The European Cardiac Resynchronization Therapy (CRT) Survey

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Dissertation for the degree philosophiae doctor (PhD)

at the University of Bergen

2011

Dissertation date: 20th October 2011

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Scientific environment

The European CRT Survey Scientific Committee

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PhD grant by Stavanger University Hospital

Stavanger University Hospital
Stavanger Hospital Trust

Data management centre: Institut für Herzinfarktforschung Ludwigshafen an der Universität Heidelberg, Ludwigshafen, Germany

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Funding support by the Heart Failure (HFA) and the European Heart Rhythm (EHRA) Associations of the European Society of Cardiology (ESC), EUCOMED (Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical), and ROCHE diagnostics Ltd.

Clinical study number: NCT 01185392

Acknowledgements

One cold winter morning back in 2006, in the corridor of the Coronary Care Unit “3G”, Professor Dickstein asked if I would be interested in taking part in a clinical “registry” on Cardiac Resynchronization Therapy. This I was told would hold the potentials for PhD thesis. He also characteristically stated: “In life doors open and doors close. One has opened for you if you would like to jump in.” I did accordingly.

I admire his great working capacity and enthusiasm. E-mails sent from me well into the early hours of the morning were commented on the next day at the morning meeting. Attempts at prompting him were answered with: “I read my e-mails”. I know of no one of equal calibre and it has been a great pleasure to work with such world class clinician and scientist. Conducting a Survey of such magnitude and running it from Stavanger would have been unthinkable had it not been for Kenneth and his enormous international network. Kenneth’s continuous perseverance as well as power to get things done has been pivotal throughout the project and I am highly indebted for all the formal and informal discussions at all places and almost whenever and from wherever. It has been a great scientific journey and I have learnt quite a lot.

However, there were trying and frustrating times when the project was in its infancy. The Survey was almost proclaimed dead on a number of occasions but thankfully revived after several cycles of resuscitation.

This work has opened a great opportunity to work with senior and experienced scientists in the fields of heart failure, electrophysiology and echocardiography who are members of the Scientific Committee. Input from them has been instrumental throughout the development of the protocol, case report form and discussions of the data management and the publication process. Excellent co-coordination of the efforts by Prof. Silvia Priori has been invaluable. Special thanks to Prof. Cecilia Linde of Karolinska, Sweden who has always been caring and supportive. Her suggestion to present the baseline findings at Hotline session at ESC meeting in Barcelona 2009 gave impetus to the Survey and has been instrumental for its success with subsequent simultaneous publication in the European Heart Journal and my invitation by the ESC to become Fellow (FESC). Critical and timely comments from Prof.

John GF Cleland of University of Hull, UK, have been constructive. The merger of two existing databases from Sweden and Germany has been a challenge. The National Coordinators Prof. Fredrik Gadler and Prof. Christoph Stellbrink have been key players in their respective countries and deserve special thanks. The members of the Scientific Committee and National Coordinators are active in continuing work on the database and we look forward to further publications from this important database.

This work would not have been possible without the voluntary participation of all the investigators at the 141 implanting centres even when the reimbursement for their efforts was unavailable.

Establishment of central database is an important aspect of such a large effort. The statistical analysis support provided by the data management centre at Ludwigshafen, Germany under the leadership of Dr. Anselm Gitt has been exemplary. Special thanks to Tobias Limbourg (PhD) for his availability and timely statistical analyses and good discussions.

The ESC web department has played an important role by supporting the website www.crt-survey.org which has been instrumental in providing the necessary information and documents for participating centres. We are grateful for these efforts.

Tessa Baak's tremendous organizational and language skills, hard work and talent to get the job done have been instrumental for the success of this Survey. Her optimism during the early difficult days of getting the Survey off the ground is much appreciated.

Combining research work and a clinical career as a trainee in the field of Interventional Cardiology has been challenging and would not have been possible without the continual support and encouragement of the then department chief Dr. Cord Manhenke. Thank you for the good and informal "talks" in the corridors and wherever the opportunities were available. The then director of the medical department, Dr. Sverre Uhlving, has always been supportive from the days I was offered a job as a resident in the department of internal medicine and later on facilitating the combination of research and clinical work. Dr. Svein Skeie who replaced him was available whenever needed and I am grateful for his constructive support on my future plans of further clinical and research stay abroad.

The clinical research experience at Stavanger Health Research has been and is of enormous support for researchers in our hospital guiding through the jungle of rules and regulations. Special thanks goes to Torbjørn Årsland for always being there when needed and sharing his enormous and deep knowledge of the intricacies of clinical research. My colleagues in the department and the staff at the catheterization labs have been always supportive. Local participants in the Survey were implanted by Prof. Dennis Nilsen and Prof. Alf Inge Larsen who also is a National Coordinator.

In my early school years, Sr. Marit Sandal who also used to be mentor for my father was not only caring but also generous in her kind words. Thanks a lot. The late Sr. Berhane Petros is unforgettable not only for her affectionate care and enthusiastic support but also for being a great neighbour.

This work would not have been possible without my PhD grant from Stavanger University Hospital which arrived when most needed. We are also thankful to the European Medical Device Trade Organization-EUCOMED members (Biotronik, Boston Scientific, Medtronic, Sorin and St. Jude Medical) and Roche Diagnostics Ltd. for financing the expenses for database management at Ludwigshafen, Germany.

From early days on, my parents prioritized their children's schooling with their limited resources. They have always been there for us and I am highly indebted for the care, love and support cherished by them. Thanks to my brothers and sister for their continuous concern and affectionate love.

Finally but importantly, a well-deserved thanks goes to the love of my heart Hellen for being there for me and for our lovely daughters Abigail and Edna. I was given the space I needed through challenges and we were able to move on even when family vacations were compromised by short deadlines from journal editors. Thank you for always reminding me of the essentials and cores of life.

Abstract

The European CRT Survey

Aims: The European Cardiac Resynchronization Therapy (CRT) Survey was a joint initiative taken by the Heart Failure (HFA) and the European Heart Rhythm (EHRA) Associations of the European Society of Cardiology (ESC) designed to evaluate the current implantation practice of Cardiac Resynchronization Therapy (CRT) in the participating countries.

Methods: Patients who had a successful CRT implantation were enrolled from 141 centres in 13 countries between November 2008 and June 2009. The participating countries were Austria, Belgium, France, Germany, Ireland, Israel, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland and UK. Baseline demographics, clinical and implantation data were collected using electronic case report form (eCRF) with a follow-up of approximately one year (9-15 months). Centres were divided into high and low volume categories and their patient selection and implantation practice was analysed. Outcomes in de novo implantations were compared to upgrades from permanent pacemakers (PPM) and implantable cardioverter defibrillators (ICDs). The follow-up data contained clinical outcomes including symptom severity, cardiovascular hospitalization and survival.

Results: 2438 patients were enrolled and follow-up data acquired from 2111 patients (87 %). The population included important groups of patients poorly represented in randomized clinical trials (RCTs), including very elderly patients, those with prior device implantation, atrial fibrillation and QRS duration < 120 ms.

Significantly more CRT implantation in patients with mild symptoms and narrow QRS width was reported at high volume centres. Similar improvement in New York Heart Association

(NYHA) class, similar reduction in QRS duration and low and similar total and cause specific mortality was observed between upgrades and de novo implantations.

Investigators reported substantial improvement in NYHA functional class at follow up and patients reported improvement in self-assessed global condition. During follow-up, 207 (10 %) patients died, 346 (16 %) were hospitalized and 501 (24 %) died or were hospitalized. NYHA functional class III/IV, atrial fibrillation, ischaemic aetiology and device type (CRT-P) were associated with poor survival. Predictors of CV hospitalization and the combined end point of CV hospitalization or mortality were NYHA functional class III/IV and atrial fibrillation. Women had a better outcome as did patients who had a CRT-D device.

Conclusions: The CRT Survey provided important information describing current European implantation practice at the time of inclusion. High-volume centres were more explorative in their implantation practice than low-volume centres. Patients undergoing upgrades from existing devices (PPM and ICDs) had similar outcomes and complications rates compared to de novo implantations. Outcomes including death and hospitalization during 1 year follow-up in this European CRT survey were consistent with results from clinical trials of CRT. At one year follow-up, 81 % of patients who received a CRT device considered their symptoms improved compared to the pre-implant assessment. This is a prospective, observational study of successful CRT implantations and the results must be interpreted with appropriate conservatism.

List of publications

1. European cardiac resynchronization therapy survey: rationale and design. Eur J Heart Fail. 2009 Mar;11(3):326-30. **Corresponding author Bogale N**.

2. Dickstein K, **Bogale N**, Priori S, Auricchio A, Cleland JG, Gitt A, et al. The European cardiac resynchronization therapy survey. Eur Heart J. 2009 Oct;30(20):2450-60.

3. **Bogale N**, Priori S, Auricchio A, Cleland JG, Gitt A, Dickstein K. The European CRT Survey: Patient selection and Implantation practice vary according to centre volume. Europace 2011 Sep 5 (epub ahead of print)

4. **Bogale N**, Witte K. Priori S, Cleland JG, Auricchio A, Gitt A, et al. The European CRT Survey: Comparison between upgraded and de novo cardiac resynchronization therapy implantations Eur J Heart Fail. 2011 Sep;13(9):974-983. Epub 2011 Jul 19.

5. **Bogale N**, Priori S, Cleland JG, Brugada J, Linde C, Auricchio A, et al. The European CRT Survey: 1 year follow-up results Eur J Heart Fail. 2011 (in press)

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Abbreviations

ACE	Angiotensin converting enzyme
ARB	Angiotensin receptor blocker
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy combined with ICD
CRT-P	Cardiac resynchronization therapy pacemaker without ICD
eCRF	electronic case report form
HFA	Heart Failure Association of the ESC
EHRA	European Heart Rhythm Association of the ESC
ESC	European Society of Cardiology
HRS	Heart Rhythm Society
ICD	Implantable cardioverter defibrillator
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
PPM	Permanent pacemakers
RBBB	Right bundle branch block
RCT	Randomized controlled trials

1. Introduction

1.1 Cardiac resynchronization therapy (CRT)

Cardiac resynchronization therapy (CRT) was introduced in 1994 following an anecdotal experience on a single patient with dramatic effects(1). The Multicite Stimulation in Cardiomyopathies (MUSTIC) trial conducted in 2001 was the first randomized trial with cross-over design in the field of CRT which documented reduced heart failure hospitalizations, improved NYHA functional class, exercise distance and peak oxygen uptake(2). In 2002, the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) further demonstrated reduction in heart failure hospitalizations, improvement in left ventricular ejection fraction and exercise capacity(3). Comparison of Medical Therapy Pacing and Defibrillation in Heart Failure (COMPANION) trial conducted in 2004 was the first to demonstrate improvement in the combined end point of death and hospitalizations followed by Cardiac Resynchronization-Heart Failure (CARE-HF) trial which demonstrated survival benefits in 2005(4, 5).

CRT is indicated in patients with symptomatic heart failure (NYHA III and IV) despite adequate medical treatment, a QRS duration ≥ 120 ms and left ventricular ejection fraction (LVEF) ≤ 35 %. The 2007 ESC/EHRA Guidelines for Cardiac Pacing(6), the 2008 ESC Heart Failure Guidelines(7) and the 2008 ACC/AHA/HRS Guidelines for Device Therapy(8) provide a class I recommendation with level of evidence A for CRT with or without an ICD in order to improve survival and reduce morbidity. More recent studies, REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction (REVERSE), Multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) and

Resynchronization-Defibrillation for Ambulatory Heart Failure trial (RAFT) (9-11) have explored the use of CRT in patients with mild symptoms, wide QRS complex and LV dysfunction and reported favourable outcomes. The results of REVERSE and MADIT-CRT have led to an expansion of the indications as described in the recent update from the ESC committee on practice guidelines(12).

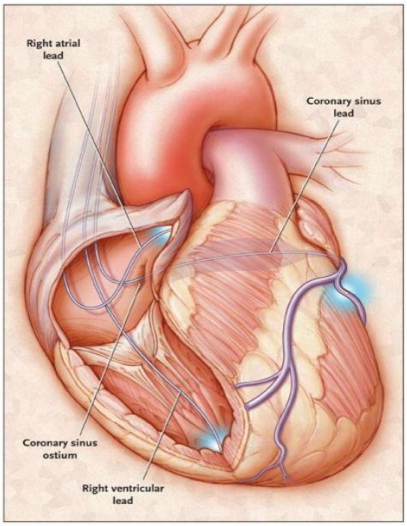

Figure 1: Biventricular Pacing for Cardiac Resynchronization Therapy (figure taken from NEJM(13))

The implantation rate of both CRT-P and CRT-D devices has increased in Europe from 2004-2008(14). However there are substantial regional, national and centre based differences in implantation practice. The decision to include ICD's in CRT's is a big challenge in daily clinical practice due mainly to lack of proper evidence. Guidelines provide limited guidance on which patients should have CRT-P or CRT-D, reflecting the lack of prospective randomized clinical trials (RCTs) designed to compare the efficacy of the two types of devices(15-17).

1.2 Surveys and registries compared to randomized controlled trials (RCTs)

Cross-sectional surveys are snapshots of clinical practice often designed to evaluate implementation of recommendations suggested by guidelines. They are usually performed for a specified period of time with or without a planned follow-up.

Non-randomized prospective registries document allocation of treatment in consecutive patients and measure outcomes in a defined cohort. They usually involve follow-up over time(18). In contrast, randomized controlled trials are designed and powered to evaluate new interventions in a blinded, controlled fashion.

The advantages of surveys and registries are that they capture data from a more heterogeneous population and should reflect actual clinical practice and answer different questions (18-20). Previous assumptions suggesting that observational studies report greater treatment benefit have been shown not to be valid (21, 22). The disadvantages are potential selection bias, incomplete data collection and may underestimate adverse experience if proper precautions are not taken at the planning phase (18, 23).

Although randomized controlled trials have specific hypothesis in well-defined populations, they have their limitations too. The disadvantages are that they select patients according to strict inclusion criteria and exclude elderly patients and patients with important comorbidities. In addition to this, often strong focus is attributed to statistical significance without taking into account clinical significance (24).

1.3 Selection of patients to CRT and response to treatment

Predicting response in patients treated with CRT is a challenge in daily clinical practice. The definition of response needs also further refinement and should not be confused with outcomes(25). There is also poor agreement between the parameters selected to define response(26).

Several patient selection criteria have been suggested to predict response. A LBBB pattern (electrical dyssynchrony) in patients with symptomatic heart failure as a surrogate indicator of dyssynchronous left ventricular contraction has shown to be robust criteria in many trials. A recent meta-analysis of existing randomized trials identifies QRS duration over 150 ms as a strong predictor of reducing adverse clinical events(27). Studies on benefit of CRT in patients with narrow QRS width with or without evidence of echocardiographic mechanical dyssynchrony report conflicting results and it remains to be addressed in further clinical trials(28-34).

Imaging and especially, echocardiographic parameters of mechanical dyssynchrony have been utilized to help finding proper candidates. However, identifying single and reproducible echocardiographic measure of dyssynchrony remains to be a challenge (35, 36).

1.4 Upgrading from permanent pacemakers and ICDs to CRT

Studies have demonstrated that right ventricular (RV) pacing is associated with heart failure-related hospitalization and death with direct relation to the cumulative percentage of RV pacing (37-39). Upgrading existing systems (permanent pacemakers and ICDs) to CRTs

in patients with deteriorated left ventricular function can improve LV functions and symptoms by a similar magnitude as seen in de novo implantations (40-43). However, upgrading existing pacemakers carries higher risk of subsequent complication than performing a de novo implant(44, 45), due to potential limited venous access, risks of damage to or requirement for extraction of old leads and infection(46, 47). Despite the fact that an upgrade procedure is not entirely risk free, no randomized placebo-controlled trial of upgrading to CRT has been performed in patients with RV pacemakers (or ICDs) and heart failure.

1.5 Initiation of the European CRT Survey

Because of the existing variations in practice, the Heart Failure (HFA) and the European Heart Rhythm (EHRA) Associations of the ESC jointly initiated this CRT Survey with the objective of describing current European practice and routines associated with CRT-P/CRT-D implantations. Sampling was done in 141 centres from 13 countries: Austria, Belgium, France, Germany, Ireland, Israel, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland and UK.

2. Objectives of the thesis

2.1 General objectives

To assess the current implantation practice of CRT devices in a wide sampling from European implanting centres.

2.1.1 Specific objectives

1. Rationale and design of the Survey
2. To describe the populations being implanted with CRT devices with regard to patient selection, implantation routines and techniques, peri-procedural complications and in hospital course
3. To explore the variations in practice based on the volume of implanting centres
4. To assess outcomes of patients upgraded from previous devices (pacemakers and ICDs) compared to de novo implantations
5. To report outcomes during the 1 year (9-15 months) follow-up

3. Subjects

The study recruited 2438 patients from 141 centres in 13 countries.

The volume based analysis included 2392 patients from 136 centres. 5 centres had missing volume information and therefore were excluded from the analysis.

692 patients were upgraded from either conventional pacemakers or ICDs. 430 of these patients had ventricular paced rhythm. The upgraded patients were compared and contrasted with regards to procedural details and outcomes with de novo implantations.

Follow-up data was acquired from 2111 patients (87 % of the Survey cohort).

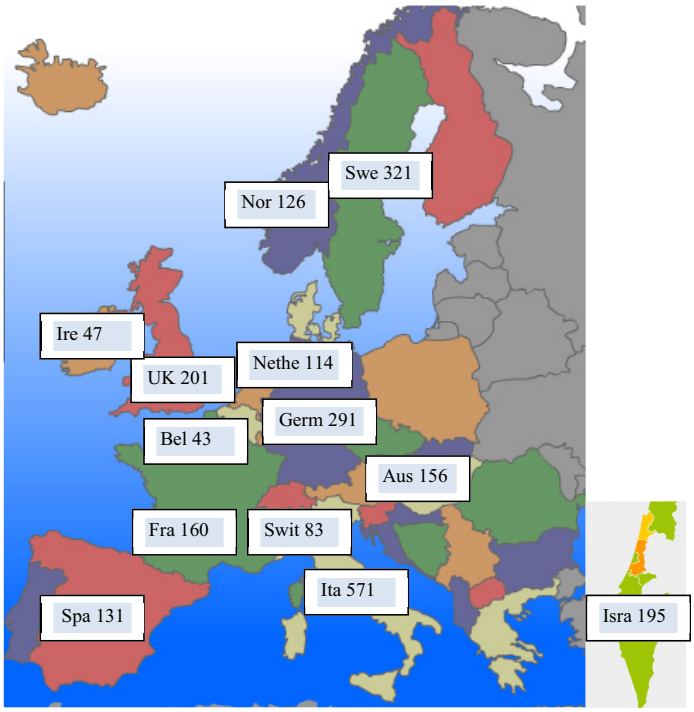

Figure 2: participating countries and patients per country

4. Methods

A Scientific Committee was established comprised of 13 professionals from the fields of heart failure, electrophysiology and echocardiography and co-coordinated by Professor Kenneth Dickstein (HFA) and Professor Silvia Priori (EHRA). Two National Coordinators (appendix 1) from the participating countries (one each from the fields of heart failure and electrophysiology) were selected to facilitate patient inclusion and follow-up in their respective countries.

An electronic case report form (eCRF) was developed by the Scientific Committee.

All CRT implanting centres in the selected 13 countries were invited to participate into the Survey and were asked to complete a one-time site questionnaire describing the type and size of the centre, reference area population, facilities, and number of invasive procedures performed. 141 of the centres responded and that is approximately 18 % of the invited centres. Germany and Sweden have on-going device registries which include CRTs and capture most of the information contained in the CRT Survey eCRF. With permission from both of the Steering Committees (appendix 2), CRT data collected consecutively in these two registries during the time frame were merged into the CRT Survey database.

Inclusion of patients started 1st November 2008 and ended 30th June 2009. All consecutive patients successfully implanted with a new CRT-P, CRT-D or upgrades were eligible. The procedure itself identified the patient as a Survey candidate. A successful implantation was defined as a completed procedure. Patients screened but not successfully implanted were not entered into the Survey. Ethical approval and written informed consent were obtained according to the rules for clinical investigations in each participating country at the time of initiation of the study.

A central data-base 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. Tessa Baak (Stavanger Heath Research Foundation) and Tobias Limbourg (Institut für Herzinfarktforschung in Ludwigshafen) followed the daily inclusion activity and provided advice regarding operational issues.

Centre volume information was acquired from the one time site questionnaire collected at the initiation of the Survey. ICD implantation rate the previous year was chosen as the basis for assignment of centre volume category as it showed to be the most appropriate. A median of 120 ICDs were implanted at the participating centres. Centres implanting $\leq$ 120 ICDs per year were therefore regarded as low volume and centres implanting $>$120 ICDs per year were regarded as high volume centres. 42 (30 %) centres were classified as high volume and 94 (67 %) as low volume centres with the average CRT implantation rate of 29 and 13 respectively. Complete centre volume information was not available in 5 (4 %) of the participating centres. A total of 1200 CRT devices were implanted at high volume centres and 1192 CRT devices at low volume centres.

Analysis of upgrades versus de novo implantations included 2367 CRT implant procedures of whom 692 (28%) were upgrades to CRT.

The 1 year (9-15 months) follow-up data were collected through the routine device follow-up schedule and the window of 6 months was allowed in order to give enough time to capture data from routine device follow-ups.

5. Statistics

All statistical work and database management was performed at Institut für Herzinfarktforschung in Ludwigshafen an der Universität Heidelberg, Germany. Absolute numbers and percentages are shown for categorical variables to describe the patient population, and medians with inter-quartile range or means with standard deviations for continuous variables. Binary variables (yes/no response variables) were compared between subgroups by the Pearson chi-square test and continuous variables (numeric values) by the Mann-Whitney-Wilcoxon-test. Odds ratios and confidence intervals were calculated where appropriate. Descriptive statistics were calculated for the available cases where it applied. A significance level of $p < 0.05$ was assumed for the statistical tests and all P-values are results of two-tailed tests. Kaplan Meier survival estimates and logistic regression analyses between the variables were performed as required (paper 4 and 5). All statistical analyses were performed using SAS© statistical software, version 9.1 (Cary, North Carolina, U.S.A.)

6. Summary of results

6.1 Paper I

Paper 1 is the rationale and design paper which summarized the difference in CRT implantation practice in Europe reporting the variations in number of implants per country and the ratio between CRT-D and CRT-P. The information provided in this paper together with the protocol and eCRF was important document for invited centres providing the necessary background material for the decision to participate in the Survey.

6.2 Paper II

Results

2438 patients were enrolled into the Survey. The mean age of patients was 68 years ±10 and 31 % were ≥ 75 years. 78 % were in NYHA functional class III or IV and 22 % in I or II. The mean ejection fraction was 27 % ± 8 and the mean QRS duration 157 ms ± 32. QRS duration was < 120 ms in 9 %. Atrial fibrillation was reported in 23 %. 26 % of patients had a previously implanted permanent pacemaker or ICD. 76 % of procedures were performed by an electrophysiologist. 82 % had an elective admission for implantation and the median duration of hospitalisation was 3 days (IQR 2-7). 73 % received a CRT-D device which was more often implanted in men, younger patients and patients with ischaemic aetiology. The mean QRS duration was reduced to 133 ms ± 27 ($p<0.0001$) at discharge. Peri-procedural complication rates were comparable to the rates reported in randomized trials.

Conclusions - This CRT Survey provides important information describing current European practice with regard to patient demographics, selection criteria, procedural routines and status at discharge. These data should be useful for benchmarking individual patient management and national practice against wider experience.

6.3 Paper III

Results - A total of 1200 CRT devices were implanted at high volume centres and 1192 CRT devices at low volume centres. 42 (30 %) centres were classified as high volume and 94 (67 %) as low volume centres with the average CRT implantation rate of 29 and 13respectively. Complete centre volume information was not available in 5 (4 %) of the participating centres. Germany, the Netherlands and UK had the highest percentage of high volume centres while Belgium, Switzerland, Austria, Sweden and Italy the highest percentage of low volume centres. No differences were noted with regard to sex, age or peri-procedural and device related complications between high volume and low volume centres. High volume centres implanted CRT devices in significantly more patients with mild symptoms and a narrow QRS width. The procedure and fluoroscopy times were substantially longer at low volume centres and devices were more frequently implanted by surgeons and interventional cardiologists. Patients stayed longer in hospital in low volume centres with a median of 4 (2-9) vs. 2 (2-6) days.

Conclusions - High volume centres explore newer indications in their CRT practice and implant devices more frequently in patients with mild symptoms and narrow QRS durations. Electrophysiologists dominate implantation practice at high volume centres and duration of hospitalisation is substantially shorter at these centres.

6.4 Paper IV

Results - This analysis included 2367 CRT implant procedures of whom 692 (28%) were upgrades to CRT. Distribution of NYHA functional class and left ventricular function were similar between the groups. Procedural duration was also similar, although fluoroscopy time was shorter in the 'upgrades'. There was no difference in the frequency of peri-procedural complications. There were similar improvements in NYHA functional class and similar reduction in QRS duration but more patients reported unchanged global patients assessment status in the upgraded group. Total and cause-specific mortality at one year was low and the same in both groups.

Conclusions – More than one quarter of all CRT procedures are upgrades from existing systems, although this group has not been subject to randomized clinical trials. Our data suggest that there are no significant differences in clinical outcomes or complication rates between upgrades and de novo procedures.

6.5 Paper V

Results - 2438 patients were enrolled and follow-up data acquired from 2111 patients (87 %). The population included important groups of patients poorly represented in randomized clinical trials, including very elderly patients and those with previous device implantation, atrial fibrillation and/or QRS duration < 120 msec.

Investigators reported substantial improvement in NYHA functional class at follow-up. Patient self-assessment indicated that 81 % of patients felt much better/a little better, 16 % reported no change and 4 % reported worsening of their status. During follow-up, 207 patients died (10 %), 346 (16 %) were hospitalized and 501 (24 %) died or were

hospitalized. NYHA functional class III/IV, atrial fibrillation, ischemic aetiology, and device type (CRT-P) and were associated with poor survival. Predictors of CV hospitalization and the combined end point of CV hospitalization or mortality were NYHA functional class III/IV and atrial fibrillation.

	COMPANION (4)	CARE-HF (5, 48)	REVERSE (9, 49)	MADIT-CRT (10)	RAFT (11)	CRT Survey
No of patients (CRT-P/CRT-D) control groups	1212 308	409 404	419 191	1089 731	894 904	2438 0
Mean follow-up (mo)	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[δ]	0[δ]	0[δ]	0[δ]	13	23
Previous device	0[δ]	0[δ]	0[δ]	0[δ]	NA[δδ]	28
Ventricular paced rhythm	0[δ]	0[δ]	0[δ]	0[δ]	8	18
RBBB	10	0[δ]	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[δ]	0[δ]	100	100	80	22
III/IV	100	100	0[δ]	0[δ]	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)§
Death or hospitalization for HF	449 (37.1)	118 (28.9)[ϕ]	26 (6.2)	187 (17.2)	297 (33.2)	501 (23.7)£

[ϕ] combined mortality and hospitalization data from CARE-HF 2005 publication (5)
§ follow-up data available for 2111 (86.6 % of the total cohort)
£ hospitalization data available for 1797 (73.7 % of the total cohort)
[δ] these were exclusion criteria in the trials
[δδ] previous ICDs were exclusion criteria in RAFT and only paced rhythm is reported

Conclusions - Outcomes including death and hospitalization during 1 year follow-up in this European survey were consistent with results from clinical trials of CRT. At one year follow-up, most patients who received a CRT device are alive and feel they have improved compared to their pre-implant assessment. This is an observational survey should not be used to try to define whether subgroups did or did not respond to therapy.

7. Discussion

This Survey, which was jointly initiated by the Heart Failure (HFA) and the European Heart rhythm (EHRA) Associations of the European Society of Cardiology (ESC), is the largest available on CRT implantation practice in Europe which included 2438 patients in 13 countries from 141 centres. The primary objective of the Survey was to describe current practice and routines associated with consecutive and successful CRT-D/CRT-P implantations in the participating centres. During the study period, the ESC guidelines on device treatment for heart failure were updated to include patients with milder symptoms, atrial fibrillation and conventional pacemaker indications (50).

The first publication was the design and rationale paper which described inclusion criteria and contents of the eCRF both at baseline and during follow-up. It was important document aimed to be invitation and information to the prospective participating centres(51).

The baseline and short term outcomes at the index hospitalization were presented in the **second publication** from this survey(52). The population included important groups of patients poorly represented in randomized clinical trials, including very elderly patients and those with prior device implantation, atrial fibrillation and/or QRS duration < 120 msec.

The target populations and diagnostic investigations that would best select patients likely to respond favourably from intervention have not been identified(53). QRS duration, a measure of electrical dyssynchrony has formed the basis inclusion criteria in randomized clinical trials. Currently, none of the commonly employed echocardiographic measurements appear robust enough to accurately evaluate mechanical dyssynchrony or predict clinical response (36). Based on clinical experience and intuition, clinicians frequently extrapolate

the data from randomized clinical trials to wider populations which is appropriate when clinical evidence is lacking and no opportunity to enrol the patient into a relevant RCT exists. It is evident from the description of the patient characteristics of the population included in this Survey that clinicians are actively exploring wider indications. Generally our cohort is remarkably similar to the cohorts recruited in randomized clinical trials. A consistent finding is the low proportion of women receiving CRTs both in randomized clinical trials and this Survey. Aggressive medical management was confirmed with high percentages of patients treated with diuretics, ACE inhibitors, ARBs, beta blockers, and aldosterone antagonists. Importantly in this real-world population, complication rates were similar to the rates reported in RCTs. On the other hand the peri-operative complication rate is not negligible and must be weighed against the potential benefits when considering CRT therapy in patients in mild symptoms.

The third publication from this Survey's cohort investigated whether the volume of implants per centre was a determinant of the propensity to use devices for "off-label" indications and reported that high volume centres explore newer indications in their CRT practice and implant devices more frequently in patients with mild symptoms and narrow QRS durations. Centres were categorized into low volume ($\leq$ 120 implantations/year) and high volume ($>$ 120 implantations/year) based on median ICD implantation the previous year which was found to be the most appropriate.

There is substantial variation across Europe with regard to adoption of the recommendations by guidelines (54). Specifically, practice varies widely with regard to decisions concerning device type (CRT-P/CRT-D)(55) due to lack evidence to assist the clinicians in making decisions regarding device type. Comparison based on centre volume

and experience in this Survey provides important information regarding existing variations in practice. Local reimbursement policies, the existence of national guidelines and high number of conventional ICD implantations are identified as important factors for national practice variations while GDP or health care spending appears to have a minor role(54). However, basing national practice on the number ICD implantations should be approached cautiously as a recent study from the USA has showed non-evidence based practice(56).

The fourth publication addressed the issue of upgrading to CRT from permanent pacemakers (PPM) and ICDs comparing to de novo implantations. The Survey cohort included 692 patients (28 %) with previous devices. A paced ventricular rhythm was reported in 430 patients (62 %) at the time of inclusion. Our data suggest that there are no significant differences in clinical outcomes or complication rates between upgrades and de novo procedures.

This practice is a substantial extrapolation beyond the evidence. Small studies have previously demonstrated favourable short and long term outcomes in patients receiving CRT as an upgrade to a standard RV pacemaker(40, 57) and the practice of upgrading pacing systems to those capable of delivering CRT is mentioned in guidelines, albeit with a class IIa (level of evidence: C) recommendation. Our analysis provides some reassurance that, upgrading a previous device to one capable of providing resynchronization therapy seems to be associated with a similarly modest medium-term complication rate to a de novo implant. Nevertheless, the efficacy of CRT in this patient group is not established with trial data (37, 58, 59). The recent RAFT trial that included a small number (135/1798) of

previously paced patients but subgroup analysis did not reveal a clinical benefit of upgrading to CRT (11).

Many patients receiving RV pacemakers are elderly and have a background of ischaemic heart disease or hypertension, both of which contribute to the development of heart failure. In addition however, RV pacing induces intra and inter-ventricular dyssynchrony(60), which seems to be similar to that of left bundle branch block (LBBB)(40, 61), although recent tissue tracking data suggest that intra-mural dyssynchrony might be different in patients paced from the RV apex(62). The imposition of abnormal contractile timing can lead to altered regional blood flow and wall stress (63-65). The severity of these perfusion abnormalities, the regional wall motion abnormalities and the associated deterioration in global left ventricular function are directly related to the duration(63) and cumulative percentage of RV pacing(39), but can be identified in some individuals after only 18 months of pacing(66). The induction of dyssynchrony by RV apical pacing seems therefore to lead to adverse LV remodelling, LV dilatation and asymmetrical hypertrophy (67), which can lead to the induction or progression of LV dysfunction (68). One recent study of patients in need of ventricular pacing due to bradycardia and with normal LVEF at the time implantation support that ventricular function assessed at 12 months was worse in patients randomized to RV compared to CRT pacing(69). The data from the present Survey confirm data from smaller studies that patients with RV pacing-associated ventricular dysfunction seem to have slightly better overall LV function and more left ventricular hypertrophy (LVH)(40, 62), which might be the morphological characteristics of the increasingly recognised ‘pacing cardiomyopathy’.

Despite differences in baseline LVEF, the present data suggest that the symptomatic response is similar in patients with and without a previous device, although a slightly higher

proportion of patients self-reported unchanged total global assessment in the upgraded group. NYHA functional class and total and cause-specific mortality at one year were similar between the groups. This is reassuring since a randomized, placebo-controlled trial in RV-paced patients with class III and IV heart failure is unlikely to be performed. The fact that the European CRT survey outcome data for patients undergoing upgrades compare favourably with those for the de novo group in whom the benefit of CRT implantation has already been confirmed in randomized studies suggests that even in the absence of a randomized trial, upgrade procedures could receive more support in guidelines.

As discussed, patients with RV pacing systems, especially those with unavoidable RV apical pacing are at high risk of LV dysfunction. The next logical step is to explore whether patients with underlying LV dysfunction, an absolute indication for rate support and mild or absent symptoms benefit from CRT at initial implant (70) or elective upgrade before they deteriorate. Whether taking the opportunity provided by generator replacement to implant an LV lead in patients with evidence of LV dysfunction and few symptoms will reduce subsequent risk of hospitalisation or death or need for upgrade should be tested in a prospective randomised, controlled trial.

The final manuscript from this Survey presents outcomes during the 1 year (9-15 months). Follow-up data including vital status were available for 2111 patients which accounts for 87 % of the total survey population. During the course of follow-up, 207 (10 %) patients died, 346 (16 %) patients were hospitalized for cardiovascular reasons and 501 (24 %) patients died or were hospitalized. The findings in this Survey are consistent with results from previous clinical trials. 81 % of the patients report improvement in self-assessed global condition.

Women are less represented than men in this Survey (24 %) as is evident in several studies (5, 9-11). However, the outcomes of treatment with CRT devices appear to be better in women than in men which may be associated with higher proportion of non-ischaemic aetiology in women.

Studies comparing survival outcomes between recipients of CRT-D and CRT-P are lacking. Findings from this Survey clearly identify allocation to device type CRT-D as important prognostic factor for survival both univariate and multi-variate analysis. However these findings should be interpreted cautiously since CRT-P recipients in this cohort were older (median age 75 vs. 68 years) and the influence of selection is evident.

Our Survey included 544 patients (23 %) with atrial fibrillation which indicated poor outcomes with regards to death, hospitalization for cardiovascular reasons and the combination of death or hospitalization. Information on the percentage of cumulative biventricular pacing, the extent of AV node ablation post device implantation or up titration of medical treatment to assure adequate pacing was not captured in the Survey. The RAFT trial included 115 patients (13 %) with atrial fibrillation or flutter (11). No benefit of CRT treatment was observed in this population compared to ICD therapy, though the Survey population is not directly similar to the RAFT population. Inadequate measure to assure pacing may explain this observation which differs from previous findings reporting benefit of CRT treatment in populations with atrial fibrillation (71-74).

7.1 Strengths of the survey

One of the strengths of this Survey is inclusion of patients which are similar to the patients in daily clinical practice who have not been adequately addressed in randomized clinical

trials. Importantly, patients with previous device, substantial number of patients over the age of 75 years, patients with atrial fibrillation, RBBB, mild symptoms and narrow QRS width are included reflecting the dilemma which exists in tailoring treatment to individual patients. Important recent clinical and implantation data are collected from 13 countries. The results permit individual countries to benchmark their practice against international practice.

7.2 Limitations

Surveys are important sources of information on how evidence acquired through randomized clinical trials are adopted in clinical trials. However, surveys have their own limitations which need to be considered during interpretation of the findings which we report. Centre participation was voluntary and among all eligible and invited, only 141 centres responded and recruited patients in the 13 countries. Although the importance of consecutive inclusion was emphasized, we cannot confirm that all patients were included consecutively and there is a potential for 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. There is a considerable variation in the sample size for some of the eCRF variables due to unavailable information, incomplete data entry and incomplete overlap between the variables collected in the 2 device registries and this Survey. The Swedish pacemaker registry data base was restructured during the follow-up phase of the Survey which resulted in acquisition of only survival data of this particular cohort.

Conclusions

1- The baseline characteristics of patients included were similar to available randomized clinical trials cohorts and complication rates were comparable. This Survey has demonstrated substantial CRT implantations in populations not addressed in current guidelines.

2- High volume centres are exploring broader indications in their CRT practice and implant devices more frequently in patients with mild symptoms and narrow QRS durations.

3-Outcomes in patients upgraded to CRT from permanent pacemakers (PPM) and ICDs are similar to outcomes following de novo implantations.

4- Outcomes including death and hospitalization during 1 year follow-up in this European survey were consistent with results from clinical trials of CRT. At one year follow-up, 81 % of patients who received a CRT device considered their symptoms improved compared to the pre-implant assessment and 90 % of them were alive. This is a prospective, observational study of successful CRT implantations and the results must be interpreted with appropriate conservatism.

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