Original Article

Current status of implantable defibrillator devices in patients with left ventricular dysfunction — The first report from the online registry database

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Background: The current status of the efficacy of implantable cardioverter-defibrillator (ICD) and cardiac-resynchronization therapy with implantable defibrillator (CRT-D) in patients with left ventricular dysfunction needs to be clarified.

Methods and Results: From the Japanese Cardiac Device Treatment Registry database, a total of 1,584 patients who had an LVEF $\leqq$ 40% and had an ICD or CRT-D were selected as subjects in this study. The difference in the clinical characteristics between the primary and secondary prevention groups and the transition of the indications for device implantation over time were examined. Primary prevention gradually increased up to about 50% in all patients. The implantations of ICD/CRT-D for primary prevention in ischemic hear disease was significantly lower than that in dilated cardiomyopathy (33% vs 51%; $p < 0.0001$). The number of implantations for CRT-D for primary prevention increased dramatically over a one-year period.

Conclusions: In Japan, the implantable defibrillator devices for primary prevention was significantly lower in ischemic heart disease compared with dilated cardiomyopathy. Further, an extension of the indications for ICD/CRT-D implantations has recently been occurring, especially with CRT-D devices for primary prevention.
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Key words: heart failure, implantable cardioverter-defibrillator (ICD), cardiac resynchronization therapy, prevention, guidelines

Introduction

It is well known that implantable cardioverter-defibrillators (ICD) and cardiac-resynchronization therapy with implantable defibrillators (CRT-D) are useful for improving the prognosis and/or sudden cardiac death event rate in patients with heart failure and fatal ventricular arrhythmias.[1–3] Further, major recent mega-trials[4–8] performed in the USA and Europe have indicated that ICD/CRT-Ds also have improved the survival in patients with heart failure and even in those without a history of cardiac arrest and/or fatal ventricular arrhythmias.

In Japan, ICD was approved by the Japanese

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Ministry of Health, Labor and Welfare (MHLW) in 1996. The first guidelines for ICD were reported by the Japanese Circulation Society in 2001.[9] Cardiac-resynchronization therapy (CRT) and CRT-D were approved in 2004 and 2006, respectively. Further, the internet registry, the Japanese Cardiac Device Treatment Registry (JCDTR)[10,11] which was administered by the Japanese Heart Rhythm Society started simultaneously started. New guidelines set forth by the Japanese Circulation Society were begun in 2007,[12] and patients with an LVEF of less than or equal to 35%, drug resistant chronic heart failure (NYHA III/IV) with or without a history of fatal ventricular arrhythmias were classified as class IIa indication.[12]

However, the impact of introduction of CRT-D and the revision of guidelines for device implantations on the selection of shock device have not been examined in Japanese patients with heart failure. Therefore, the purpose of this study was to comprehend the current status of implantable defibrillator devices (ICD/CRT-D) in patients with left ventricular dysfunction and the indication for those on the basis of the data from the JCDTR.

Methods

The JCDTR Questionnaire consisted of three parts, implantation information, patient characteristics and pharmacologic treatment at the time of the implantation (**Table 1**). The data was collected by online registry using the university hospital medical information network (UNIM). Approval proceeding for this study was performed by each participating institution.

A total of 2,924 patients were enrolled into the JCDTR from 155 facilities. 1,584 patients (54% of the total patient population) who had an LVEF $\leqq$ 40% and ICD/CRT-D implanted from January 1st 2006 to May 9th 2008, were selected as the subjects for this study.

We investigated 1) the difference of clinical characteristics in patients with an ICD/CRT-D between those that received the device for primary vs secondary prevention for sudden cardiac death, 2) the number of implantations and complications during the ICD/CRT-D implantations, 3) the transition of indications for implantation of the ICD/CRT-D over the years.

Statistical Analysis: The values for the continuous variables are presented as the mean +/− the standard deviation, and the values for categorical variables are presented as percentages. The differences in the clinical characteristics and medications used at baseline between those receiving a device for primary prevention and those for secondary prevention were tested by the chi-square test.

Table 1 JCDTR Questionnaire

◆ Information on the implantation
1. Name of Institute, Date of Registry
2. Age and sex of the Patients
3. Date of the implantation
4. Name of the operators
5. The purpose of the implantation primary or secondary prevention
6. Implantation indications on the basis of the Japanese Guidelines
7. Name of the implanted device
8. Implanted leads atrium, ventricle 1, ventricle 2
9. Defibrillation threshold minimum energy for defibrillation
10. Complications
◆ Patient Characteristics
1. Patient history VT, VF, torsades de pointes, syncope, unknown
2. Structural heart disease
3. Disease other than cardiac disease
4. NYHA classification
5. LVEF, measurement methods used
6. CAG
7. QRS duration and dyssynchrony
8. Signal averaging
9. TWA
10. EPS
11. Holter ECG
◆ Medications given at implantation
1. Antiarrhythmic drugs
2. Diuretics, ACE/ARB, ext
3. Anitiplatelets or anticoagulants

Results

Clinical characteristics

The number of patients receiving a device for primary prevention was 673, and it was lower than that for secondary prevention, 911. There were no significant differences in the age or ratio of males to females between the primary and secondary prevention groups (**Table 2**).

There was no significant difference in the distribution of structural heart disease except for ischemic heart disease (IHD) and dilated cardiomyopathy

Table 2 Clinical characteristics in the patients with an ICD/CDT-D implanted for primary and secondary prevention

	Primary	Secondary	Total	primary vs secondary
Numbers	673	911	1,584	
Age	64 ± 13	65 ± 11	64 ± 12	p = 0.58
Male/Female (ratio)	3.1	3.6	3.4	p = 0.18
	n (%)	n (%)	n (%)	
1) Structural Heart Disease				
IHD	219 (33)	440 (48)	659 (42)	p < 0.0001
DCM	344 (51)	317 (35)	661 (42)	p < 0.0001
HCM	23 (3)	37 (4)	60 (4)	n.s
HHD	4 (1)	12 (1)	16 (0.1)	n.s
VHD	30 (5)	32 (4)	62 (4)	n.s
CHD	1 (0.1)	9 (1.)	10 (0.6)	n.s
Miscellaneous	52 (8)	64 (7)	116 (7)	n.s
2) NYHA				
I	42 (6)	133 (15)	175 (11)	p < 0.0001
II	179 (27)	382 (42)	561 (35)	p < 0.0001
III	386 (57)	302 (33)	688 (43)	p < 0.0001
IV	66 (10)	94 (10)	160 (10)	P = 0.738
3) LVEF	26 ± 7%	29 ± 8%	28 ± 8%	p < 0.0001
4) EPS	237 (35)	358 (39)	595 (38)	p = 0.097

IHD: ischemic heart disease, DCM: dilated cardiomyopathy, HCM: hypertrophic cardiomyopathy, HHD: hypertensive heart failure, VHD: valvular heart disease, CHD: congenital heart disease, EPS: electrophysiogical study, LVEF: left ventricular ejection fraction

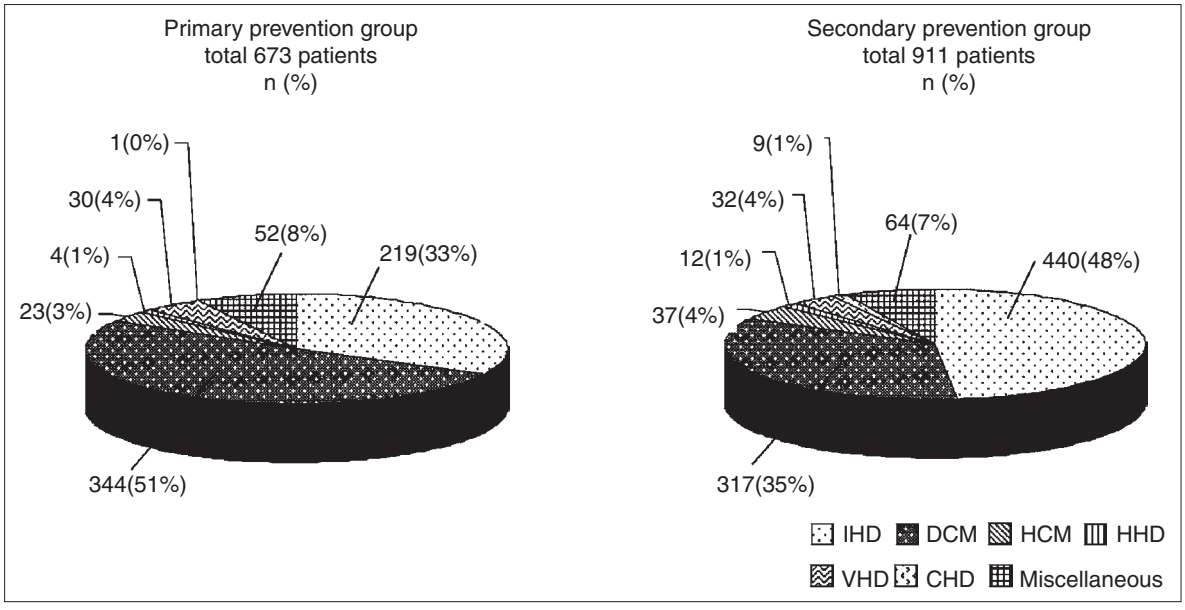

Figure 1 Underlying heart disease in patients with an ICD/CRT-D
IHD: ischemic heart disease, DCM: dilated cardiomyopathy, HCM: hypertrophic cardiomyopathy, HHD: hypertensive heart failure, VHD: valvular heart disease, CHD: congenital heart disease, LVEF: left ventricular ejection fraction

(DCM) between the primary and secondary prevention groups (**Figure 1**, **Table 2**). Both IHD and DCM were major structural heart diseases in the patients with an ICD/CRT-D device, and occupied in 84% in the primary prevention group and 83% in the secondary prevention group. The implantation of

Table 3 Medications for arrhythmias and congestive heart failure at the registry

	Primary	Secondary	Total	primary vs secondary
Numbers	673	911	1,584	
	n (%)	n (%)	n (%)	
1) Antiarrhythmic Medications				
Class IA	11 (2)	8 (1)	19 (1)	n.s
Class IB	33 (5)	62 (7)	95 (6)	n.s
Class IC	3 (0.4)	10 (1)	13 (0.8)	n.s
Class III	272 (40)	623 (68)	895 (57)	$p < 0.0001$
amiodarone	248 (37)	582 (64)	530 (34)	$p < 0.0001$
sotalol	19 (3)	36 (4)	55 (4)	n.s
Ca antagonist	59 (9)	74 (8)	133 (8)	n.s
2) Medications given for congestive heart failure				
Diuretics	521 (77)	624 (69)	1,145 (72)	$p < 0.0001$
ACE/ARB	510 (76)	632 (69)	1,062 (67)	$p = 0.005$
β-blockers	467 (69)	590 (65)	1,057 (67)	$p = 0.053$
carvedilol	427 (63)	533 (59)	960 (61)	$p = 0.046$
Spironolactone	321 (48)	351 (39)	672 (42)	$p = 0.0003$
Digoxin	150 (22)	121 (13)	271 (17)	$p < 0.0001$
Nitorate	79 (12)	118 (13)	197 (12)	n.s
α-blockers	1 (0.1)	2 (0.2)	3 (0.2)	n.s
Statin	169 (25)	222 (24)	391 (25)	n.s

ICD/CRT-D for secondary prevention in IHD was significantly higher than that in DCM (48% vs 35%; $p < 0.0001$, **Figure 1** and **Table 2**). Inversely, the implantation of ICD/CRT-D for primary prevention in IHD was significantly lower than that in DCM (33% vs 51%; $p < 0.0001$, **Figure 1** and **Table 2**).

In the distribution of the NYHA classification, the percentage of class I and II in the secondary prevention group was higher than those in the primary prevention group. Inversely, the percentage of class III in the primary prevention group was higher than that in the secondary prevention group (**Table 2**). LVEF in the primary prevention group was significantly lower than that of the secondary prevention group (**Table 2**). There was no significant difference on the ratio of electrophysiological studies (EPS) performed between primary and secondary prevention groups (35% vs 39%, $p = 0.097$, **Table 2**).

In the medications used for the arrhythmias, there were no significant differences between the primary and secondary prevention groups, except for the class III drugs (**Table 3**). In particular, the percentage of amiodarone given for secondary prevention was much higher than that for primary prevention (64% versus 37%, $p < 0.0001$). The percentage of the medications used for heart failure, such as diuretics, β-blockers, ACE/ARBs, spironolactone and digoxin, given for the primary prevention was significantly higher than that for the secondary prevention (**Table 3**).

Number of implantations and complications in ICD and CRT-D implantations

The total number of ICD implantations was 750 and that of CRT-D implantations was 804. With regard to the so called upgrade, the number of implantations upgraded from an ICD to a CRT-D device was 22 and that from CRT-P to CRT-D device was 8, so far their number of those patients was very small, and accounted for less than 2% of all implantations.

The incidence of complications during the ICD and CRT-D implantations, was very low. Further, the percentage of total complications was significantly higher for CRT-D than ICD implantation (**Table 4**).

Number of ICD and CRT-D implantations and change in the purpose for their implantations (**Figure 2**)

ICD and CRT-D (the upper panels): The percentage of both ICD and CRT-D implantations for primary prevention (22%) increased dramatically from the first half of the year in 2006 to the first half

Table 4 Complications in ICD/CRT-D implantations

	ICD (n = 748)	CRT-D (n = 836)	Total (n = 1,584)	ICD vs CRT-D
	n (%)	n (%)	n (%)	
Pneumothorax	6 (0.8)	6 (0.7)	12 (0.8)	n.s
Cardiac tamponade	3 (0.4)	4 (0.5)	7 (0.4)	n.s
Infection	2 (0.3)	3 (0.4)	5 (0.3)	n.s
Exacerbation of CHF	1 (0.1)	1 (0.1)	2 (0.1)	n.s
Cerebral infarction	0 (0.0)	1 (0.1)	1 (0.06)	n.s
Death	0 (0.0)	1 (0.1)	1 (0.06)	n.s
Bleeding/hematoma	5 (0.7)	8 (1.0)	13 (0.8)	n.s
Dissection of the CS	—	6 (0.7)	6 (0.4)	—
LV dislodgment/failure	—	3 (0.4)	3 (0.4)	—
Twitching	—	3 (0.4)	3 (0.4)	—
Total	17 (2.3)	36 (4.3)	54 (3.4)	p = 0.023

CHF: congestive heart failure, CS: coronary sinus, LV: left ventricle

of the year in 2007. The total number of implantations for secondary prevention was 911, and it was greater than that for primary prevention, 673. However, the ratio of primary prevention to secondary prevention has changed to about 50%.

ICD (the middle panels): The total number of ICD implants decreased from 386 to 281 within one year. However, the percentage of ICD implanted for secondary prevention was relatively high around 70 to 80%.

CRT-D (the bottom panel): The number of CRT-D implantations for secondary prevention increased from 114 to 195, and further, that for primary prevention increased dramatically from 105 to 312, around a three-fold increase. The percentage of CRT-D implantations for primary prevention increased from 47% in 2006 to 64% in the first half of the year in 2007, and then remained steady throughout 2008.

Discussion

Base on several mega-trials[4–7] on the primary prevention of sudden cardiac death, the expansion of indications for the use of ICD/CRT-D devices for primary prevention and the number of implantations of ICD/CRT-D devices has been increasing in the USA and Europe.

In Japan, ICD was first approved by the MHLW in 1996, which was 10 years behind the USA. The first CRT-D was also finally approved by the MHLW in August of 2006. However, the current status of those devices still remains unclear in Japan. Therefore, the internet registry, JCDTR, which is administered by the Japanese Heart Rhythm Society started in August 2006 in order to comprehend the actual conditions and transition of the indications for the implantation of ICD/CRT-D devices in Japanese patients.

Only new implantations of both ICD and CRT-D devices and so-called upgrades from an ICD or CRT-P to CRT-D performed from January 2006 were only enrolled in the JCDTR. The data from the JCDTR has recently been reported.[10,11] Further, the number of facilities that enroll patients into the JCDTR continues to gradually increase.

Comparing the current status of ICD implantations with other countries

Several worldwide surveys and registries have examined ICD utilization.[13–15] In the United States, there were 82% primary and 18% secondary prevention indications in the ICD therapy (ACT) registry. On the other hand, there were 42% primary and 58% secondary prevention indications in the Italian ICD registry (IIR).[16] In this study, the percentage of patients receiving an implantation for primary prevention gradually increased and then stabilized at about 50%. Thus, the ratio of primary to secondary prevention group in Japan was close to that of the Italian ICD registry. However, there was a big difference in comparison to that of the United States, probably due to the different guidelines and clinical backgrounds in patients implanted with ICD or CRT-D devices.

Clinical characteristics between primary and secondary prevention

In comparing the patients implanted for primary prevention with those for secondary prevention, a lower LVEF, an NYHA class higher than class III,

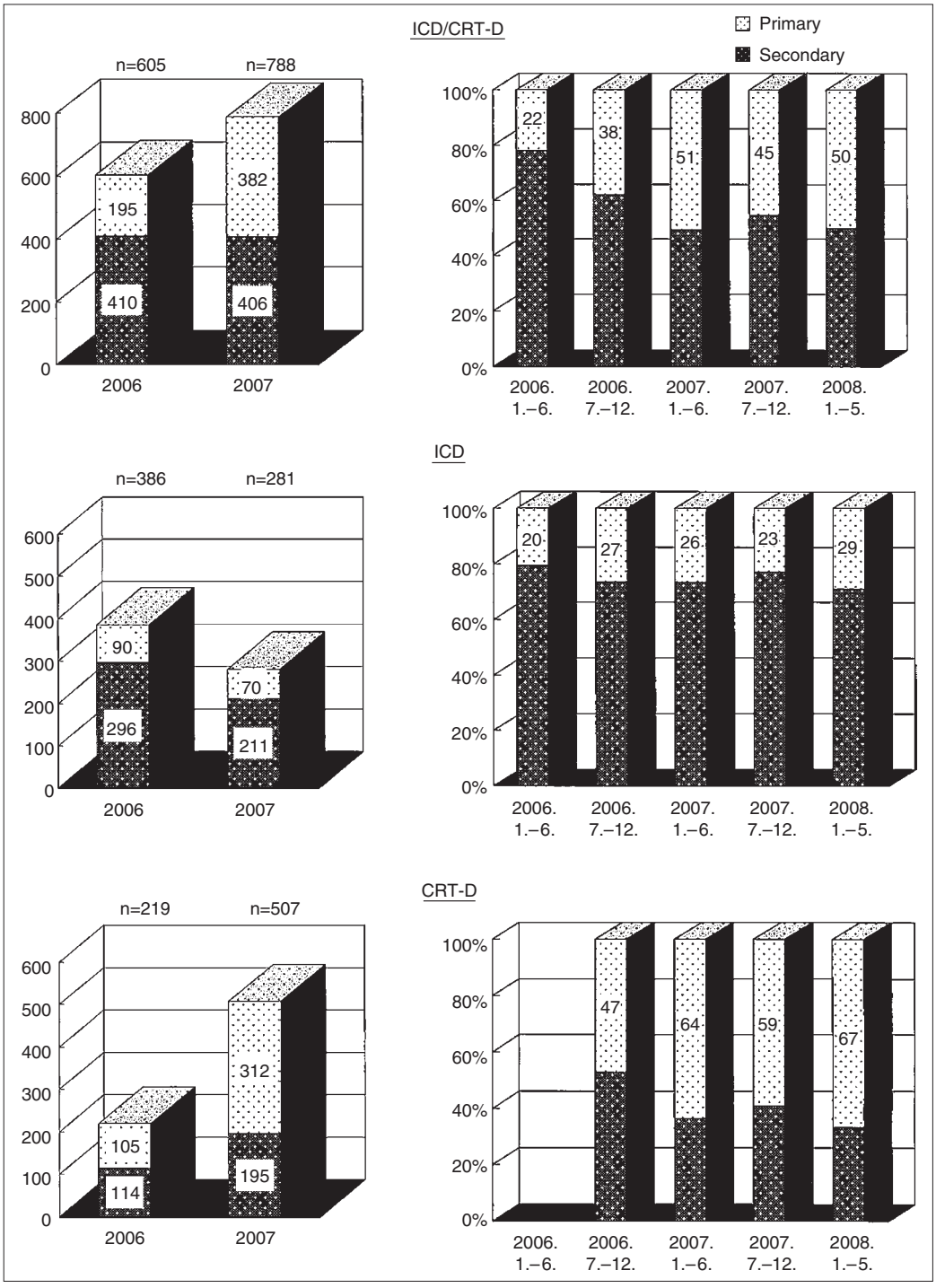

Figure 2 Number of patients with ICD/CRT-D implantations and change in the purpose for the implantations.
The upper panel: number of implanted ICD/CRT-Ds (left panel) and the transition of the ICD/CRT-D implantations (right panel) between the primary and secondary prevention groups. In the left panel, the number of patients in whom ICD/CRT-Ds were implanted from January to May in 2008 was not shown.
The middle panel: number of implanted ICDs (left panel) and the transition of the ICD implantations (right panel) between the primary and secondary prevention groups. In the left panel, the number of patients in whom ICDs were implanted from January to May in 2008 was not shown.
The bottom panel: number of implanted CRT-Ds (left panel) and the transition of the CRT-Ds implantations (right panel) between the primary and secondary prevention groups. In the left panel, the number of patients in whom CRT-Ds were implanted from January to May in 2008 was not shown.

and a greater amount of medications for heart failure was observed in the primary prevention group. Those data suggested that the ratio of severe heart failure was relatively higher in the primary prevention group than in the secondary prevention group.

Both IHD and DCM were the major structural heart disease noted in the patients with an ICD/CRT-D device, and were 84% in the primary prevention group and 83% in the secondary prevention group. The implantable defibrillator devices for primary prevention was significantly lower in IHD compared with CDM. Further, the ratio of primary prevention to secondary prevention was 0.5 in patients with IHD and 1.1 in patients with DCM. There may be several reasons why the implantation for primary prevention in patient with IHD was lower in Japan compared to that in the USA. One of the major reasons is probably due to the different guideline for patients in IHD. Further, Japanese physicians believe the risk in Japanese patients with IHD and a lower LVEF is less than that in the USA. Tanno et al.[17] reported that it might be inappropriate to apply MADIT II[5] criteria to Japanese patients, because the survival rate in their study was comparable with that in the MADIT II[5] defibrillator group. They also stated the reason was that a significantly greater percentage of the more recent patients were found to be in NYHA class I and that they had undergone more percutaneous coronary intervention procedures than in MADIT II.[5]

Number and transition of indications for ICD and CRT-D implantations

In this study, the percentage of ICD implanted for secondary prevention remained steady throughout 2008. Inversely, the CRT-D implantations increased and the ratio of CRT-D to ICD implantations increased dramatically from 2006 to 2007. The percentage of CRT-D implantations for primary prevention had increased from 45% to 65% within a half year. The specific reasons for the rapid increase of the percentage of CRT-D prophylactic implantation are unclear. One of the major reasons is that CRT-D was approved by Japanese MHLW in August 2006. The others are the new guidelines on ICD implantation, the favorable results of COMPANION[8] and MIRACLE[18] trials, the progressive technologic advances of devices and the cooperation between cardiologists in the heart failure clinics and electrophysiologic laboratories of the Japanese hospitals.

Conclusions:

This paper is the first report from the JCDTR database. We report the current status of implantable defibrillator devices in patients with a low LVEF of $\leqq$40%, and observed the following findings; 1) the percentage of patients receiving an implantation for primary prevention gradually increased from 20% to 40% in 2006, and then stabilized at about 50% through 2007, 2) in comparing the patients receiving an implantation for primary prevention with those implanted for secondary prevention, less IHD, more DCM, a lower LVEF, a NYHA class higher than class III, a greater amount of medications for CHF, and more CRT-D implantations were observed, 3) an expansion of the indications for ICD/CRT-D implantations has been occurring recently, especially CRT-D devices implanted for primary prevention.

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