European Journal of Heart Failure (2012) **14**, 61–73
doi:10.1093/eurjhf/hfr158

The European CRT Survey: 1 year (9–15 months) follow-up results

Nigussie Bogale[1]*, Silvia Priori[2,3], John G.F. Cleland[4], Josep Brugada[5], Cecilia Linde[6], Angelo Auricchio[7], Dirk J. van Veldhuisen[8], Tobias Limbourg[9], Anselm Gitt[9], Daniel Gras[10], Christoph Stellbrink[11], Maurizio Gasparini[12], Marco Metra[13], Geneviève Derumeaux[14], Fredrik Gadler[6], Laszlo Buga[4], and Kenneth Dickstein[1], on behalf of the Scientific Committee, National Coordinators, and Investigators

[1]Stavanger University Hospital, 4068 Stavanger and Institute of Medicine, University of Bergen, Norway; [2]University of Pavia Maugeri Foundation, Pavia, Italy; [3]Cardiovascular Genetics Program, New York State University, NY, USA; [4]Castle Hill Hospital, Hull York Medical School, University of Hull, Kingston-upon-Hull, UK; [5]Thorax Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain; [6]Karolinska University Hospital, Stockholm, Sweden; [7]Division of Cardiology, Fondazione Cardiocentro Ticino, Lugano, Switzerland; [8]University Medical Center Groningen, Groningen, The Netherlands; [9]Institut für Herzinfarktforschung Ludwigshafen an der Universität Heidelberg, Ludwigshafen, Germany; [10]Nouvelles Cliniques Nantaises, Nantes, France; [11]Department of Cardiology and Intensive Care Medicine, Bielefeld Medical Center, Germany; [12]IRCCS Istituto Clinico Humanitas, Rozzano (MI), Italy; [13]Institute of Cardiology, Department of Experimental and Applied Medicine, University of Brescia, Brescia, Italy; and [14]Université Claude Bernard Lyon I, Lyon, France

Received 16 September 2011; accepted 30 September 2011

Aims The European CRT Survey is a joint initiative of the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the European Society of Cardiology evaluating the contemporary implantation practice of cardiac resynchronization therapy (CRT) in Europe.

Methods and results Patients who had a successful CRT implantation were enrolled from 141 centres in 13 countries between November 2008 and June 2009. Baseline demographics, clinical and implantation data were collected, with a follow-up of ~1 year (9–15 months). The current report describes clinical outcomes including symptom severity, cardiovascular (CV) hospitalization, and survival. A total of 2438 patients were enrolled, and follow-up data were acquired from 2111 patients (87%). The population included important groups of patients poorly represented in randomized controlled trials, including very elderly patients and those with prior device implantation, atrial fibrillation, and/or QRS duration <120 ms. Investigators reported substantial improvement in New York Heart Association (NYHA) functional class at follow-up. Patient self-assessment indicated that 81% of the patients felt improved, 16% reported no change, and 4% reported deterioration. During follow-up, 207 (10%) patients died, 346 (16%) had a CV hospitalization, and 501 (24%) died or had CV hospitalization. Worse NYHA functional class, atrial fibrillation, ischaemic aetiology, and device type (CRT-P, i.e. CRT alone) were associated with poorer survival. Women had a better outcome, as did patients who had a CRT-D (with an implantable cardioverter defibrillator function) device.

Conclusions Outcomes including death and hospitalization in this European CRT survey were consistent with results from clinical trials of CRT. At 1 year follow-up, most patients who received a CRT device considered their symptoms improved compared with their pre-implant assessment. Although prospective, this is an observational study of successful CRT implantations, and outcomes in subgroup analyses must be interpreted with appropriate conservatism.
Clinical study no: NCT 01185392

Keywords Cardiac resynchronization therapy (CRT) • Survey • Heart failure • 1 year (9–15 months) follow-up

Introduction

Cardiac resynchronization therapy (CRT) improves symptoms and reduces morbidity and mortality.[1–7] The 2007 ESC/EHRA Guidelines for Cardiac Pacing,[8] the 2008 ESC Heart Failure Guidelines,[9] and the 2008 ACC/AHA/HRS Guidelines for Device Therapy[10] provide class I A recommendation for CRT treatment with or without an implantable cardioverter defibrillator (ICD)

* Corresponding author: Tel: +47 97577673, Fax: +47 51519921, Email: nigussie.bogale@lyse.net

function in patients with New York Heart Association (NYHA) functional class III and IV, QRS width ≥120 ms. and left ventricular ejection fraction (LVEF) ≤35% in order to improve symptoms and reduce mortality. More recent studies have explored the effect of CRT in patients with mild symptoms and markers of cardiac dyssynchrony most of whom were already indicated for an ICD,[5–7] resulting in a focused ESC guideline update on device therapy.[11] Meanwhile, there has been a substantial increase in implantation rates for CRT across Europe, although with marked differences amongst countries.[12,13]

Surveys and registries differ from randomized controlled trials (RCTs) in several ways, and both approaches have their strengths and limitations. RCTs are designed to evaluate the response to interventions, but also measure outcomes,[14] by scientifically validated methods. However, they often exclude patients with co-morbidities and rely on statistical precision and consistency across subgroups.[15] Surveys capture data from a much more heterogeneous population and are closer to actual clinical practice.[16–18] However, they are subject to selection bias and missing data, and only measure outcomes rather than the response to therapy.[14]

We performed a survey to evaluate contemporary European practice related to CRT implantations with or without an ICD as a joint initiative of the Heart Failure Association (HFA) and the European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC). The first publications, describing the patients and implant procedures, provided important information on clinical characteristics, diagnostic criteria, adverse events, in-hospital course, status at discharge, physician adherence to guideline recommendations, and the influence of the volume of implants at a centre.[19,20] These reports show major differences between guidelines and clinical practice. Substantial numbers of patients had milder symptoms, narrow QRS width, and had a previous device (permanent pacemakers and ICDs). This publication reports the 1 year (9–15 months) follow-up results of patients included into this survey.

Methods

Design

The rationale and design of the CRT Survey have been published previously.[21] All centres implanting CRT with or without an ICD were invited to participate. Centres were asked to enrol consecutive successful implantations performed between 1 November 2008 and 30 June 2009. The variables captured at 1 year follow-up included survival, hospitalization, patient global assessment (self-reported), NYHA functional class, electrocardiogram (ECG), key echocardiographic data, and device-related complications.

Participating countries and centres

A total of 141 centres from the following 13 ESC countries participated: Austria, Belgium, France, Germany, Ireland, Israel, Italy, The Netherlands, Norway, Spain, Sweden, Switzerland, and the UK. The number of patients from each is shown in Appendix 3.

Data collection

Data were collected using electronic case report forms (eCRFs). The contents for both index hospitalization and follow-up variables have been reported.[21] A follow-up assessment was planned 9–15 months post-implantation. The window of 6 months was allowed in order to give enough time to capture data from routine device follow-ups.

Two national co-ordinators, one each from the fields of heart failure and electrophysiology, were selected and given the responsibility of facilitating recruitment and follow-up in their respective countries (Appendix 1). Germany and Sweden have ongoing device registries in most of their centres which includes CRT which capture most of the information contained in the CRT Survey eCRF. With permission from both of the Steering Committees (Appendix 2), CRT follow-up data were merged into the CRT Survey database.

A central database was created at the data management centre, Institut für Herzinfarktforschung in Ludwigshafen an der Universität Heidelberg, Germany which also maintained and interrogated the database and performed analyses. A web site, www.crt-survey.org, supported by the ESC Web department provided all the relevant documents and permitted online data entry. Ethical approval and written informed consent were obtained according to the rules for clinical investigations in each participating country at the initiation of the study.

Statistical methodology

Absolute numbers and percentages are shown for categorical variables to describe the patient population, and means [with standard deviations (SD)] or medians (with quartiles) for continuous variables. Categorical variables were compared between subgroups by the Pearson χ^2 test and continuous variables (numeric values) by the Mann–Whitney–Wilcoxon test. Descriptive statistics were calculated for the available cases. Logistic regression analysis was performed for selected variables. Kaplan–Meier survival estimates were performed for age, gender, aetiology, rhythm, QRS durations, and device type. A significance level of $P < 0.05$ was assumed for the statistical tests, and all *P*-values are results of two-tailed tests. All statistical analyses were performed using SAS© statistical software, version 9.1 (Cary, North Carolina, USA).

Results

This survey enrolled 2438 patients during the 8 month inclusion period. One-year follow-up data (9–15 months), including vital status, were available for 2111 (87%) patients. Most patients received CRT with an ICD function (CRT-D) rather than CRT alone (CRT-P). The characteristics of patients who did not have follow-up data were similar to those of the overall population. During follow-up, 207 (10%) patients died, 346 (16%) were hospitalized for cardiovascular causes, and 501 (24%) were hospitalized or died.

Mortality (*Table 1*)

Patients who died were slightly older, were likely to be men, were more likely to have ischaemic heart disease, diabetes mellitus, chronic lung disease, and atrial fibrillation, had lower LVEF, were less likely to be prescribed beta-blockers and more likely to be prescribed diuretics, had worse NYHA functional class, and were more likely to be hospitalized for heart failure the previous year, as shown by unadjusted description of baseline characteristics in the table.

Patients with narrow QRS complex, left bundle branch block (LBBB), or paced ventricular rhythm had similar survival rates, but those with right bundle branch block (RBBB) had a worse

Table 1 Baseline characteristics of survivors vs. dead patients, patients with and without cardiovasular hospitalization, and the composite of both with follow-up data (n = 2111)

	Dead	Alive	*P*-value	CV hospitalization	No CV hospitalization	*P*-value	Death or CV hospitalization	No death or CV hospitalization	*P*-value
Patients (n, %)	207 (9.8)	1904 (90.2)		346 (14.3)	1451 (59.8)		501 (20.7)	1621 (66.8)	
Demographics									
Age (years, median)	71 (65–76)	70 (62–76)	<0.01	69 (61–75)	70 (62–76)	0.32	70 (63–76)	70 (62–76)	0.44
Age >75	71 (34)	575 (30)	0.22	100 (29)	446 (31)	0.50	156 (31)	491 (30)	0.76
Women	32 (16)	456 (24)	<0.01	68 (20)	363 (25)	<0.05	92 (18)	400 (25)	<0.01
HF aetiology[a]									
Ischaemic	118 (61)	888 (50)	<0.01	170 (53)	702 (52)	0.51	258 (56)	750 (50)	<0.05
Non-ischaemic	53 (28)	725 (41)	<0.001	126 (40)	503 (41)	0.77	164 (36)	614 (41)	0.05
Other	22 (11)	157 (9)	0.25	17 (5)	88 (7)	0.46	37 (8)	142 (9)	0.37
Past medical history[b]									
HF hospitalization last year	119 (69)	914 (54)	<0.001	215 (63)	764 (53)	<0.01	296 (64)	740 (52)	<0.0001
Diabetes mellitus	78 (45)	479 (28)	<0.0001	106 (31)	409 (28)	0.38	165 (35)	394 (28)	<0.01
Chronic lung disease	48 (28)	265 (16)	<0.0001	67 (20)	230 (16)	0.12	99 (21)	216 (15)	<0.01
NYHA functional class[c]									
I	3 (2)	27 (2)	0.91	2 (1)	22 (2)	0.17	4 (1)	26 (2)	0.17
II	21 (11)	364 (21)	<0.01	48 (14)	316 (22)	<0.001	66 (14)	320 (21)	<0.0001
III	119 (65)	1251 (71)	0.09	243 (72)	969 (69)	0.24	330 (70)	1050 (70)	0.91
IV	41 (22)	127 (7)	<0.0001	45 (13)	105 (7)	<0.001	71 (15)	97 (7)	<0.0001
LVEF %	24 ± 7	27 ± 8	<0.0001	26 ± 8	27 ± 8	<0.05	26 ±8	27 ± 8	0.21
Rhythm[d]									
Sinus	133 (65)	1391 (74)	<0.01	220 (65)	1063 (74)	<0.001	320 (65)	1209 (76)	<0.0001
Atrial fibrillation	64 (31)	410 (22)	<0.01	106 (31)	305 (21)	<0.001	154 (31)	323 (20)	<0.0001
Other	9 (4)	71 (4)	0.68	13 (4)	61 (4)	0.72	20 (4)	63 (4)	0.92
QRS complex[d]									
Normal	28 (14)	240 (74)	0.76	45 (13)	170 (12)	0.49	66 (13)	205 (13)	0.78
LBBB	126 (61)	1270 (68)	0.05	233 (69)	1020 (72)	0.31	324 (66)	1079 (68)	0.37
RBBB	21 (10)	108 (6)	<0.05	23 (7)	96 (7)	0.97	39 (8)	91 (6)	0.08
Other	34 (17)	246 (13)	0.18	36 (11)	139 (10)	0.63	66 (13)	214 (13)	0.97
Ventricular paced rhythm	38 (18)	341 (18)	0.94	51 (15)	241 (17)	0.39	81 (16)	300 (19)	0.22
QRS durations	162 ± 33	157 ± 31	0.13	156 ± 33	157 ± 31	0.50	158 ± 32	157 ± 31	0.86
QRS durations[e]									
<130 ms	22 (14)	286 (18)	0.15	54 (18)	247 (18)	070	69 (16)	240 (18)	0.39
130 to <160 ms	53 (33)	455 (29)	0.30	100 (32)	387 (29)	0.22	134 (32)	379 (29)	0.23
160–180 ms	51 (32)	532 (34)	0.57	101 (33)	454 (34)	0.70	140 (33)	446 (34)	0.82

Continued

Table 1 *Continued*

	Dead	Alive	*P*-value	CV hospitalization	No CV hospitalization	*P*-value	Death or CV hospitalization	No death or CV hospitalization	*P*-value
>180 ms	35 (22)	297 (19)	0.39	54 (18)	254 (19)	0.55	79 (19)	255 (19)	0.79
Device type[f]									
CRT-D	129 (63)	1365 (72)	<0.01	264 (77)	1088 (76)	0.51	357 (72)	1146 (71)	0.78
CRT-P	77 (37)	521 (28)	<0.01	77 (23)	349 (24)	0.51	139 (28)	461 (29)	0.78
Medical treatment[g]									
Beta-blocker	123 (73)	1426 (85)	<0.0001	293 (86)	1193 (84)	0.40	379 (82)	1181 (84)	0.34
Diuretics	159 (94)	1456 (87)	<0.01	309 (90)	1227 (86)	<0.05	421 (91)	1205 (86)	<0.01
ACE inhibitors	106 (63)	1135 (67)	0.22	223 (65)	962 (68)	0.45	296 (64)	955 (68)	0.15
ARB	31 (18)	410 (24)	0.08	81 (24)	345 (24)	0.77	105 (23)	337 (24)	0.54
Aldosterone antagonist	80 (47)	755 (45)	0.54	171 (50)	623 (44)	<0.05	225 (49)	614 (44)	0.07

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT-D and CRT-P, cardiac resynchronization with or without an implantable cardioverter defibrillator function, respectively; CV, cardiovascular, HF, heart failure; LBBB, left bundle branch block; LVEF, left venticular ejection fraction; NYHA, New York Heart Association; RBBB, right bundle branch block.
Patient information available in the six rows, respectively (dead/alive, CV hospitalization/no CV hospitalization and death or CV hospitalization/ no death or CV hospitalization):
[a]459/1506, 313/1343, and 193/1770.
[b]466/1419, 344/1439, and 173/1701.
[c]471/1493, 338/1412, and 184/1769.
[d]494/1595, 339/1429, and 206/1872.
[e]161/1570, 309/1342, and 422/1320.
[f]496/1607, 341/1437, and 206/1886.
[g]461/1403, 342/1422, and 169/1685.

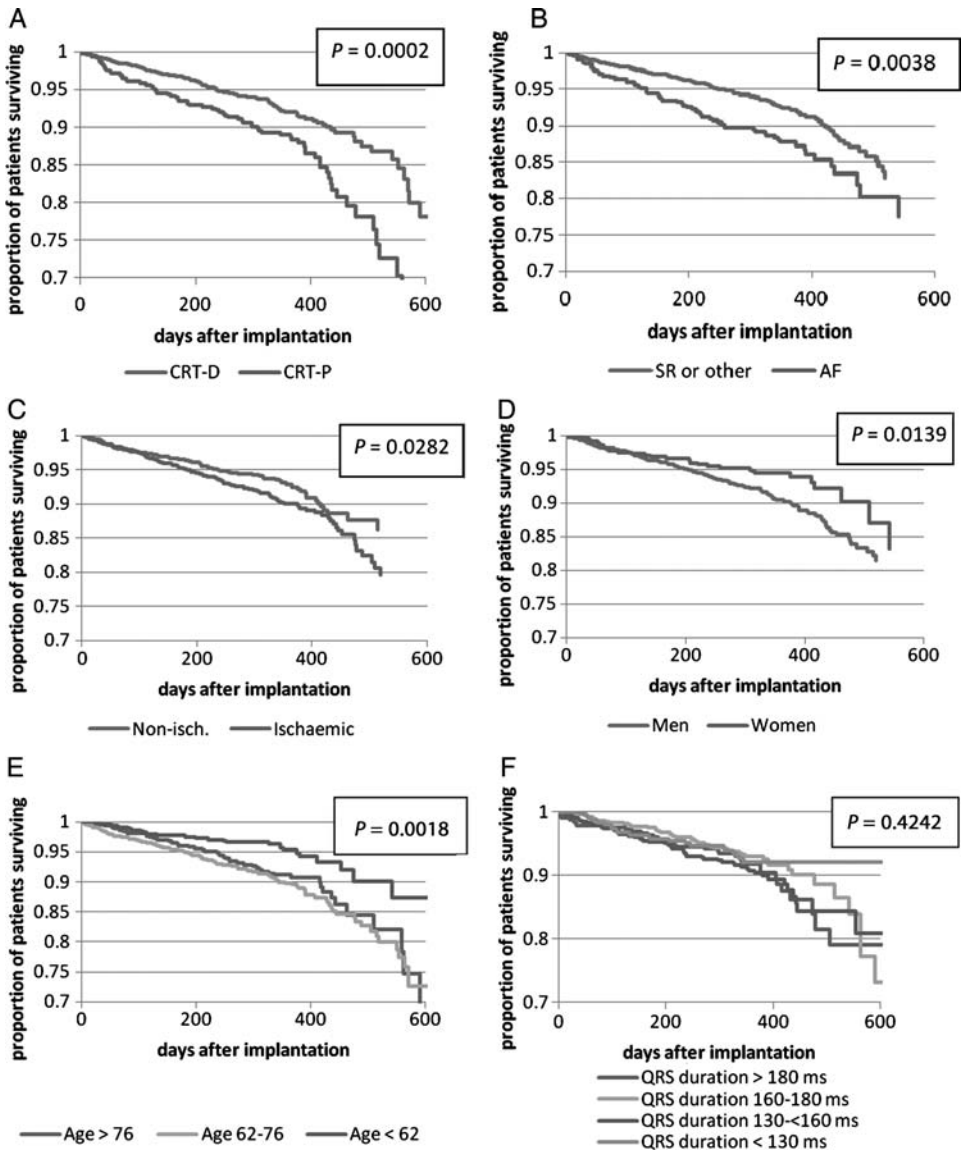

Figure 1 Kaplan–Meier survival estimates of death (unadjusted analyses). (*A*) Device type CRT-D vs. CRT-P; (*B*) sinus rhythm vs. atrial fibrillation; (*C*) non-ischaemic vs. ischaemic aetiology; (*D*) men vs. women; (*E*) age groups; (*F*) QRS durations. CRT-D, cardiac resynchronization therapy with an implantable cadioverter defibrillator (ICD) function; CRT-P, cardiac resynchronization therapy alone.

outcome. Survivors were more likely to have received a CRT-D. Unadjusted Kaplan–Meier survival estimates suggested a better prognosis in patients who received a CRT-D than patients with a CRT-P ($P < 0.0002$, *Figure 1A*).

Cardiovascular hospitalization and cardiovascular hospitalization or death (*Table 1*)

Women were hospitalized less frequently than men (25% vs. 20%, $P < 0.05$). Age, aetiology of disease, and prevalence of co-morbidities, with the exception of atrial fibrillation, and the proportion of patients that received a CRT-D was similar in patients who did or did not have a CV hospitalization. QRS duration and morphology were similar amongst patients who were or were not hospitalized. Patients who were hospitalized had a slightly lower LVEF, were more likely to be prescribed diuretics and aldosterone antagonists, had more severe symptoms, and were more likely to be hospitalized for heart failure in the year before implantation.

The characteristics of patients who did or did not reach the composite outcome of cardiovascular hospitalization or death were similar to the pattern shown for survival.

Aetiology (*Table 2*, *Figure 1*)

Patients with ischaemic heart disease were older (71 vs. 68 years, $P < 0.0001$), more likely to be men, more likely to have a QRS duration <130 ms (20% vs. 16%, $P < 0.05$), and less likely to have a QRS duration of between 130 and <160 ms (31% vs. 36 %, $P < 0.05$) compared with patients who did not have ischaemic heart

Table 2 Selected variables for ischaemic and non-ischaemic aetiology (*n*, %)

	Ischaemic	Non-ischaemic	*P*-value
Age (years, median)	71 (65–77)	68 (60–75)	<0.0001
Women	168 (15)	339 (32)	<0.0001
QRS duration[a]			
<130 ms	188 (20)	132 (16)	<0.01
130 to <160 ms	282 (30)	241 (28)	0.23
160–180 ms	286 (31)	304 (36)	<0.01
>180 ms	175 (19)	172 (20)	0.44
Device type[b]			
CRT-D	842 (77)	671 (63)	<0.0001
CRT-P	251 (23)	391 (37)	<0.0001

CRT-D and CRT-P, cardiac resynchronization with or without an implantable cardioverter defibrillator function, respectively.
[a]Information available for 931 patients in the ischaemic and 849 in the non-ischaemic group.
[b]Information available for 1093 patients in the ischaemic and 1064 in the non-ischaemic group.

disease. Patients with ischaemic heart disease had a somewhat worse outcome on both unadjusted and multivariable analyses.

Atrial fibrillation (*Table 3*, *Figure 1*)

Patients with atrial fibrillation were older (72 vs. 69 years, $P < 0.0001$), and more patients in this category had QRS durations < 130 ms (22% vs. 17%, $P < 0.05$), RBBB (9% vs. 6%, $P < 0.01$), and were allocated to a CRT-P rather than a CRT-D (39% vs. 29%, $P < 0.0001$). Patients with atrial fibrillation had a worse outcome on both unadjusted and multivariable analyses.

QRS durations

Except for a slightly higher mortality in patients with RBBB, outcomes were similar regardless of QRS morphology or duration or presence of paced ventricular rhythm. Patients with QRS <130 ms were more likely to have ischaemic heart disease and be in atrial fibrillation.

Device type (*Table 4*)

CRT-D recipients were substantially younger (68 vs. 75 years, $P < 0.0001$), more likely to be women, and had significantly more previous ventricular fibrillation/sustained ventricular tachycardia (20% vs. 2%, $P < 0.0001$). The proportions of patients with different QRS morphology and durations were similar regardless of device type implanted.

Predictors of death and cardiovascular hospitalization (*Table 5*, and *Figure 1* and *2*)

Multivariable analyses were performed using the variables listed in *Table 1*. These showed that NYHA functional class III–IV, atrial fibrillation, ischaemic aetiology, and allocation to device type CRT-P were independently associated with poorer survival.

Table 3 Selected variables for atrial fibrillation and sinus rhythm or other (*n*, %)

	Atrial fibrillation	Sinus rhythm or other	*P*-value
Age (years, median)	71 (65–77)	69 (61–76)	<0.0001
Women	112 (21)	441 (25)	0.06
RBBB[a]	50 (9)	104 (6)	<0.01
QRS duration[b]	82 (22)	261 (16)	<0.05
<130 ms			
130 to <160 ms	107 (28)	481 (31)	0.38
160–180 ms	111 (29)	538 (34)	<0.05
>180 ms	80 (21)	294 (19)	0.44
Device type[c]			
CRT-D	338 (62)	1340 (75)	<0.0001
CRT-P	207 (38)	442 (25)	<0.0001

CRT-D and CRT-P, cardiac resynchronization with or without an implantable cardioverter defibrillator function, respectively; RBBB, right bundle branch block.
[a]Information available for 543 patients in atrial fibrillation and 1791 in sinus rhythm or other group.
[b]Information available for 380 patients in atrial fibrillation and 1574 in sinus rhythm or other group.
[c]Information available for 543 patients in atrial fibrillation and 1782 in sinus rhythm or other group.

Table 4 Selected variables for CRT-D and CRT-P recipients (*n*, %)

	CRT-D	CRT-P	*P*-value
Age (years, median)	68 (61–74)	75 (68–80)	<0.0001
Age ≥75	396 (23)	337 (52)	0.0001
Women	363 (21)	194 (30)	<0.0001
RBBB[a]	120 (7)	34 (5)	0.10
QRS duration[b]			
<130 ms	269 (18)	75 (8)	0.37
130 to <160 ms	450 (30)	137 (30)	0.82
160–180 ms	493 (33)	155 (33)	0.86
>180 ms	277 (19)	95 (21)	0.35
Previous VF/sustained VT	295 (20)	15 (2)	< 0.0001

CRT-D and CRT-P, cardiac resynchronization with or without an implantable cardioverter defibrillator function, respectively; RBBB, right bundle branch block; VF, ventricular fibrillation; VT, ventricular tachycardia.
[a]Information available for 1675 patients in the CRT-D and 646 in the CRT-P group
[b]Information available for 1482 patients in the CRT-D and 462 in the CRT-P group

Variables associated with re-hospitalization or for the combination of death or hospitalization were NYHA III–IV functional class and atrial fibrillation.

Upgraded patients vs. *de novo* implantations

A recent report from this database shows that outcomes in patients upgraded to CRT from permanent pacemakers and ICDs were similar to those who received *de novo* implantations.[22]

Table 5 Multivariate analysis for death, hospitalization, and death and hospitalization during the 1-year (9–15 months) follow-up period

	Variables	OR	95% CI	*P*-value
Death	NYHA III–IV	1.91	(1.16–3.17)	0.0116
	Atrial fibrillation	1.81	(1.24–2.66)	0.0022
	Ischaemic aetiology	1.75	(1.20–2.54)	0.0034
	Device type: CRT-P	1.65	(1.11–2.44)	0.0130
	Age groups[a]	1.05	(0.80–1.38)	0.7211
	QRS durations[b]	0.96	(0.81–1.14)	0.0831
	Women	0.63	(0.39–1.02)	0.0589
CV hospitalization	NYHA III–IV	1.76	(1.24–2.51)	0.0017
	Atrial fibrillation	1.53	(1.12–2.09)	0.0073
	Ischaemic aetiology	1.02	(0.77–1.34)	0.9102
	Device type: CRT-P	0.95	(0.69–1.31)	0.7645
	Age groups[a]	1.04	(0.85–1.28)	0.6750
	QRS durations[b]	1.05	(0.92–1.19)	0.5094
	Women	0.71	(0.51–1.00)	0.0476
Death or CV hospitalization	NYHA III–IV	1.80	(1.32–2.46)	0.0002
	Atrial fibrillation	1.69	(1.28–2.22)	0.0002
	Ischaemic aetiology	1.232	(0.95–1.56)	0.1196
	Device type: CRT-P	1.10	(0.83–1.46)	0.4989
	Age groups[a]	1.05	(0.88–1.26)	0.5874
	QRS durations[b]	1.02	(0.91–1.15)	0.7188
	Women	0.68	(0.50–0.92)	0.0134

CI, confidence interval; CRT-P, cardiac resynchronization without an implantable cardioverter defibrillator function; NYHA, New York Heart Association; OR, odds ratio.
[a]Age groups divided as <62, 62–76, and > 76 based on quartiles (the oldest group as reference).
[b]QRS durations divided as <130, 130–160, 160–180, and >180 ms based on quartiles (the widest group as reference).

Clinical status (*Figure 3A* and *B*)

Investigators reported a substantial improvement in NYHA functional class. At the time of implant, 1902 (78%) patients were in NYHA III–IV of whom 160 (8%) died. At follow-up 976 (50%) patients were in NYHA III–IV. Of 536 (22%) patients who were in NYHA I–II at the time of implant, only 1% died. The proportion in NYHA I–II had risen to 995 (50%) patients at follow-up. For patients' self-reported assessment of their global condition, 81% felt much better/a little better, 16% reported no change, and 4% reported worsening.

Complications

Table 6 reports device-related complications during the course of follow-up, with an overall rate of 10%. Lead displacement and phrenic nerve stimulation were the most common adverse events at ~ 3%. Infection was reported in 1.6% of cases.

Discussion

This survey suggests that implanting a CRT-P or a CRT-D device is associated with broadly similar impact on symptoms and rates of hospitalization and survival as observed in landmark RCTs of patients with predominantly NYHA functional class III–IV heart failure, despite embracing a far broader range of patients that were also older and with more co-morbidity than in the landmark trials. Comparison of baseline characteristics and outcomes of the survey cohort with selected RCTs is provided in *Table 7*. In CARE-HF, the 1-year mortality in patients assigned to CRT was 9.7% and ~ 25% of patients had been hospitalized for a major cardiovascular event or died and by 18 months 62% were alive and in NYHA I–II.[23] A further analysis of CARE-HF that imputed the additional effect of adding an ICD function to CRT suggests that this would have provided an additional mortality benefit.[24] This survey suggests that implanting CRT devices into a broader population of patients who do not meet the inclusion criteria of the landmark trials is associated with a favourable outcome. However, this is no substitute for information from a RCT, and the data must be interpreted with caution.

The population included important groups of patients poorly represented or excluded from RCTs, including women, very elderly patients, and those with prior device implantation, atrial fibrillation, and/or narrow QRS durations.[19] Women had a lower mortality than men despite being older and more likely to receive a CRT-P than a CRT-D. Lower mortality may reflect a lower prevalence of ischaemic disease in women, but randomized trials comparing ICD with CRT-D have suggested greater benefit in women. However, the effect of a CRT-P or a CRT-D on

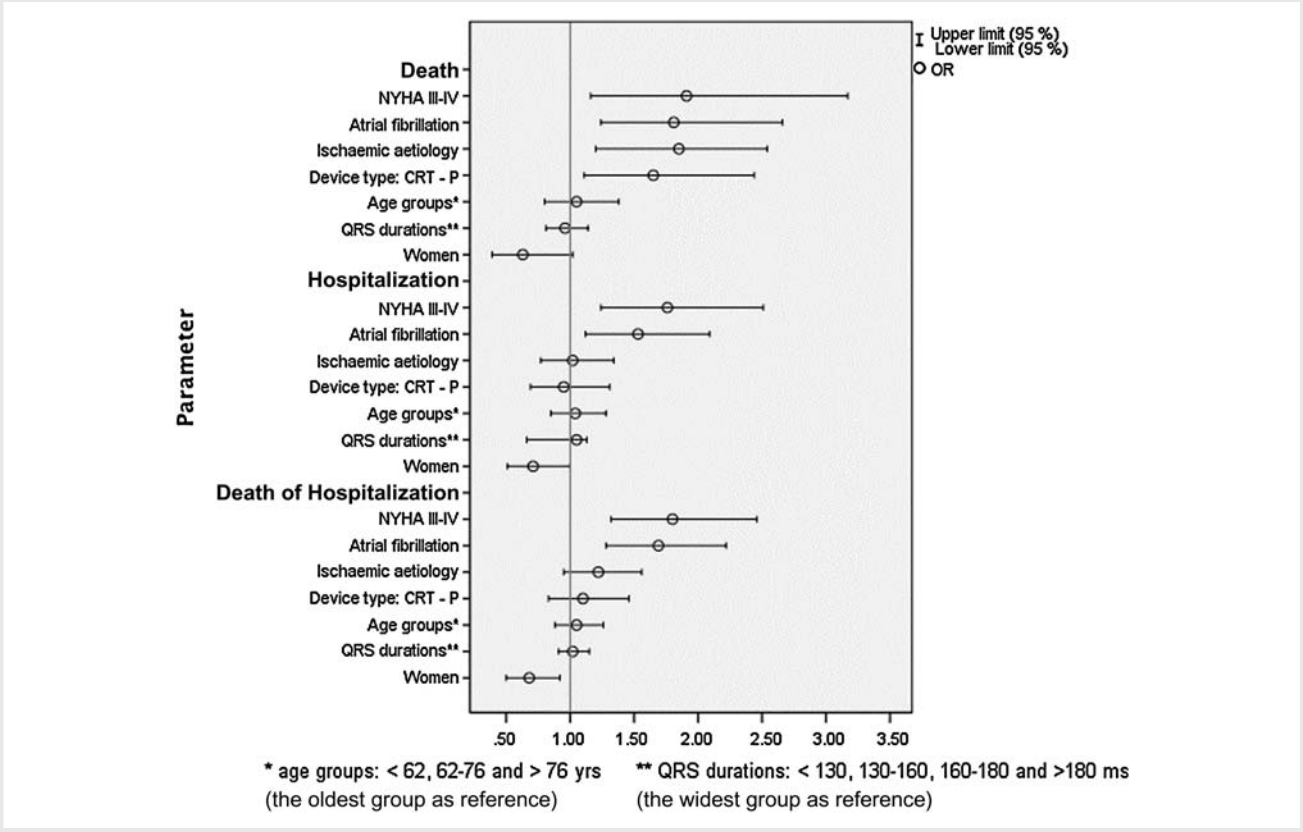

Figure 2 Forest plot presentation of parameters predicting death, hospitalization and death, or hospitalization. CRT, cardiac resynchronization therapy; NYHA, New York Heart Asscoiation; OR, odds ratio.

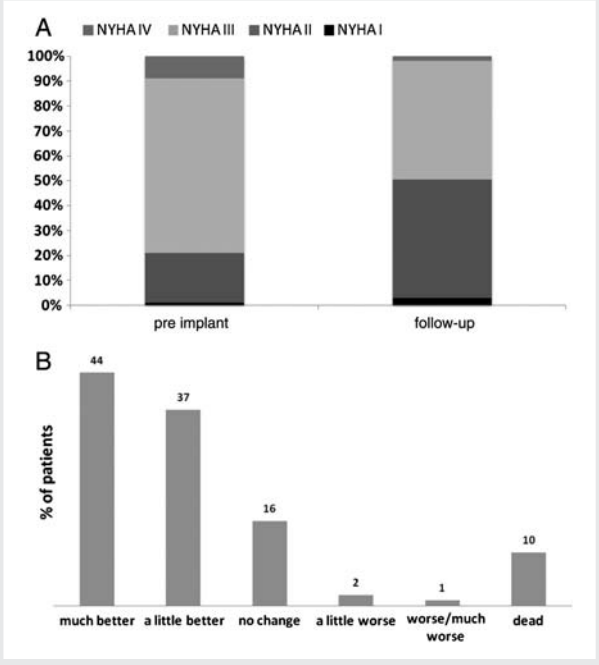

Figure 3 New York Heart Asscoiation (NYHA) functional class shift pre-implantation to follow-up (*A*); patient self-reported global assessment and rate of death during follow-up (*B*).

mortality was similar in men and women in both CARE-HF and COMPANION. This survey cannot determine whether the better outcome in women reflects a better outcome to CRT or a better intrinsic prognosis amongst women. This survey suggests that age is not a strong determinant of 1-year outcome in patients who receive a CRT-P or CRT-D device, which is surprising since age is usually a strong predictor of survival in patients with heart failure. This could reflect a greater benefit of CRT in older patients, although randomized trials suggest a similar response in younger and older patients.

Many more CRT-D than CRT-P devices are implanted in all ESC countries, although a substantial minority receive a CRT-P in some countries. The COMPANION study[3] and an imputed analysis of CARE-HF[25] suggest a modest additional survival benefit from a CRT-D. Patients who received a CRT-D device had a substantially lower mortality in both univariate and multivariate analysis, as has been reported in large patient series reported by others.[26] However, these findings should be interpreted cautiously since CRT-P recipients were older and had more atrial fibrillation. Moreover statistical analyses cannot correct for unrecorded confounders, hence the need for RCTs. The reasons for selecting a CRT-D in preference to a CRT-P device may account for much of the difference in outcome, although the inconclusive data from randomized trials support an additional therapeutic effect.

Our survey included 544 patients (23 %) with atrial fibrillation. These patients were older, more likely to receive a CRT-P, and

had higher morbidity and mortality. Clinical trials provide conflicting evidence regarding whether prevalent atrial fibrillation carries independent prognostic information after correction for differences for age and symptoms, although new-onset atrial fibrillation is associated with a sharp increase in mortality, suggesting that patients with chronic atrial fibrillation are a survivor subgroup.[27]

The RAFT trial included 115 patients (13%) with atrial fibrillation or flutter.[7] No benefit of CRT-D compared with ICD was observed in this population. Information on the percentage of cumulative biventricular pacing, the extent of AV node ablation post-device implantation, or up-titration of medical treatment to ensure adequate pacing was not captured in this survey, which can potentially explain the observation of poorer outcome of patients with atrial fibrillation and the disparity with other observational data sets.[28–33]

Landmark RCTs comparing CRT-P and CRT-D against medical therapy included few patients with a QRS duration <140 ms but did not identify a marked interaction between QRS duration and the effect of CRT on mortality. Patients with RBBB have a worse overall prognosis than those with LBBB, and may benefit less from CRT, although many patients who have additional left-sided fascicular blocks may still benefit.[2,4,34] More recently, trials comparing ICD and CRT-D have suggested that only patients with either QRS >150 ms or LBBB benefit from a CRT-D,[6,7] although controversy surrounds which is more important. We found similar outcomes regardless of QRS duration. However, as patients with longer QRS duration would be expected to have a worse prognosis, the similar outcome could still be interpreted as a greater response in those with longer QRS duration. A substantial long-term trial to confirm or refute a benefit from implanting a CRT-P or CRT-D device compared with no device in patients regardless of QRS duration is required. Information from trials comparing ICD and CRT-D do not adequately address this

Table 6 Device-related complications during 1 year (9–15 months)

Parameters	(*n*, %)
Device-related complications[a]	170 (10.3)
Lead displacement	55 (3.3)
Lead malfunction	13 (0.8)
Device-related arrhythmias	18 (1.1)
Phrenic nerve stimulation	51 (3.1)
Device replacement	6 (0.4)
Infection	27 (1.6)

[a]Information available for 1648 patients.

Table 7 Comparison of characteristics and outcomes between selected RCTs and CRT survey cohorts

	COMPANION[3]	CARE-HF[4,38]	REVERSE[5,39]	MADIT-CRT[6]	RAFT[7]	CRT Survey
No. of patients (CRT-P/CRT-D)	1212	409	419	1089	894	2438
Control groups	308	404	191	731	904	0
Mean follow-up (months)	14.8–16.5	37.4	12	28.8	40	12
Baseline characteristics (%)						
Mean age (years)	67	66	62	65	66	68
Men	67	74	79	75	83	76
Ischaemic heart disease	55	38	55	55	67	51
Atrial fibrillation	0[a]	0[a]	0[a]	0[a]	13	23
Previous device	0[a]	0[a]	0[a]	0[a]	NA[b]	28
Ventricular paced rhythm	0[a]	0[a]	0[a]	0[a]	8	18
RBBB	10	0[a]	10	13	9	6
QRS duration (ms)	160	165	153	65% >150	158	160
Mean LVEF	22	24.8	27	24	23	26
NYHA class						
I–II	0[a]	0[a]	100	100	80	22
III–IV	100	100	0[a]	0[a]	20	78
Outcomes in the CRT-D/P treated group (n, %)						
Mortality during follow-up	246 (20.3)	101 (24.7)	9 (2.2)	74 (6.8)	186 (20.8)	207 (9.8)[c]
Death or hospitalization for HF	449 (37.1)	118 (28.9)[d]	26 (6.2)	187 (17.2)	297 (33.2)	501 (23.7)[e]

CRT-D and CRT-P, cardiac resynchronization with or without an implantable cardioverter defibrillator function, respectively; HF, heart failure; LVEF, left venticular ejection fraction; NYHA, New York Heart Association; RBBB, right bundle branch block.
[a]These were exclusion criteria in the trials.
[b]Previous ICDs were exclusion criteria in RAFT and only paced rhythm is reported.
[c]Follow-data available for 2111 (86.6 % of the total cohort).
[d]Combined mortality and hospitalization data from CARE-HF 2005 publication.
[e]Hospitalization data available for 1797 (73.7 % of the total cohort).

question. A large trial, Echo-CRT, is addressing the question of whether dyssynchrony measured by echocardiography can identify a group of patients with shorter QRS duration who benefit from CRT-D rather than ICD implantation, but will not answer the question of the impact of CRT compared with no device nor the impact of devices in patients with narrow QRS who do not have dyssynchrony.

Ischaemic heart disease predicts a worse outcome amongst patients with heart failure, and patients with ischeamic heart disease had a worse outcome in this survey. Randomized trials confirm that patients with ischaemic heart disease have a worse prognosis and less benefit from CRT in terms of ventricular remodelling[35] but, in terms of benefits on morbidity and mortality, the relative benefits in patients with and without ischaemic heart disease is similar[4,6,35] and therefore the absolute reduction in mortality may be somewhat greater in patients with ischeamic heart disease.

The lack of insight into the mechanism of benefits of CRT is frustrating and may reflect the fact that the main mechanism of benefit varies from one patient to the next and from one time and situation to another.[36] Mitral regurgitation, prevention of tachy- and bradyarrythmias, ventricular remodelling, as well as atrioventricular and biventricular resynchronization may all play different roles at different times in this patient population.[14,36] Like many successful interventions in heart failure, the lack of specificity is its secret of success.

Limitations

Surveys are important sources of information on how evidence acquired through RCTs, usually on highly selected patients managed according to detailed protocols, are adopted in clinical practice. However, surveys also have many limitations. Centre participation was voluntary and, among ~800 invited implanting centres in the 13 participating ESC countries, 141 centres responded and recruited patients during the 8 months inclusion period. The 2009 EHRA white Book reports ~30 000 annual CRT implantations in the participating countries (primary implants and replacements).[37] Although the importance of consecutive inclusion was emphasized, we cannot confirm that all patients were included consecutively, and there are several sources for potential investigator selection bias. Importantly, only successful implantations were entered into the database which selects the patient population, and could lead to an under-reporting of adverse experience in connection with implantation. The accuracy of the data has not been audited. NYHA functional class was investigator reported and the length of follow-up is short. There is a considerable variation in volume of participating centres[20] and the sample size for some of the eCRF variables due to incomplete data entry and lack of appropriate data fields in two device registries. However, the most important limitation of surveys is their inability to distinguish between outcome and response.[14]

Conclusions

This survey suggests that a group of patients representative of those encountered in routine clinical practice who received a CRT device considered their symptoms had improved compared wiht their pre-implant assessment. Overall survival was >90%. These favourable outcomes suggest that the benefits of CRT observed in RCTs can be replicated in routine clinical practice. However, further randomized trials comparing CRT-Ps with CRT-Ds would be desirable in patients with atrial fibrillation and in patients who do not have a substantial increase in QRS duration.

Funding

Stavanger University Hospital; HFA and EHRA of the ESC; EUCOMED (Biotronik, Boston Scientific, Medtronic, Sorin, and St. Jude Medical—members of the European Medical Device Trade Organization); Roche Diagnostics Ltd.

Conflict of interest: N.B., none to declare. S.P. is a consultant for Medtronic, Boston Scientific, and Biotronik. J.G.F.C. has received research grants from Medtronic and honoraria for speaking and consultation from Medtronic, St Jude, and Biotronik. J.B. has received research grants from Medtronic, Boston Scientific, St Jude Medical, Biotronik, and Sorin. C.L. is a consultant to Medtronic, a member of the Advisory Board for St Jude, and has received a research grant from Medtronic. A.A. is a consultant for Biotronik, St Jude EBR, Medtronic, Merck, and Philips. D.J.v.V has received consultancy fees from Medtronic. T.L., none to declare. A.G., none to declare. D.G. is a consultant to St Jude Medical, Medtronic, and Biotronik. C.S. has been sponsored by Medtronic, Biotronik, Boston Scientific, and SJM in the past. M.G. is a member of the advisory board to Medtronic and Boston Scientific. M.M. has received honoraria for participation in advisory board meetings and speeches from Corthera, Daiichi, Novartis, Servier, Sorin. and Stroder pharmaceuticals. G.D. has received travel support for scientific meetings from Actelion, Astra Zeneca, Boehringer Ingelheim, Medtronic, Pfizer, Sanofi, and Servier, and grants paid to the institution from Astra Zeneca, Actelion, Bayer, Brahms, General Electrics, Medtronic, Pfizer, Servier, Toshiba, and Trophos. F.G., none to declare. L.B., none to declare. K.D. has received speaker's honoraria from Medtronic and Biotronik.

Acknowledgements

We thank Stavanger University Hospital, the HFA and EHRA of the ESC, EUCOMED, and Roche Diagnostics Ltd for financial support. We are grateful to Tessa Baak (Stavanger Health Research, Norway) for excellent administrative assistance, and Dr Claus Jünger and Florian Schelz at Institut für Herzinfarktforschung in Ludwigshafen, Germany and Morten Aarflot at Stavanger University Hospital for statistical assistance.

Appendix 1. Members of the European CRT Survey Scientific Committee and National Co-ordinators

Scientific Committee

Kenneth Dickstein (HFA Co-ordinator)
Silvia Priori (EHRA Co-ordinator)
Angelo Auricchio
Nigussie Bogale
Josep Brugada
John G.F. Cleland

Geneviève Derumeaux
Anselm Gitt
Daniel Gras
Michel Komajda
Cecilia Linde
John Morgan
Dirk J. van Veldhuisen

National Co-ordinators (HF, heart failure; EP, electrophysiology)
Austria: Friedrich Fruhwald HF, Bernhard Strohmer EP
Belgium: Marc Goethals HF, Johan Vijgen EP
France: Jean Noel Trochu HF, Daniel Gras EP
Germany: Michael Kindermann HF, Christoph Stellbrink EP
Ireland: Ken McDonnald HF, David Keane EP
Israel: Tuvia Ben Gal HF, Michael Glikson EP
Italy: Marco Metra HF, Maurizio Gasparini EP
The Netherlands: Alexander Maass HF, Luc Jordaens EP, Marco Alings EP
Norway: Alf Inge Larsen HF, Svein Færestrand EP
Spain: Juan Delgado HF, Lluis Mont EP
Sweden: Hans Persson HF, Fredrik Gadler EP
Switzerland: Hans Peter Brunner-La Rocca HF, Stefan Osswald EP
UK: Ian Squire HF, John Morgan EP

Appendix 2. Steering Committee members of the Swedish Device registry and the German device registry

Sweden
Cecilia Linde
Fredrik Gadler
Johan Brant

Germany
Dietrich Andresen
Christian Butter
Bernd Gonska
Werner Jung
Karl-Heinz Kuck
Jochen Senges
Christoph Stellbrink

Appendix 3. List of contributing countries and centres (numbers of patients contributed)

Austria (156)
A. ö. Landeskrankenhaus, Universitätsklinikum Graz
Landeskrankenhaus-Innsbruck-Universitätskliniken
Krankenhaus der Elisabethinen Linz
Landesklinikum Thermenregion Mödling
Landeskrankenhaus Salzburg
Landesklinikum St. Pölten
Krankenhaus Hietzing mit Neurologischem Zentrum am Rosenhügel
Wilhelminenspital der Stadt Wien
A. ö. Krankenhaus Wiener Neustadt
Kaiser Franz Josef Spital

Belgium (43)
Clinique St Jean
Cliniques Universitaires Ucl
UZ Gent
Virga Jesse Ziekenhuis

France (160)
Hôpital du Bocage
Saint Etienne
Nouvelles Cliniques Nantaises
Hôpital Louis Pradel
Hôpital Princesse Grace

Germany (291)
Stadtisches Klinikum Dessau
Städt. Klinikum Brandenburg GmbH
Krankenhaus Reinbek
Universitätsklinikum Aachen-UKA
Klinik Rotes Kreuz
Saarland-Heilstätten GmbH Kliniken Völklingen
Universitätskliniken des Saarlandes
Kreiskliniken Altotting-Burghausen
Klinikum St. Marien Amberg
Hufeland Krankenhaus GmbH
Städt. Klinikum Frankfurt
Städt. Klinikum München Klinik Bogenhausen
Krankenhaus St. Franziskus Mönchengladbach
St. Josefs-Krankenhaus Potsdam
Klinikum Lippe-Detmold
Städt. Kliniken Bielelfed-Klinikum Mitte
Krankenhaus München- Neuperlach (Kardiologie)
Klinikum der Universität München-Großhadern
Universitätsklinikum Heidelberg
Universitätsklinikum Münster (Kardiologie)
Klinikum Coburg
Herzzentrum Ludwigshafen
Herzzentrum Brandenburg
Allgemeines Krankenhaus Celle
Klinikum Ernst von Bergmann Potsdam
Herzzentrum Coswig

Ireland (47)
Mater Misercordea University Hospital
South Infirmary Victoria University Hospital
St Vincent's University Hospital

Israel (195)
Sheba Medical Center
Barzilai Medical Center
Wolfson Medical Center
Kaplan Medical Center
Rabin Medical Center
Haemek Medical Cente

Italy (571)
Ospedale Moriggia-Pelascini
Ospedale Fatebenefratelli Sgc
Ospedale S. Giovanni di Dio Fatebenefratelli
P.O. Frosinone Ceccano
Ospedale S.Maria Misericordia-Perugia
Presidio Ospedaliero di Rivol

Ospedale S.Andrea
P.O. Genova-Ponente P.A. Micone
A.O. Ospedale S.Gerardo Monza
Policlinico Di Monza-Monza
IRCCS Instituo Clinico Humanitas Rozzano
IRLCS Multimedica
A.O. Ospedale Treviglio Caravaggio Trev-Treviglio
A.O. Desenzano Del Garda
Spedali Civili Di Brescia
Fondazone Poliambulanza Ist. Osp.
A.O. Maggiore Della Caritá Novara
Presidio OspedalieroDi Montebelluna
Azienda Ospedaliero S. Maria Miseric Udine
Presidio Ospedaliero Di Camposampiero
Presidio Ospedaliero Di Cittadella
Azienda Ospedaliera Di Padova
Presidio Ospedaliero Di Vicenza
Ospedale Civile Destra Secchia
Osp. Le S.M. Annunziata Bagno A Rip-Bagno A Ripoli
Stabilimento Di Cisanello
Istituto Fisiologia Clinica
Pia Fondazione (Tricase)-Tricase
Ospedale S.Maria Di Loreto Mare
Aziena Ospedaliero S. Giovanni Di Dio
Clinica Sant'Anna
Ospedale 'Umberto I'
Clinica Mediterranea

The Netherlands (114)

Academisch Medisch Centrum
Amphia Ziekenhuis
Catharina Ziekenhuis
Isala Klinieken Zwolle
Medisch Centrum Alkmaar
Medisch Spectrum Twente
Erasmus MC
Kennemer Gasthuis
University Medical Center Groningen

Norway (126)

Ålesund Hospital
Haukeland University Hospital
Kristiansand Hospital
Oslo University Hospital, Rikshospitalet
Oslo University Hospital, Ullevål
Stavanger University Hospital
St. Olavs Hospital

Spain (131)

Hosp. De Cruces
Hospital Gregorio Maranon, Madrid
Hosp. Virgen de la Victoria
Hospital Universitario De Tenerife
Hospital Dr. Peset, Valencia
Centro Medico Salus Baleares S.l. – Benidorm, Alicante
Hospital Clinico Y Provincial, Barcelona
Hospital Sta. Creu Y St. Pau, Barcelona
Hospital General U. De Alicante, Alicante

Sweden (321)

Danderyds Sjukhus AB
Länssjukhuset, Kalmar
Karolinska Universitetssjukhuset, Solna
Akademiska sjukhuset
Blekingesjukhuset
Centrallasarettet Västerås
Falu lasarett
Hudiksvalls sjukhus
Kärnsjukhuset Skövde
Lässjukhuset Gävle
Länssjukhuset Kalmar
Norrlands Universitetssjukhus
Sahlgrenska Universitetssjukhuset
St Görans sjukhus
Sundsvalls sjukhus
Universitetssjukhuset Örebro
Universitetssjukhuset Lund
Varbergs sjukhus

Switzerland (83)

Cardiocentro Ticino
HCF Hopital Cantonal Fribourg
Hopitaux Universitaires de Geneve, Geneve 14
Universitatsspital Basel

UK (201)

Southampton General Hospital
Kings College Hospital
Queen Elizabeth Hospital
Leeds General Infirmary
Hull Royal Infirmary
Papworth Hospital
University Hospital of Wales

References

1. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**:873–880.
2. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–1853.
3. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
4. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
5. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;**52**:1834–1843.
6. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338.
7. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–2395.
8. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluza M Guidelines for cardiac pacing cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Europace* 2007;**9**:959–98.

9. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;**29**:2388–23442.
10. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Circulation* 2008;**117**:e350–e408.
11. Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J, Ponikowski P, Priori SG, Sutton R, van Veldhuisen DJ, Vahanian A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, Anker SD, Blanc JJ, Gasparini M, Hoes AW, Israel CW, Kalarus Z, Merkely B, Swedberg K, Camm AJ. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. *Eur Heart J* 2010;**31**:2677–2687.
12. van Veldhuisen DJ, Maass AH, Priori SG, Stolt P, van Gelder IC, Dickstein K, Swedberg K. Implementation of device therapy (cardiac resynchronization therapy and implantable cardioverter defibrillator) for patients with heart failure in Europe: changes from 2004 to 2008. *Eur J Heart Fail* 2009;**11**:1143–1151.
13. Merkely B, Roka A, Kutyifa V, Boersma L, Leenhardt A, Lubinski A, Oto A, Proclemer A, Brugada J, Vardas PE, Wolpert C. Tracing the European course of cardiac resynchronization therapy from 2006 to 2008. *Europace* 2010;**12**:692–701.
14. Cleland JG, Tavazzi L, Daubert JC, Tageldien A, Freemantle N. Cardiac resynchronization therapy: are modern myths preventing appropriate use? *J Am Coll Cardiol* 2009;**53**:608–611.
15. Kaul S, Diamond GA. Trial and error. How to avoid commonly encountered limitations of published clinical trials. *J Am Coll Cardiol* 2010;**55**:415–427.
16. Gitt AK, Bueno H, Danchin N, Fox K, Hochadel M, Kearney P, Maggioni AP, Opolski G, Seabra-Gomes R, Weidinger F. The role of cardiac registries in evidence-based medicine. *Eur Heart J* 2010;**31**:525–529.
17. Granger CB, Gersh BJClinical trials registries in cardiovascular disease: competitive or complementary? *Eur Heart J* 2010;**31**:520–521.
18. Leurs LJ, Buth J, Harris PL, Blankensteijn JD. Impact of study design on outcome after endovascular abdominal aortic aneurysm repair. A comparison between the randomized controlled DREAM-trial and the observational EUROSTAR-registry. *Eur J Vasc Endovasc Surg* 2007;**33**:172–176.
19. Dickstein K, Bogale N, Priori S, Auricchio A, Cleland JG, Gitt A, Limbourg T, Linde C, van Veldhuisen DJ, Brugada J. The European cardiac resynchronization therapy survey. *Eur Heart J* 2009;**30**:2450–2460.
20. Bogale N, Priori S, Gitt A, Alings M, Linde C, Dickstein K, on behalf of the Scientific Committee, National coordinators, and the investigators. The European cardiac resynchronization therapy survey: patient selection and implantation practice vary according to centre volume. *Europace* 2011;**13**:1445–1453.
21. CRT Survey Scientific Committee. European cardiac resynchronization therapy survey: rationale and design. *Eur J Heart Fail* 2009;**11**:326–330.
22. Bogale N, Witte K, Priori S, Cleland J, Auricchio A, Gadler F, Gitt A, Limbourg T, Linde C, Dickstein K, on behalf of the Scientific Committee, National coordinators, and the investigators. The European Cardiac Resynchronization Therapy Survey: comparison of outcomes between *de novo* cardiac resynchronization therapy implantations and upgrades. *Eur J Heart Fail* 2011;**13**:974–983.
23. Cleland JG, Freemantle N, Daubert JC, Toff WD, Leisch F, Tavazzi L. Long-term effect of cardiac resynchronisation in patients reporting mild symptoms of heart failure: a report from the CARE-HF study. *Heart* 2008;**94**:278–283.
24. Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JG. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. *Eur Heart J* 2007;**28**:42–51.
25. Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JG. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. *Eur Heart J* 2007;**28**:42–51.
26. Auricchio A, Metra M, Gasparini M, Lamp B, Klersy C, Curnis A, Fantoni C, Gronda E, Vogt J. Long-term survival of patients with heart failure and ventricular conduction delay treated with cardiac resynchronization therapy. *Am J Cardiol* 2007;**99**:232–238.
27. Swedberg K, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, Metra M, Torp-Pedersen C, Poole-Wilson P. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J* 2005;**26**:1303–1308.
28. Delnoy PP, Ottervanger JP, Luttikhuis HO, Elvan A, Misier AR, Beukema WP, van Hemel NM. Comparison of usefulness of cardiac resynchronization therapy in patients with atrial fibrillation and heart failure versus patients with sinus rhythm and heart failure. *Am J Cardiol* 2007;**99**:1252–1257.
29. Dong K, Shen WK, Powell BD, Dong YX, Rea RF, Friedman PA, Hodge DO, Wiste HJ, Webster T, Hayes DL, Cha YM. Atrioventricular nodal ablation predicts survival benefit in patients with atrial fibrillation receiving cardiac resynchronization therapy. *Heart Rhythm* 2010;**7**:1240–1245.
30. Gasparini M, Auricchio A, Regoli F, Fantoni C, Kawabata M, Galimberti P, Pini D, Ceriotti C, Gronda E, Klersy C, Fratini S, Klein HH. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. *J Am Coll Cardiol* 2006;**48**:734–743.
31. Gasparini M, Auricchio A, Metra M, Regoli F, Fantoni C, Lamp B, Curnis A, Vogt J, Klersy C. Long-term survival in patients undergoing cardiac resynchronization therapy: the importance of performing atrio-ventricular junction ablation in patients with permanent atrial fibrillation. *Eur Heart J* 2008;**29**:1644–1652.
32. Brignole M, Botto G, Mont L, Iacopino S, De Marchi G, Oddone D, Luzi M, Tolosana JM, Navazio A, Menozzi C. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J* 2011;**32**:2420–2429.
33. Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? *J Am Coll Cardiol* 2009;**53**:355–360.
34. Egoavil CA, Ho RT, Greenspon AJ, Pavri BB. Cardiac resynchronization therapy in patients with right bundle branch block: analysis of pooled data from the MIRACLE and Contak CD trials. *Heart Rhythm* 2005;**2**:611–615.
35. Wikstrom G, Blomstrom-Lundqvist C, Andren B, Lonnerholm S, Blomstrom P, Freemantle N, Remp T, Cleland JG. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. *Eur Heart J* 2009;**30**:782–788.
36. Cleland JG, Tageldien A, Buga L, Wong K, Gorcsan J 3rd. Should we be trying to define responders to cardiac resynchronization therapy? *JACC Cardiovasc Imaging* 2010;**3**:541–549.
37. The EHRA White Book. July 2009. http://www.escardio.org/communities/EHRA/publications/Documents/ehra-white-book-2009.pdf. 2010.
38. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac REsynchronization-Heart Failure (CARE-HF) trial extension phase]. *Eur Heart J* 2006;**27**:1928–1932.
39. Linde C, Gold M, Abraham WT, Daubert JC. Baseline characteristics of patients randomized in the Resynchronization Reverses Remodeling In Systolic Left Ventricular Dysfunction (REVERSE) study. *Congest Heart Fail* 2008;**14**:66–74.