. Regarding lead placement in the left ventricular vein as assessed by the question, "How satisfied are you with final lead placement?", 60.4% rated the site as optimal, 29.3% as adequate, and 10% as suboptimal. The final site of the left ventricular lead in each vein stated was anterior in 2.15%, anterolateral in 13.1%, lateral in 42.4%, posterolateral in 45.1%, and middle cardiac vein in 2.1% of patients.

Management of Patients in Atrial Fibrillation

In the case of implants in patients with atrial fibrillation, a wide variety of answers were received from all groups (Fig. 9). Some hospitals (27.4%) implant 3 catheters including the atrium and perform electrical cardioversion, while others (9.5%) implant 2 and use cardioversion, and implant an atrial catheter if sinus rhythm is maintained. However, most (42.8%) implant 2 directly in the right and left ventricles. Another large group (21.4%) use individualized treatment according to clinical characteristics. A large majority of hospitals (63%) do not routinely perform node ablation in all patients in atrial fibrillation, but only when clinically indicated; however, 5.9% generally perform the procedure in all patients with atrial fibrillation who receive a CRT device. Patients in atrial fibrillation at the time of implantation who achieved sinus rhythm over their clinical course accounted for 0%-20% of the total (mean, 11.1 [10%]).

Perioperative Complications of Cardiac Resynchronization Therapy Device Implantation

The reports of complications were generally few, but included procedural mortality (0.3% [1.5%] and hemorrhage in the pacemaker pocket (6.1% [7.1%]) as the most common, as well as pneumothorax, cardiac tamponade/pericardial effusion, hemothorax, coronary sinus dissection, phrenic nerve pacing, and lead dislodgement.

Postimplantation Programming and Follow-up

In terms of device optimization following implantation, most hospitals (54.7%) evaluate QRS complex width and set the VV and atrioventricular intervals using this information, but 27.3% use the

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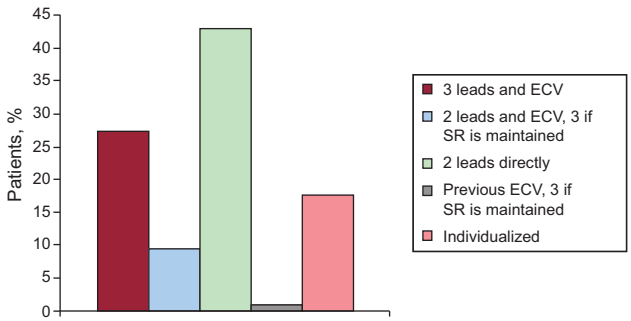

Figure 9. Management of patients in atrial fibrillation. ECV, electrical cardioversion; SR, sinus rhythm.

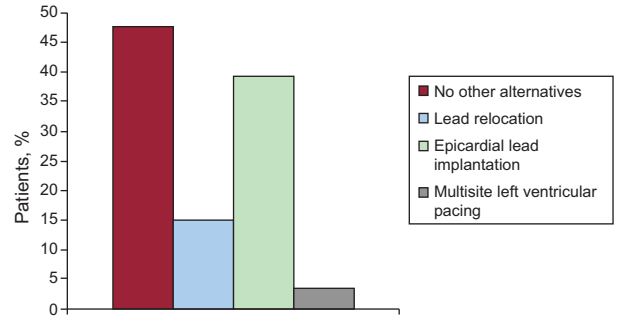

Figure 10. Alternative treatment for cardiac resynchronization therapy nonresponders.

automatic algorithms provided by some devices. A large group (19%) keeps the parameter within nominal parameters and performs optimization only when necessary, while another group (27.3%) performs echocardiographic optimization.

In most hospitals, the implanter group also provides clinical follow-up of the patient (67.8%). The CRT responder rate observed in Spanish hospitals is 73.8 (9%). This benefit was observed in patients immediately after CRT implantation in 17.8%, at 1 month in 50%, after 6 months in 15.4%, and at no time point in 21.4%. For nonresponders ineligible for transplantation, 47.6% of hospitals acknowledge no alternatives other than medical therapy optimization (Fig. 10). However, 15.4% resite the lead at an alternative site, and many perform an epicardial (surgical) procedure if the lead cannot be placed in a lateral vein, considered ideal or if the vein does not exist (39.2%). Only a few groups perform multisite pacing (2 in the left ventricle) (3.5%).

Late Complications

Regarding late complications observed with CRT, most centers acknowledge a significant percentage of inappropriate shocks in patients with an ICD-CRT device as primary prevention (8.4 [6.7%]). Lead dislodgement and phrenic nerve pacing were virtually the only late complications of the left ventricular lead that were reported.

Remote Patient and Device Management

Patients using a device that allowed remote monitoring had the following distribution: fewer than 10% of patients at 36.9% of hospitals, 10%-40% of patients at 17.8% of hospitals, 40%-60% of patients at 9.5% of hospitals, 60%-80% of patients at 7.1%[5] of hospitals, and more than 80% of patients at only 22.6% of hospitals. However, the hospitals that use remote monitoring acknowledge that this modality has shortened visit intervals by 35.7%. These institutions believe that this has helped improve the prognosis in 21% of patients and to optimize programming in 20%. These data are subjective estimations that would have required an additional controlled study specifically designed for this purpose.

DISCUSSION

Activity Data Listed in the Register and Adherence to Clinical Guidelines

The number of CRT implanter centers has gradually increased in Spain up to the 88 identified: 24 hospitals reported 10 or fewer implants, 12 (14.2%) reported 50 or more implants/year, and no hospitals reported more than 100 implants per year. The total number of implants reported was 2147. Based on the EUCOMED data, the estimated total number is 2518, or more than 85% of the total number of implants in Spain. Dividing this number among all Spanish hospitals gives a mean of 27 (21) implants per hospital, a figure which reflects the wide dispersion of hospitals for a relatively low total volume compared with the European data. The main reason for the low rate of inclusion in Spain is improper referral of patients (patients are not referred) (Fig. 11). It should be stressed that information should be given to the primary healthcare physicians and internists who, along with cardiologists, follow these patients and refer them when needed. Most hospitals do not report an increase in the number of devices indicated following the publication of the new CRT clinical guidelines in 2010, probably because the indications of functional class II and in atrial fibrillation were already recognized, as observed in the 2008 European Register.[4] Although the new guidelines include recommendations on the type of device (pacemaker or ICD), most centers do not report an influence on the number of devices indicated.

Patient Screening

The management of patients with acute heart failure is increasingly complex and costly, precisely at a time of stronger budgetary restraints due to the economic crisis. This situation may compromise appropriate treatment for many patients, particularly for the use of new therapies. Cardiologists' skill in selecting ideal patients and improving efficiency is key. In our study, clinical evidence was the basis for most indications (eg, the presence of left bundle-branch block, sinus rhythm, and high functional class). As with all registers and clinical studies, it will always be extremely difficult to determine how many patients were unable to gain access to this therapy. Although many hospitals are currently using CRT in patients with narrow QRS complex and mechanical asynchrony and in patients with conventional cardiac pacing, the number of patients included by the hospitals for this reason is very low.

Management of Patients in Atrial Fibrillation

The management of patients in atrial fibrillation who receive a CRT device varies considerably in Spain, and most hospitals do not routinely perform node ablation in all patients in atrial fibrillation but only when clinically indicated. These data are certainly conditioned by the experience of each hospital in the percentage of patients who are in atrial fibrillation at the time of implantation and who achieve sinus rhythm over their clinical course.

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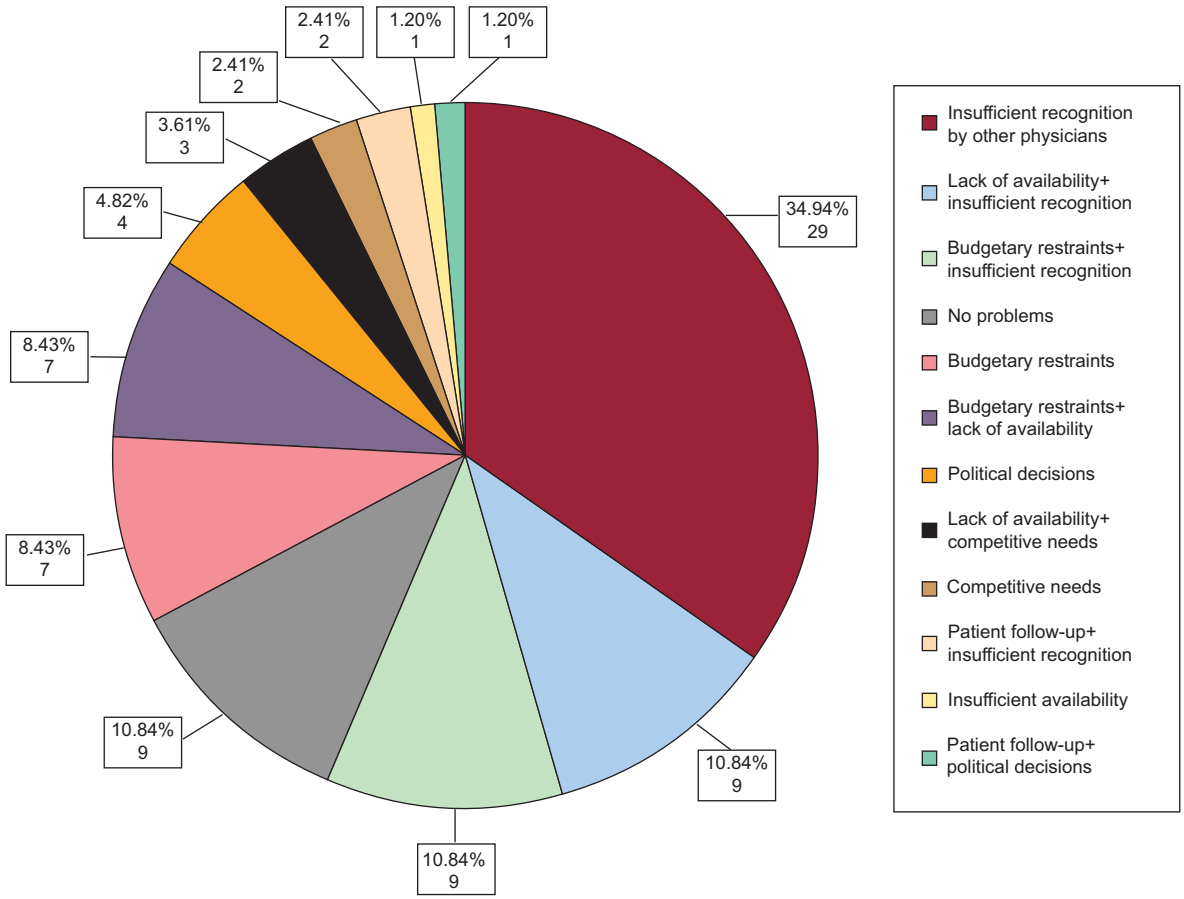

Figure 11. Main reasons for the low rate of inclusion in Spain. Multiple answers have been combined for greater understanding.

Postimplantation Programming and Follow-up

Most hospitals currently perform optimization by empirically considering only the QRS complex width and the atrioventricular interval. There is no evidence to recommend echocardiographic optimization of pacing intervals in all patients after CRT.[8–11] Empirical programming of the atrioventricular interval around 120 ms and the VV interval to achieve the narrowest QRS in the surface electrocardiogram appears to be adequate in terms of cost-effectiveness. Optimal pacing intervals vary over time as ventricular remodeling processes develop and also with changes in hemodynamic and sympathetic tone conditions occurring during exercise. Remote monitoring for the management of patients with CRT is still not widely used in Spain. However, the hospitals that use it acknowledge that they have greatly reduced visit intervals as a result and believe that the technique has enhanced patient improvement.

Comparison With European Data

The arrhythmia (European Heart Rhythm Association) and heart failure groups of the European Cardiology Society maintained a CRT register in Europe from November 2008 to June 2009.[4] This European register included 140 hospitals selected from 13 countries, with a total of 2438 patients, a figure probably well below 10% of implants performed in Europe. The mean age of patients included in this register was 70 years. In all, 78% patients were in New York Heart Association functional class III or IV and 22% were in class I and II. These figures are somewhat similar to our data, but are from 2 years earlier and precede the publication of large class II studies, probably because the experience of these hospitals (many of whom certainly participated in those studies) was already positive in this regard. The EUCOMED[7] data provide information on the number of implants and types of devices in Europe. The mean number of CRT implants is 131 per million inhabitants, including ICD-CRTs (100) and pacemaker-CRTs (31). Germany (175 implants/million) is the country with the highest number of implants, whereas Spain (51 implants/million) continues to rank last among the countries reporting data to EUCOMED. Figures were above the mean for Italy (200), the Netherlands (163), and the Czech Republic (163), but below the mean for Portugal (59) and Spain (51), among others.

Differences Among Autonomous Communities

Noticeable differences in the rate of implants were seen among the various autonomous communities. The mean rate estimated in this study was 46 per million inhabitants, with levels above the mean in the Chartered Community of Navarre, Cantabria, the Community of Madrid, Basque Country, Extremadura, the Valencian Community, and Castile an León, in that order. All others were below the mean: Andalusia, Aragon, the Principality of Asturias, the Balearic Islands, the Canary Islands, Castile-La Mancha, Catalonia, Galicia, the Region of Murcia, and La Rioja. As with other device implants, the differences can be partly explained by demographic differences in the population and by the number and extent of development of arrhythmia units in the various autonomous communities.[12–17]

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Limitations

Despite efforts to locate hospitals with an active CRT implant program, some hospitals may not have been identified. However, the total number of implants reported, which is similar to that reported by EUCOMED, suggest that the data presented are indicative of the actual situation in Spain. We have no information on patients assessed for CRT who did not receive an implant or on unsuccessful attempts at implantation.

CONCLUSIONS

The new indications recommended by the guidelines are gradually being implemented, according to data obtained from patients in class II or with atrial fibrillation. Nevertheless, the number of CRT device implants is still well below the European average. Further efforts are needed to ensure that this treatment reaches all potential patients in Spain who could benefit from it.

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CONFLICTS OF INTEREST

None declared.

APPENDIX. LIST OF PUBLIC AND PRIVATE HOSPITALS, ACCORDING TO AUTONOMOUS COMMUNITY, THAT PARTICIPATED AND PHYSICIANS WHO COMPLETED THE SURVEY

Andalusia	
Hospital de Jaén, Jaén	Rocio Cozar
Hospital Clínico Virgen de la Victoria, Malaga	Javier Alzueta
Hospital Nuestra Señora de Valme, Seville	Juan Leal
Hospital Costa del Sol, Malaga	F. Ruiz Mateas
Hospital Universitario Virgen del Rocío, Seville	A. Pedrote
Hospital Universitario Puerta del Mar, Cadiz	Lucas Cano
Hospital Universitario Virgen Macarena, Seville	Ernesto Diaz Infante
Hospital Carlos Haya, Malaga	Manuel Rodríguez
Hospital Clínico San Cecilio, Granada	Jose Miguel Lozano
Hospital Juan Ramón Jiménez, Huelva	Joaquín Barba
Hospital Universitario Reina Sofía, Cordoba	Amador López Granados
Hospital Torrecárdenas, Almeria	Franc Tornes
Hospital Virgen de las Nieves, Granada	Silvia López
Aragon	
Hospital Clinico Universitario Lozano Blesa, Zaragoza	Gonzalo Rodrigo
Hospital Universitario Miguel Servet, Zaragoza	Antonio Asso
Principality of Asturias	
Hospital Universitario Central de Asturias, Oviedo	José Rubin, David Calvo
Balearic Islands	
Hospital Son Llàtzer, Palma de Mallorca	Xavier Fosch Mur
Hospital Son Dureta, Palma de Mallorca	Carmen Expósito
Clínica USP-Palmaplanas, Palma de Mallorca	Antonio Berruezo
Canary Islands	
Hospital Universitario de Canarias, San Cristobal de La Laguna	Aníbal Rodríguez, Francisco Bosa

Appendix (*Continued*)

Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria	Eduardo Caballero Dorta
Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife	Rafael Romero, Julio Hernández
Hospital Universitario Insular de Gran Canaria, Las Palmas de Gran Canaria	Olga Medina
Cantabria	
Hospital Marqués de Valdecilla, Santander	Victor Exposito
Castile-La-Mancha	
Complejo Hospital Universitario de Albacete, Albacete	A. Sacristán
Hospital Nuestra Señora del Prado, Talavera de la Reina	Alfonso Macías
Complejo Hospitalario de Toledo, Toledo	Miguel Angel Arias
Hospital General de Ciudad Real, Ciudad Real	Javier Jimenez Diaz
Castile and León	
Hospital Universitario de León, Leon	Marisa Fidalgo, J.M. Glez Rebollo
Hospital General Yagüe, Burgos	Javier Garcia
Hospital Nuestra Señora de Sonsoles, Avila	A. Borasteros
Hospital Clínico Universitario de Valladolid, Valladolid	Jerónimo Rubio
Hospital Universitario del Rio Hortega, Valladolid	Diego Pérez, Benito Herrero
Complejo Hospitalario de Salamanca, Salamanca	Claudio Ledesma
Catalonia	
Hospital Universitari Germans Trias i Pujol, Badalona	Roger Villuendas
Hospital Sant Joan de Déu, Esplugues de Llobregat	Giorgia Sarquella
Hospital Clínic, Barcelona	Chema Tolosana
Hospital Universitari Joan XXIII, Tarragona	Alfredo Bardají
Hospital del Mar, Barcelona	Victor Bazan
Hospital de la Santa Creu i Sant Pau, Barcelona	Xavier Viñolas
Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat	Ignasi Anguera
Hospital Universitari Arnau de Vilanova, Lleida	F. Worner, J. Tomás, Berta Daga
Hospital Universitari Vall d'Hebron, Barcelona	Angel Moya, Jordi Pérez Rodón
Valencian Community	
Hospital Clínic Universitari, Valencia	Ricardo Ruiz Granell
Consorci Hospital General Universitari, Valencia	Aurelio Quesada
Hospital Universitari i Politècnic La Fe, Valencia	M.J. Sancho Tello, Chimo Osca
Hospital de Xàtiva, Xàtiva	Manuel Rodriguez Serra
Hospital General de Castelló, Castelló de la Plana	Jose Diago, Eloy Domínguez
Hospital Dr. Peset, Valencia	Llorens Miralles
Hospital Universitari Sant Joan d'Alacant, Sant Joan d'Alacant	Vicente Bertomeu
Hospital General Universitario de Alicante, Alicante	Juan Gabriel Martinez
Hospital del Vinalopó, Elche	Juan Antonio Fernández
Hospital de Torrevieja, Torrevieja	Miguel Godoy
Extremadura	
Complejo Hospitalario de Cáceres, Caceres	Javier Portales
Hospital Infanta Cristina, Badajoz	J. Fernandez de la Concha, J.J. Guerrero
Galicia	
Hospital Povisa, Vigo	María Vazquez

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Appendix (*Continued*)

Hospital do Meixoeiro, Vigo	Xulio Beiras Torrado
Hospital Juan Canalejo, A Coruña	L. Perez Alvarez, Enrique Ricoy
Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela	Javier Garcia Seara
Community of Madrid	
Hospital Central de la Defensa Gómez Ulla, Madrid	Miguel Rubio
Fundación Jiménez Díaz, Madrid	Jose M. Rubio
Hospital Universitario La Paz, Madrid	Jose Luis Merino, Jorge Silvestre, Rafael Peinado
USP Hospital San Camilo, Madrid	Concepción Moro
Hospital Ramón y Cajal, Madrid	A. Hernández-Madrid, R. Matía, Inmaculada Sánchez
Hospital Universitario de Getafe, Getafe	F.G. Cosío, Ambrosio Núñez
Hospital Severo Ochoa, Leganés	Angel Grande
Hospital 12 de Octubre, Madrid	María López Gil, Jesús Rodríguez
Hospital Clínico San Carlos, Madrid	Javier Moreno
Hospital Gregorio Marañón, Madrid	Felipe Atienza
Hospital Quirón, Madrid	José Angel Cabrera
Hospital de Sanchinarro, Madrid	Jesús Almendral
Hospital Puerta de Hierro, Majadahonda	Ignacio Fernández Lozano
Hospital de Fuenlabrada, Fuenlabrada	Joaquín Alonso, Alejandro Curcio
Region of Murcia	
Hospital Universitario Virgen de la Arrixaca, El Palmar	Arcadio García Alberola
Hospital de Lorca, Lorca	Jorge Silvestre
Chartered Community of Navarre	
Hospital de Navarra, Pamplona	José Ramón Carmona
Clínica Universidad de Navarra, Pamplona	Ignacio García Bolao
Basque Country	
Hospital Nuestra Señora de Aránzazu, San Sebastián	Tx. Porres
Hospital de Basurto, Bilbao	J.M. Ormaetxe, M. Fe Arcocha
Hospital de Galdakao, Galdakao	J. Zumalde
Hospital de Cruces, Baracaldo	Andrés Bodegas
Hospital Txagorritxu, Vitoria	José Ferrer
La Rioja	
Hospital San Pedro, Logroño	Diego Lorente

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