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CLINICAL RESEARCH

Clinical trial design

European Cardiac Resynchronization Therapy Survey II: rationale and design

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The Cardiac Resynchronization Therapy (CRT) Survey II is a 6 months snapshot survey initiated by two ESC Associations, the European Heart Rhythm Association and the Heart Failure Association, which is designed to describe clinical practice regarding implantation of CRT devices in a broad sample of hospitals in 47 ESC member countries. The large volume of clinical and demographic data collected should reflect current patient selection, implantation, and follow-up practice and provide information relevant for assessing healthcare resource utilization in connection with CRT. The findings of this survey should permit representative benchmarking both nationally and internationally across Europe.

Keywords

Heart failure • Cardiac resynchronization therapy • CRT Survey • Devices

Background

The benefits of cardiac resynchronization therapy (CRT) on clinical outcomes in patients with symptomatic heart failure and electrical dyssynchrony are convincing.^{1–7} Therefore, current guidelines give strong recommendations for CRT in patients who do not respond sufficiently to medical therapy.^{8,9} However, implantation rates in most countries do not reflect adequate implementation of current guideline recommendations. Further efforts are therefore warranted to describe current clinical practice and permit benchmarking across Europe.

Cardiac Resynchronization Therapy Survey II is a 6 months snapshot survey to assess current clinical practice with regard to CRT in a large sample size from a broad geographical area. The survey will capture essential logistical and procedural details in connection with consecutive CRT-P/CRT-D implantations and provide information permitting centres and countries to benchmark their practice with national and international practice. Data on important safety measures and major short-term events associated with CRT

implantations during the index hospitalization will be reported with long-term follow-up in a subset. The details of centre routines including facilities, device activity profiles, and reimbursement policies, as well as patient selection, implantation practice and outcomes in individual patients will provide information permitting assessment of health resource utilization and identification of the obstacles to adequate CRT implementation at individual centres and countries.

The first Cardiac Resynchronization Therapy Survey

Between 2008 and 2009, the European Society of Cardiology (ESC) in cooperation with the European Heart Rhythm Association (EHRA) and the Heart Failure Association (HFA), conducted a 6 month survey of patients receiving CRT, the results of which were published in 2009.^{10–12} This first CRT Survey was based on data from 13 countries with 2438 implantations and provided valuable insights into current clinical practice in this field. Overall large differences in implantation rates were found across countries with a

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What's new?

- The first CRT Survey performed in 2008, demonstrated that clinicians were exploring indications broader than those recommended in the ESC Guidelines. Substantial numbers of patients with mild symptoms, atrial fibrillation, a narrow QRS complex, a previous device or advanced age received CRT devices.
- Recent evidence based on randomized clinical trials as well as updated ESC Guidelines should have a major impact on clinical practice.
- CRT Survey II will capture clinical and demographic data, describe current implantation and follow-up practice and provide information relevant for assessing health care resource utilization in connection with CRT.
- The Survey should permit representative benchmarking both nationally and internationally in 47 ESC member states.

marked underutilization of therapy. However, and unexpectedly, the survey also showed that large numbers of CRT-P/CRT-D devices were implanted outside of recommendations in the guidelines.^{13,14} Thus, a CRT device was frequently implanted in patients with atrial fibrillation (23%), narrow QRS (<120 ms) (9%), previous devices (26%), mild symptoms (22% in NYHA class I or II) and in patients with advanced age (31% \geq 75 years). In summary, the first CRT Survey demonstrated that clinicians were exploring indications broader than those recommended in the ESC Guidelines.

We believe that such heterogeneous CRT implementation practices across patient groups and countries still exist. Moreover, the importance of optimal implantation techniques to reduce the risk of complication and of left ventricular lead placements to enhance response to CRT has become increasingly clear. Therefore, EHRA and HFA have now planned a more extensive survey. This Survey, CRT Survey II, is designed to detect and reflect the substantial changes in device guideline recommendations recently published by both EHRA and HFA.^{8,9} These recommendations emphasize the importance of QRS duration and morphology, clinical status, and also provide new indications for CRT in patients requiring upgrades to CRT, patients with atrial fibrillation and in those who need permanent ventricular pacing due to high degree atrioventricular block.¹⁵

Most of the current information available regarding CRT implantations and complications has been obtained from randomized control trials (RCT) usually performed in relatively high volume centres with experienced implanters. Randomized control trials have strict inclusion criteria, and include selected patient groups, tending to exclude both elderly patients and those with a large number of co-morbidities. It is estimated that as few as one-third of patients with heart failure would actually qualify to participate in a heart failure RCT.¹⁶ Thus, extrapolating from the findings of RCTs to the broad clinical population may not always be appropriate.

Surveys and registries provide useful data that can complement RCTs in producing evidence-based medicine.¹⁷ Surveys enrol all eligible patient groups, preferably consecutively, including high-risk

patients that tend to be excluded from RCTs and thus are more representative of the general clinical population permitting more extensive subgroup comparisons. Surveys and registries can therefore be used to confirm or refute whether data from RCT can be extrapolated to RCT-excluded patient subgroups. Surveys may also identify the true magnitude of complications in routine clinical practice and capture adverse events that may occur in high-risk patient groups. Variations in patient selection criteria and implantation routines are identified, permitting both benchmarking and assessment of adherence to current ESC Guidelines.

Design

Participating countries

The HFA and EHRA will invite investigators from 47 ESC member countries to participate in the survey. Information from the 2014 EHRA White Book¹⁸ regarding the number of implanting centres and CRT devices implanted in 2013 in these countries is listed in Appendix I. Each country enrolled in the Survey will have a single national coordinator, selected by the corresponding National Cardiology Society. The National Coordinator's role is to recruit centres and implanters and facilitate the successful performance of the survey. Each country will retain the rights to publish on their national data and benchmark internationally. The National Coordinators will have responsibility for the publication process of their national data.

Survey population

All hospitalized patients accepted for *de novo* implantation of a CRT-P/CRT-D, or for upgrades from an implantable cardioverter defibrillator or permanent pacemaker to a CRT-P/CRT-D, are eligible for inclusion. Patients should be included consecutively. Ethics approval for participation in the survey will be obtained in those countries where it is required.

Data collection and management

The CRT Survey II includes two internet-based questionnaires. Initially, a one-time site description questionnaire will be completed by each site prior to inclusion of the first patient. This information will describe the organization of the device programme at each site and provide information useful for assessing health resource utilization. Specifically, it will cover description of hospital type, the size of the catchment area, the number and type of invasive procedures and device implantations performed, the cardiac facilities such as on-site cardiac surgery, invasive laboratory types, types of imaging equipment employed, the number and speciality of implanting physicians and the follow-up options and routines provided for patients receiving CRT devices. Importantly, the type and source of hospital reimbursement will be recorded. An abbreviated summary of the contents of the one-time site questionnaire can be found in Appendix II.

The second form is an internet-based electronic case report form (eCRF) for each patient included in the survey. It will be initiated prior to implantation of the device to ensure that all consecutive successful and non-successful implantations are reported. This streamlined eCRF has been revised substantially by the Steering Committee

in collaboration with representatives from the CRT manufacturers to capture the information that proved most useful in the first CRT Survey as well as to reflect the changes in clinical practice that have occurred in response to the most recent European Guideline recommendations. The eCRF includes information regarding patient demographics, aetiology of heart failure, co-morbidities, pharmacological therapy, electrocardiogram morphology and QRS duration, imaging information, indication for CRT implantation, laboratory status, procedural details including left ventricular (LV) lead position, device programming as well as discharge status, important peri-procedural or post-procedural complications and follow-up plans. Importantly and in contrast to the first CRT Survey, data from unsuccessful CRT implantations will also be included and identify obstacles for successful implantations of the LV lead. Vital status at 1 year will be obtained in the majority of patients. An abbreviated summary of the contents of the eCRF can be found in Appendix III.

Data collection, management, and analysis in the first CRT Survey was organized by Institut für Herzinfarktforschung in Ludwigshafen. Institut für Herzinfarktforschung will again organize data management and perform statistical analyses for CRT Survey II. The centre has an effective, licensed, online data capture system, which allows data entry in any local language.

Conclusions

Cardiac Resynchronization Therapy (CRT) Survey II follows on from the success of the first ESC CRT Survey, which provided valuable information regarding implantation practices in 13 ESC member countries. This second Survey will include 47 ESC member countries and benefit in design from our previous experience. The large volume of clinical data collected should reflect current selection, implantation and follow-up practice and provide information relevant for assessing healthcare resource utilization in connection with CRT devices. The findings of this Survey should permit representative benchmarking both nationally and internationally across Europe.

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References

- Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T *et al*. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–50.
- Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L *et al*. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–49.
- Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C *et al*. Effects of multi-site biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**:873–80.
- Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E *et al*. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–53.
- Linde C, Abraham WT, Gold MR, StJSM, Ghio S, Daubert C *et al*. 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**:1834–43.

- Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP *et al*. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–38.
- Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S *et al*. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–95.
- McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K *et al*. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in Collaboration with the Heart Failure Association (HFA) of the ESC. ESC Committee for Practice Guidelines. *Eur J Heart Fail* 2012;**14**:803–69. No abstract available. Erratum in: *Eur J Heart Fail* 2013;**15**:361–2.
- Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA *et al*. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. *Europace* 2013;**15**:1070–118.
- Dickstein K, Priori S, Auricchio A, Brugada J, Cleland J, Derumeaux G *et al*. European Cardiac Resynchronization Therapy Survey: rationale and design. The CRT Survey Scientific Committee. *Eur J Heart Fail* 2009;**11**:326–30.
- Dickstein K, Bogale N, Priori S, Auricchio A, Cleland J, Gitt A *et al*. The European Cardiac Resynchronization Therapy Survey. *Eur Heart J* 2009;**20**:2450–60.
- Bogale N, Priori S, Cleland JG, Brugada J, Linde C, Auricchio A *et al*. Scientific Committee, National Coordinators, and Investigators. The European CRT Survey: 1 year (9–15 months) follow-up results. *Eur J Heart Fail* 2012;**14**:61–73.
- Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ecotr H *et al*. 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. Guidelines for cardiac pacing and cardiac resynchronization therapy. *Europace* 2008;**10**:707–25.
- Dickstein K, Vardas PE, Auricchio A, Daubert JC, Linde C, McMurray J *et al*. 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. *Europace* 2010;**12**:1526–36.
- Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfese L *et al*. Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial Investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013;**368**:1585–93.
- Masoudi FA, Havranek EP, Wolfe P, Gross CP, Rathore SS, Steiner JF *et al*. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. *Am Heart J* 2003;**146**:250–7.
- Gitt AK, Bueno H, Danchin N, Fox K, Hochadel M, Kearney P *et al*. The role of cardiac registries in evidence-based medicine. *Eur Heart J* 2010;**31**:525–9.
- Kuck KH, Hindricks G, Padeletti L, Raatikainen P, Arnar DO. The EHRA White Book 2014. The Current Status of Cardiac Electrophysiology in ESC Member Countries. www.escardio.org/EHRA.

Appendix I

Number of cardiac resynchronization therapy (CRT) devices implanted in 2013 by country.

Data from the EHRA White Book for 2014.

(Listed in descending order by number of implantations per year).

Bolded countries were included in the First Survey.

Country	Number of centres	CRTs per year
Italy	361	12148
Germany	465	8859
France	159	*8605
United Kingdom	109	7762
Poland	25	3000

Continued

Continued

Country	Number of centres	CRTs per year
Spain	130	2545
Netherlands	57	2069
Czech Republic	17	1716
Belgium	35	1221
Israel	20	1216
Austria	18	1178
Russian Federation	42	1012
Denmark	5	1001
Hungary	13	984
Sweden	*33	967
Portugal	26	*564
Greece	16	500
Switzerland	31	477
Slovakia	5	452
Finland	14	437
Norway	9	426
Egypt	13	414
Ireland	17	378
Serbia	6	329
Bulgaria	8	260
Kazakhstan	9	209
Romania	17	200
Lithuania	3	165
Slovenia	2	131
Lebanon	5	100
Ukraine	13	89
Croatia	7	81
Morocco	5	75
Estonia	2	70
Algeria	8	64
Latvia	2	63
Belarus	5	54
Georgia	6	40
Bosnia and Herzegovina	2	25
Cyprus	3	25
Luxembourg	1	22
Azerbaijan	2	17
Macedonia FYR	2	16
Malta	1	16
Iceland	1	14
Armenia	2	10
Montenegro	1	10

*Data from 2012.

Appendix II

A summary of the contents of the one-time site questionnaire for CRT Survey II.

Hospital information

- Hospital details, primary contact, implanting physicians

Hospital facilities

- Total number of hospital beds, number of cardiology department beds
- Type of hospital: university, teaching, community, or private hospital
- Number of inhabitants of catchment area
- Cardiac surgery on site, angiography/percutaneous coronary intervention on site
- Total number of catheterization laboratories, dedicated electrophysiological labs, other sites where devices are implanted, hybrid/surgical/radiology

Follow-up

- Heart failure clinic for patient follow-up? Dedicated CRT clinic for follow-up? A remote device monitoring follow-up service? Are all patients followed-up at implanting centre?

Reimbursement

- Reimbursed for CRT devices? what is the source?(Public health provider/Private insurance/Private payer)

Cardiology activity profile

- Coronary angiograms in 2014
- Percutaneous coronary intervention procedures in 2014
- CRT-P implanted in 2014
- CRT-D implanted in 2014
- ICD implanted in 2014
- New non-CRT pacemaker implantations in 2014

Number and specialty of CRT implanting physicians in 2014

- Electrophysiologists
- Interventional cardiologists
- Heart failure physicians
- Cardiac surgeons
- General cardiologists

Does your centre participate in

- An active device registry?
- Randomized clinical trials?
- Observational studies?
- A dedicated lead extraction/management program?

Appendix III

A summary of the contents of the electronic case report form for CRT Survey II.

Demographics

- Date of admission, age, gender, elective admission, referral from another centre

Heart failure aetiology

- Ischaemic, non-ischaemic, other
- History of revascularization (percutaneous coronary intervention/coronary artery bypass graft)

Past history and major comorbidity

- Chronic obstructive pulmonary disease, diabetes, myocardial infarction, atrial fibrillation, chronic kidney disease, heart failure (HF) hospitalization during last year, previous device implantation (PPM/ICD)

Pre-implant clinical evaluation

- NYHA class, weight, height, blood pressure
- Pharmacologic therapy prior to implantation

Pre-implant electrocardiogram

- Heart rate, rhythm, PR interval, paced rhythm, atrioventricular (AV) block, AV nodal ablation?

Electrocardiogram indication for CRT therapy

- QRS duration and morphology

Clinical indication for CRT

- Device implantation primarily based on treatment of symptoms?
- To improve prognosis? LV dysfunction?
- Indication for an ICD? (primary or secondary prevention?)
- LV dysfunction and bradycardia requiring permanent pacing

Preimplant imaging prior to CRT implantation

- Echo, magnetic resonance imaging, computed tomography, scintigraphy
- Various indices of LV function and size

Laboratory measurement

- Hb, Na, K, BNP, NT-proBNP, creatinine (eGFR)

Procedure

- Date, type of device, operator, location of procedure, duration, fluoroscopy time, prophylactic antibiotics, test shock
- Was a venogram performed?

- If LV lead placement is unsuccessful what was main reason? (coronary sinus not located, no suitable coronary vein, other complication)
- LV lead type: unipolar, bipolar, multipolar
- LV position evaluation evaluated in bi-plane x-ray projection [left anterior oblique (LAO) site evaluation: anterior, lateral, posterior, right anterior oblique (RAO) site evaluation: basal, mid basal, apical]

Peri-procedural complications

- Death, bleeding, pneumothorax, pericardial tamponade, haemothorax, coronary sinus dissection

Post-procedural complications

- Pocket haematoma, phrenic nerve stimulation, lead dislocation or displacement, lead malfunction

Post-implant electrocardiogram

- Paced QRS duration

Device programming

- AV/VV programming prior to discharge?
- Availability of remote monitoring?

Discharge status and major adverse events

- Vital status
- Adverse events following implantation during index hospitalization
- (Myocardial infarction, stroke, infection, HF decompensation, arrhythmias, worsening renal function, other)

What follow-up is planned?

- CRT clinic? HF clinic?

One year follow-up (optional)

- Vital status
- Date of last contact
- Current NYHA class