Cardiac Resynchronization Therapy (CRT): Patient Selection and Guideline Adherence.

An Analysis of CRT Practice in Europe Based on the European Society of Cardiology CRT Survey II with 11088 patients in 42 countries.

Camilla Jacqueline Hansine Normand

Thesis for the degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Name: Camilla Jacqueline Hansine Normand

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Scientific Environment

Main supervisor: Professor Kenneth Dickstein, MD, PhD

Co-supervisor: Dr Nigussie Bogale MD, PhD

Cardiology Division, Stavanger University Hospital, Stavanger, Norway

Institute of Internal Medicine, University of Bergen, Bergen, Norway

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Contents

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Abbreviations

ACC	American College of Cardiology
AF	Atrial Fibrillation
AHA	American Heart Association
AV	Atrioventricular
CCS	Canadian Cardiovascular Society
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy –Defibrillator
CRT-P	Cardiac Resynchronization Therapy –Pacemaker
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EF	Ejection Fraction
EHRA	European Heart Rhythm Society
ESC	European Society of Cardiology
GDP	Gross Domestic Product
HF	Heart Failure
HFA	Heart Failure Association
HFrEF	Heart failure Reduced Ejection Fraction
HRS	Heart Rhythm Society
ICD	Implantable Cardioverter Defibrillator
IHF	Institut für Herzinfarktforschung

IQR	Interquartile Ranges
IRB	Institutional Review Board
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
NC	National Coordinator
NYHA	New York Heart Association
OR	Odds Ratio
PM	Pacemaker
RBBB	Right Bundle Branch Block
RCT	Randomized Control Trial
RV	Right Ventricle
SAP	Statistical analysis plan
SC	Scientific Committee
STEMI	ST Elevation Myocardial Infarction

List of Papers

1.**Normand C**, Linde C, Singh J, Dickstein K. Indications for Cardiac Resynchronization Therapy: A Comparison of the Major International Guidelines. JACC Heart Fail 2018;**6**(4):308-316.

2.Dickstein K, **Normand C,** Auricchio A, Bogale N, Cleland JG, Gitt AK, Stellbrink C, Anker SD, Filippatos G, Gasparini M, Hindricks G, Blomstrom Lundqvist C, Ponikowski P, Ruschitzka F, Botto GL, Bulava A, Duray G, Israel C, Leclercq C, Margitfàlvi P, Cano O, Plummer C, Sarigul NU, Sterlinski M, Linde C. CRT Survey II: a European Society of Cardiology Survey of Cardiac Resynchronisation Therapy in 11 088 Patients-Who is Doing What to Whom and How? Eur J Heart Fail 2018.

3.**Normand C**, Linde C, Bogale N, Blomstrom-Lundqvist C, Auricchio A, Stellbrink C, Witte KK, Mullens W, Sticherling C, Marinskis G, Sciaraffia E, Papiashvili G, Iovev S, Dickstein K. Cardiac Resynchronization Therapy Pacemaker or Cardiac Resynchronization Therapy Defibrillator: What determines the choice?-Findings from the ESC CRT Survey II. Europace 2019;**21**(6):918-927.

Submitted

4 **Normand C,** Linde C, Blomström-Lundqvist C, Stellbrink C, Gasparini M, Anker S, Plummer C, Umutay Sarigul N, Papiashvili G, Iovev S, Dickstein K. Adherence to ESC Cardiac Resynchronization Therapy Guidelines – Findings from the ESC CRT Survey II.

Abstract

Background/Aims

Cardiac Resynchronization Therapy (CRT) reduces morbidity and mortality in patients with heart failure and electrical dyssynchrony. [1-7] Recommendations for which patients should receive a CRT device are outlined in cardiology society guidelines. However, these recommendations vary and for certain recommendations are imprecise. The purpose of this PhD is to explore why there are variations in international guideline recommendations and how these may contribute to differences in practice using the cohort of CRT Survey II with 11 088 patients in 42 European Society of Cardiology (ESC) member countries.

Methods

The recommendations provided by the major international guidelines were reviewed to identify areas of consistency and inconsistency in CRT recommendations. Data were collected on consecutive patients implanted with a CRT device in 42 ESC countries. These data were analysed to assess CRT practice and guideline adherence and relate them to variations in guideline recommendations.

Results

There was mainly consistency in the international guidelines regarding who should receive a device. However, some inconsistencies were identified. These included patients with non-left bundle branch block (LBBB) and patients with heart failure and a pacemaker requirement, implanted with a CRT to avoid right ventricular pacing dependence. Some of these inconsistencies could be explained by the timing of the release of the guidelines. However, others appeared to be related to CRT trial evidence being interpreted differently by different societies. In the European CRT population we found that implanters adhered well to European guidelines with

only 2% of patients being implanted outside guideline recommendations. However, practice did vary in the different countries and these variations were more pronounced in areas where guideline recommendations are inconsistent or undetermined.

Discussion

Adherence to guidelines for CRT in Europe is high. However, in areas where there is limited CRT trial evidence this results in imprecise and inconsistent recommendations in international guidelines and may contribute to promoting variations in CRT practices in different countries.

1.Introduction

1.1 Heart Failure and Electrical Dyssynchrony

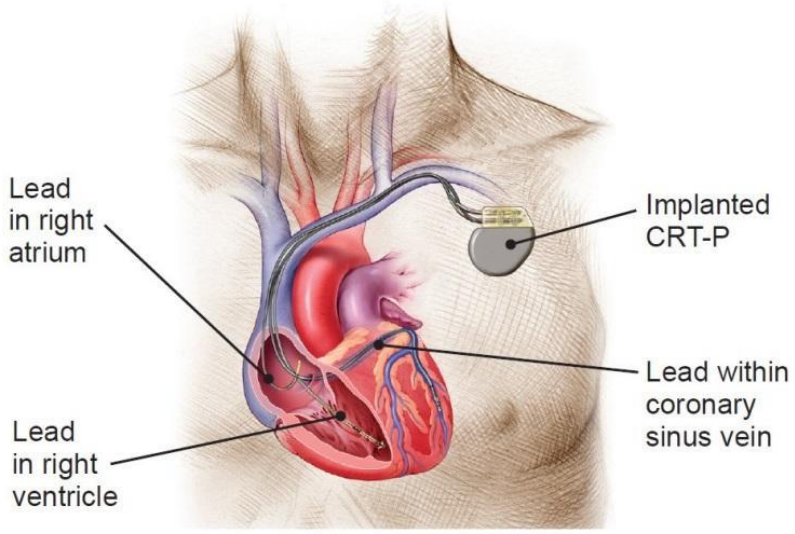
Heart failure (HF) is a complex clinical syndrome characterized by symptoms and signs including breathlessness, fatigue and fluid retention. It is associated with increased hospitalization and mortality rates. The principal treatment for heart failure is pharmacological. [8]

A common finding in heart failure patients is that their left ventricle (LV) is dilated and their heart pumps ineffectively. [9] These patients are described as having heart failure due to reduced ejection fraction (HFrEF) or systolic heart failure. Certain patients with systolic heart failure also show signs of electrical dyssynchrony on their electrocardiogram (ECG) exhibited by a prolonged QRS duration. This prolongation of the QRS duration is due to disruption of the normal electrical conduction system due to myocardial damage caused by ischaemia or cardiomyopathy. [10] This disruption leads to abnormal ventricular depolarization and dyssynchronous ventricular systolic contraction. This dyssynchrony results in a reduction in the efficiency of cardiac contractile forces, which further aggravates the systolic dysfunction. [10] Cardiac resynchronization therapy (CRT) is a device treatment that may partially restore synchronous contraction.

1.2 Cardiac Resynchronization Therapy

A CRT device has an additional lead compared with a traditional two-lead pacemaker. This third lead, shown in figure 1, is placed on the left ventricle via a cardiac vein and acts with the right ventricle (RV) lead to enable biventricular pacing. Such pacing improves the synchrony of ventricular contraction in patients with a prolonged QRS duration. [10] CRT has been shown in large randomized control trials (RCT) to decrease both morbidity and mortality. [1-7]

Figure 1 – Cardiac Resynchronization Therapy



(From bostonscientific.com)

1.3 CRT Guideline Recommendations

Optimal medical treatment for heart failure is detailed in the various guidelines produced by international cardiology societies. The task forces producing the guidelines review the current evidence available including randomised controlled trials and meta-analysis of such trials and use these to provide recommendations for treatment. These recommendations are supplemented by information on the quality of the evidence behind these guidelines. Table 1 and 2 show how the European Society of Cardiology (ESC) present their recommendations and evidence levels. Other international societies use similar schemes. [8]

Table 1 - Classes of Recommendation (ESC Guidelines) [8]

Classes of recommendations	Definition	Suggested wording to use
Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.**	**Is recommended/is indicated**
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.**	
Class IIa	***Weight of evidence/opinion is in favour of usefulness/efficacy.***	**Should be considered**
Class IIb	***Usefulness/efficacy is less well established by evidence/opinion.***	**May be considered**
Class III	**Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.**	**Is not recommended**

Table 2 - Levels of Evidence (ESC Guidelines)[8]

Level of evidence A	**Data derived from multiple randomized clinical trials or meta-analyses.**
Level of evidence B	**Data derived from a single randomized clinical trial or large non-randomized studies.**
Level of evidence C	**Consensus of opinion of the experts and/ or small studies, retrospective studies, registries.**

However, despite the fact that the guideline task forces review the same evidence, their guideline recommendations occasionally differ. [11]

1.4 The Evidence for CRT and Evolution of European Guidelines

The initial pivotal CRT RCTs from 2001 and 2002 showed improved exercise tolerance and quality of life in patients receiving this therapy. [1,2] From 2004 CRT was shown to improve not only morbidity, but also mortality of patients with severe heart failure and left ventricular dysfunction. [3,7] In that year, the first ESC guidelines to recommend CRT for the use in heart failure were published. They provided a recommendation class I (is recommended), evidence level A for patients with reduced ejection fraction (EF) and QRS duration $\geq$ 120 ms in New York Heart Association (NYHA) functional class III –IV. [12] These were mirrored by the 2007 ESC Guidelines for Cardiac Pacing and Cardiac Resynchronization Therapy.[13] These guidelines also introduced other patient groups who might benefit from CRT, including patients with atrial fibrillation and patients with low ejection fraction, heart failure and a concomitant indication for

permanent pacing. However, due to the limited evidence available for these indications, they were only awarded a recommendation class IIa (should be considered) and the lowest evidence level C. [13] These guidelines also introduced the idea that patients with overlapping indications for a CRT and an Implantable Cardioverter Defibrillator (ICD) should be implanted with a CRT-D device. (class I recommendation, evidence level B).

Following the publication of the REVERSE, MADIT-CRT and RAFT CRT trials demonstrating morbidity and mortality benefits also in those patients with less symptoms of heart failure, the 2010 focus update of ESC guidelines expanded their recommendation class I for patients with reduced ejection fraction and QRS ≥ 120 ms to include NYHA Class II patients. [4-6, 14]

The observation that patients with left bundle branch block (LBBB) appear to better respond to CRT than those without LBBB came from subgroup analysis of the REVERSE and MADIT-CRT trials. [15, 16] Although the 2010 ESC focused update stated that the evidence was strongest for patients with a LBBB pattern, a lower recommendation class was not provided for patients with non-LBBB until the 2012 ESC guidelines on the diagnosis and treatment of acute and chronic heart failure. [14 17]

In 2013 the results of Echo CRT were published and showed that CRT did not reduce hospitalization rates or mortality for patients with a QRS duration <130 ms and may actually be increasing mortality in this heart failure population. [18] This lead the task force of the ESC HFA Guidelines for Treatment of Acute and Chronic Heart Failure of 2016 to raise the lower recommendation class for CRT implantation to 130 ms. [8] These same guidelines were also influenced by the result of the BLOCK HF trial, which showed that patients with systolic heart

failure, reduced LVEF and a high degree AV block had greater mortality with a traditional two lead pacemaker compared with a CRT. [19] This patient group was awarded a recommendation class I evidence level A for CRT. [8]

1.5 CRT-P vs. CRT-D

CRT devices can be implanted with a pacemaker component (CRT-P) or with a pacemaker and a defibrillator component (CRT-D). Implanting the defibrillator lead of the CRT-D results in a slightly greater risk of complications during implantation. A CRT-D device has also a slightly higher cost than a CRT-P device.[20] However, most patients with heart failure who qualify for a CRT device also have an overlapping indication for an ICD due to their increased risk of sudden cardiac death. [8] For patients with a wide QRS complex the decision to implant a CRT-P vs. CRT-D is challenging as no randomized study has been powered to compare CRT-P vs. CRT-D. As a consequence, limited advice is provided by international guidelines on choice of device type. [11]

1.6 Surveys and Registries

RCTs provide the evidence for heart failure treatment, however they have strict inclusion and exclusion criteria, thereby limiting the inclusion of elderly patients and patients with comorbidities. [21]. It is estimated that less than one third of patients >65 years of age with heart failure would quality for inclusion in a RCT. [22] Registries and surveys on the other hand include a wide range of patients and thereby more accurately describe clinical practice [23] Despite their limitation of being prone to bias, they provide an opportunity to assess guideline implementation and adherence. Information on guideline adherence can therefore be fed back to guideline task forces. [24, 25]

Good adherence to guideline-directed pharmacological treatment has been shown to be associated with improved patient prognosis. [26] However, there is limited research on adherence to device therapy guidelines and published studies include few patients.

1.7 CRT Survey II

CRT Survey II is a 15-month survey of CRT practice in ESC member countries. CRT implanters across Europe were asked to enter data related to CRT implantation for consecutive patients implanted with a CRT device in 2015-2016 for both successful and unsuccessful implantations. These devices included both upgrades from a previous device (ICD or pacemaker) and de novo devices. Data on both CRT-P and CRT-D implantation was collected. CRT Survey II collected data on 11088 patients in 42 countries. It represents the largest survey of CRT practice in Europe and thereby provides an opportunity to assess clinical practice and guideline adherence in ESC member countries.

1.8 Overall Aim of the Thesis

This PhD thesis explores how evidence on CRT is interpreted by international guideline task forces. It examines how these guidelines are applied in clinical practice, including when guidelines provide inconsistent recommendations and how this effects clinical practice.

It specifically:

- Describes clinical practice in ESC member states
- Explores variations in guideline adherence and identifies factors associated with this adherence

- Specifically addresses choice of device type, CRT-P vs. CRT-D – an area where there is limited advice provided by international guidelines.

2. Methods

2.1 Paper 1 - Guideline Comparison

The most recent international guidelines on CRT were identified using the databases MEDLINE and EMBASE. Focused searches were conducted using both keyword search and free text search. Search terms included: guideline, 'cardiac resynchronisation therapy, cardiac resynchronization therapy, CRT and heart failure. Each guideline was then thoroughly reviewed and the various recommendations compared and contrasted with the other CRT guidelines. Explanations for inconsistencies in the guidelines were sought by relating the guideline recommendation to the timing of the guideline publication and to the relevant evidence available at that time.

2.2 Paper 2, 3 and 4 - CRT Survey II

2.2.1 Design and Objectives of CRT Survey II

CRT Survey II was designed as a joint initiative between the two ESC associations EHRA and HFA to capture information regarding current clinical practice for CRT. A scientific committee (SC) was established including members of each association together with representatives from all five major device companies. The role of the SC was to decide on data points for collection, to develop the statistical analysis plan (SAP) and to contribute to the publication process.

2.2.2 Patient Recruitment and Data Collection

A national coordinator (NC) for each country was nominated by the head of the respective national arrhythmia societies. The NC was responsible for recruiting centres for participation in

the survey. Centres were requested to provide data on consecutive patients implanted with either a CRT-P or a CRT-D, whether the device was de-novo or an upgrade from a previous device. Battery changes were excluded. Data was collected on patients implanted with a CRT device between 1st of October 2015 and 31st of December 2016.

The data were entered using an online electronic case report form (eCRF). The implanter completed an eCRF for each patient, whether the CRT procedure was successful or unsuccessful. The data were stored and managed by our data management company Institut für Herzinfarktforschung (IHF) based in Ludwigshafen, Germany.

Each implanter was also asked to complete a one-time site questionnaire detailing the demographics and facilities available at each implanting centre. The details of the eCRF and the one-time site questionnaire are included in appendix 1 and 2 respectively.

2.2.3 Statistical Analysis

All data analyses were performed using SAS®, release 9.3 and 9.4 (SAS Institute Inc., Cary, NC, USA) on a Microsoft® Windows® 7 and 10 Enterprise platform. All percentages were relative to the total number of patients with available information. The medians were reported with interquartile ranges (IQR). P-values were calculated using Mann-Whitney-Wilcoxon test when comparing medians and Chi²-Test when comparing percentages. Missing values were not imputed. Regression analyses were performed for paper 3 and 4 based on multivariate analysis. Factors postulated to be associated with implantation of a CRT-P (paper 3) or influencing the recommendation class supporting implantation (paper 4) were made binomial and included in a

multiple regression analysis with a probability model. Odds ratios (OR) for implantation with a CRT-P vs. CRT-D (paper 3) or under class I vs. non-class I (paper 4) indications were calculated. The Hosmer and Lemeshow test for goodness of fit was used to test the validity of the regression model.

2.2.4 Ethical Considerations

We took great care in designing the eCRF to ensure that it was completely anonymized. It was approved by ESC data experts and deemed to be completely anonymized. The patients were not followed up after hospitalization. The lack of follow-up after hospitalization and the anonymized nature of the data collected obviated the need for Institutional Review Board (IRB) approval in most countries. However, in order to participate in the survey, countries had to provide proof that they had either informed their local IRB about the survey and did not require formal approval or that they had received IRB approval.

3. Results

3.1 Paper 1 – Indications for Cardiac Resynchronization Therapy: A Comparison of the Major International Guidelines.

This paper summarizes the most recent international guideline recommendations for CRT and their corresponding levels of evidence. Overall, there is great consensus in the guidelines with equal recommendation classes and evidence levels for CRT implantation in the various groups. For CRT in patient groups with the strongest evidence base, such as those with sinus rhythm, QRS >150 ms duration and LBBB, all the guidelines reviewed provide the strongest recommendation and evidence levels for implantation. (Table 3)

Table 3- Comparison of Recommendations for Patients with Sinus Rhythm and LBBB

	QRS ≥150 ms		QRS 130–149 ms		QRS 120–129 ms	
Guideline (Year)	NYHA Functional Class III/IV	NYHA Functional Class II	NYHA Functional Class III/IV	NYHA Functional Class II	NYHA Functional Class III/IV	NYHA Functional Class II
ESC HFA (2016)*	I, A	I, A	I, B	I, B	III, A	III, A
ESC EHRA (2013)	I, A	I, A	I, B	I, B	I, B	I, B
ACC/AHA/HRS (2013)	I, A	I, B	IIa, B	IIa, B	IIa, B	IIa, B
CCS (2017)	I, High	I, High	I, High	I, High	III, Moderate	III, Moderate
Australian Guidelines (2011)	A		A		A	
NICE (2014)	CRT-P or CRT-D†	CRT-D	CRT-P or CRT-D†	CRT-D	CRT-P or CRT-D†	CRT-D

Values are Class of Recommendation, Level of Evidence, unless otherwise indicated. Australian guidelines provide only grade of recommendation (A), not evidence level for these recommendations. NICE guidelines provide guidance on type of device rather than recommendation or evidence level. *The ESC HFA guidelines do not specify NYHA functional class, rather they state that the guidelines refer to symptomatic patients with heart failure. †Not for NYHA functional class IV.

ACC/AHA/HRS = American College of Cardiology/American Heart Association/Heart Rhythm Society; CCS = Canadian Cardiology Society; CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; ESC EHRA = European Society of Cardiology European Heart Rhythm Association; ESC HFA = European Society of Cardiology European Heart Rhythm Association; LBBB = left bundle branch block.

However, discrepancies exist and many of these relate to QRS duration and morphology. Recommendations for CRT implantation in patients with sinus rhythm and a QRS duration between 120 ms and 129 ms vary greatly between the different cardiology societies. This is particularly visible with the two ESC associations, with ESC EHRA providing a class I

recommendation (is recommended) for this indication and the ESC HFA providing a class III recommendation (is not recommended) (Table 3).

Another inconsistency in these international guidelines relates to class of recommendations awarded patients with sinus rhythm and non-LBBB (table 4). In this patient group large variations in recommendation classes between the different guidelines exist. For example, for a patient in NYHA functional class III with a QRS duration >150 ms in sinus rhythm with non-LBBB, the Australian guidelines provide an A recommendation (their strongest) while the other guidelines analysed provide either a class IIa or IIb.

Table 4- Comparison of Recommendations for Patients with Sinus Rhythm and Non-LBBB

	QRS ≥150 ms		QRS 130–149 ms		QRS 120–129 ms	
Guidelines (Year)	NYHA Functional Class III/IV	NYHA Functional Class II	NYHA Functional Class III/IV	NYHA Functional Class II	NYHA Functional Class III/IV	NYHA Functional Class II
ESC HFA (2016)*	IIa, B	IIa, B	IIb, B	IIb, B	III, A	III, A
ESC EHRA (2013)	IIa, B	IIa, B	IIb, B	IIb, B	IIb, B	IIb, B
ACC/AHA/HRS (2013)	IIa, A	IIb, B	IIb, B	III, B	IIb, B	III, B
CCS (2017)	IIb, Low	IIb, Low			III, Moderate	III, Moderate
Australian Guidelines (2011)	A		A		A	
NICE (2014)	CRT-P or CRT-D†	CRT-D	CRT-P‡		CRT-P‡	

Values are Class of Recommendation, Level of Evidence, unless otherwise indicated. Australian guidelines provide only grade of recommendation (A), not evidence level for these recommendations. NICE guidelines provide guidance on type of device rather than recommendation or evidence level. *The ESC HFA guidelines do not specify NYHA class, rather they state that the guidelines refer to symptomatic patients with heart failure. †Not for NYHA functional class IV. ‡Only for NYHA functional class IV.
Abbreviations as in Table 1 and 2.

Variations were also noted in recommendations for patients with reduced LVEF and high degree AV block who are likely to be dependent on RV pacing (table 5). This indication was awarded a

class IIa (should be considered) recommendation by both the 2013 ESC EHRA guidelines and the 2013 American guidelines. The 2016 ESC HFA guidelines provided a recommendation class I (is recommended). One year later the Canadian guidelines provided a class IIb recommendation (may be considered) for the same indication.

Table 5- Less Conventional Indication for CRT

Guidelines (Year)	Atrial Fibrillation and HF	Expected High % of Ventricular Pacing With Reduced LVEF and Symptomatic HF
ESC HFA (2016)	IIa, B	I, A
ESC EHRA (2013)	IIa, B	IIa, B
ACC/AHA/HRS (2013)	IIa, B	IIa, C
CCS (2017)	IIb, Low	IIb, Moderate

Values are Class of Recommendation, Level of Evidence.
Abbreviations as in Tables 1 and 2.

3.2 Paper 2 -CRT Survey II: a European Society of Cardiology Survey of Cardiac Resynchronization Therapy in 11 088 Patients -Who is Doing What to Whom and How?

CRT Survey II collected data on 11 088 patients in 42 ESC member countries (table 6).

Table 6 – CRT Survey II Cohort by Country

Country	National coordinator	Patients entered
Algeria	Seddik Ait-Messaoudene	66
Armenia	Svetlana Grigoryan	2
Austria	Marianne Gwechenberger	407
Belgium	J.B. le Polain de Waroux	262
Bulgaria	Svetoslav Iovev	264
Croatia	Sandro Brusich	115
Czech Republic	Alan Bulava	931
Denmark	Helen Høgh Petersen	254
Egypt	Mostafa Nawar	22
Estonia	Jüri Voitk	58
Finland	Sami Pakarinen	351
France	Christophe Leclercq	754
Georgia	Giorgi Papiashvili	24
Germany	Carsten W. Israel	675
Greece	Antonis Sideris	137
Hungary	Gabor Duray	467
Iceland	Sigfús Gizurarson	19
Ireland	Ricky Sheahan	85
Israel	Michael Geist	39
Italy	Giovanni Luca Botto	526
Kazakhstan	Roin Rekvava	34
Latvia	Oskars Kalejs	79
Lebanon	Marwan M. Refaat	30
Lithuania	Germanas Marinskis	173
Luxembourg	Laurent Groben	36
Macedonia FYR	Nikola Gjorgov	70
Malta	Mark Sammut	26
Montenegro	Ljilja Music	6
Marocco	Salima Abdelali	12
Netherlands	Alexander Maass	202
Norway	Torkel Steen	370
Poland	Maciej Sterlinski	1241
Portugal	Francisco Morgado	58
Romania	Dan Dobreanu	214
Russian Federation	Amiran Revishvili	71
Slovakia	Peter Margitfalvi	472
Slovenia	Igor Zupan	119
Spain	Oscar Cano Pérez	847
Sweden	Elena Sciaraffia	255
Switzerland	Christian Sticherling	320
Turkey	Umutay Nedim Sarigül	424
UK	Chris Plummer	571
Total		**11 088**

In the 42 countries surveyed 97% of patients had symptomatic heart failure (NYHA functional class II, III or IV), 69% had sinus rhythm, 73% had LBBB morphology on their ECG, 87% had a QRS duration ≥ 130 ms and 87% had a LVEF $\leq 35\%$. (Table 7)

Table 7- Demographics of Patients in CRT Survey II

NYHA class	
I	3% (370/10 848)
II	38% (4083/10 848)
III	55% (5909/10 848)
IV	5% (486/10 848)
BMI (kg/m^2), median (IQR)	27 (25–31)
Systolic blood pressure (mmHg), median (IQR)	122 (110–137)
Diastolic blood pressure (mmHg), median (IQR)	72 (66–80)
Laboratory measurement (most recent), median (IQR)	
BNP (ng/L)	422 (150–1115)
NT-proBNP (ng/L)	2400 (1049–5517)
Serum creatinine (μmol/L)	100 (83–129)
Haemoglobin (g/dL)	13 (12–15)
Pre-implant ECG	
Heart rate (b.p.m.), median (IQR)	70 (60–80)
Atrial rhythm	
Sinus	69% (7496/10 836)
Atrial fibrillation	26% (2778/10 836)
Atrial paced	3% (303/10 836)
Other	2% (259/10 836)
PR interval (ms), median (IQR)	180 (160–210)
AV block II/III	19% (2026/10 700)
Pacemaker dependent	14% (1511/10 752)
Intrinsic QRS morphology	
LBBB	73% (7861/10 800)
Non-LBBB	27% (2939/10 800)
Intrinsic QRS duration (ms), median (IQR)	160 (140–174)
<120	8% (711/9535)
120–129	5% (505/9535)
130–149	19% (1779/9535)
150–179	47% (4486/9535)
>180	22% (2054/9535)
Clinical indication for CRT	
HF with wide QRS	60% (6550/10 923)
HF or LV dysfunction and indication for ICD	48% (5228/10 923)
PM indication and expected RV pacing dependence	23% (2494/10 923)
Evidence of mechanical dyssynchrony	12% (1260/10 923)
Other	5% (487/10 923)
LVEF (%), median (IQR)	29 (23–34)
<25	28% (2979/10 805)
25–35	60% (6426/10 805)
>35	13% (1400/10 805)
LVEDD (mm), median (IQR)	63 (58–69)
Mitral regurgitation	
Mild	46% (4644/10 000)
Moderate	27% (2646/10 000)
Severe	7% (690/10 000)
None	20% (2020/10 000)

Note: total can be ≥100% due to rounding off. In parenthesis, number of patients in each category compared to the total cohort for each data-point.
AV, atrio-ventricular; BMI, body mass index; BNP, brain natriuretic peptide; CRT, cardiac resynchronisation therapy; ECG, electrocardiogram; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LBBB, left bundle branch block; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New Year Heart Association; PM, pacemaker; RV, right ventricular.

On the other hand, 3% of patients had asymptomatic heart failure and 8% had a QRS duration <120 ms. 32% of patients were aged ≥ 75 years, 28% were upgraded from a previous device and 24% of patients implanted with a CRT device were female.

The survey also demonstrated inter-country variations in patients' selection parameters. Figure 2 shows NYHA functional class, bundle branch morphology, QRS duration, upgrades from a previous device and choice of device type for the countries with the top 10 highest survey recruitment.

Figure 2 CRT Survey II Patients in the Top 10 Recruiting Countries

Figure 2a- NYHA Function Class

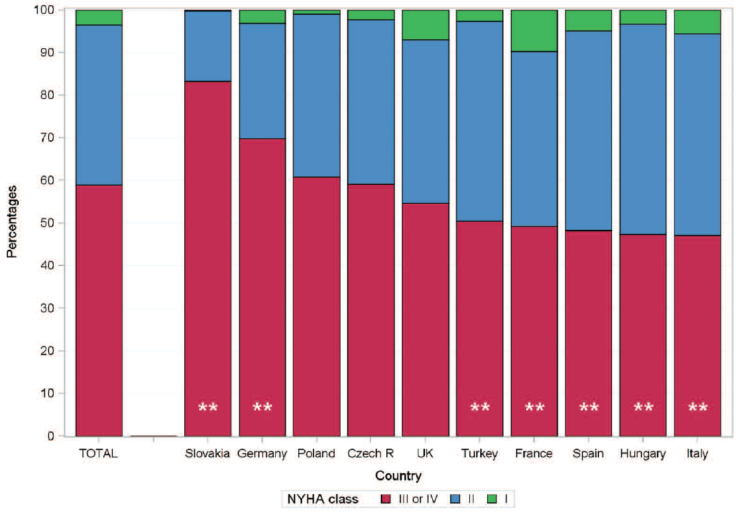


Figure 2b- Bundle Branch Morphology

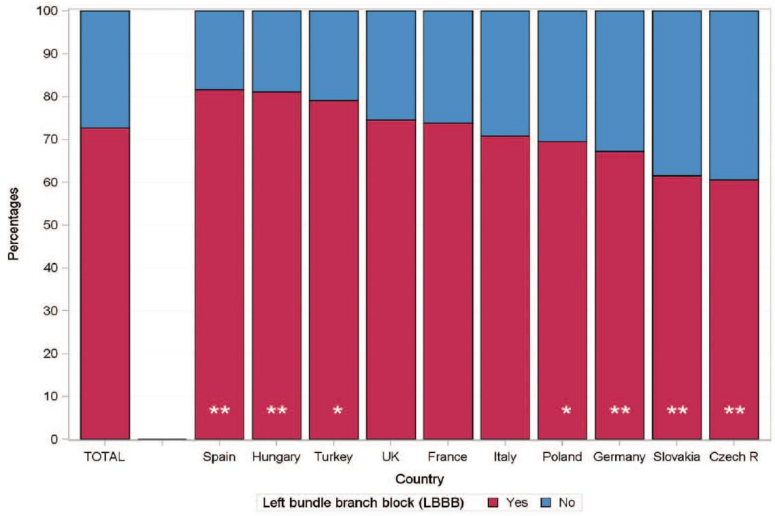


Figure 2c- QRS Duration

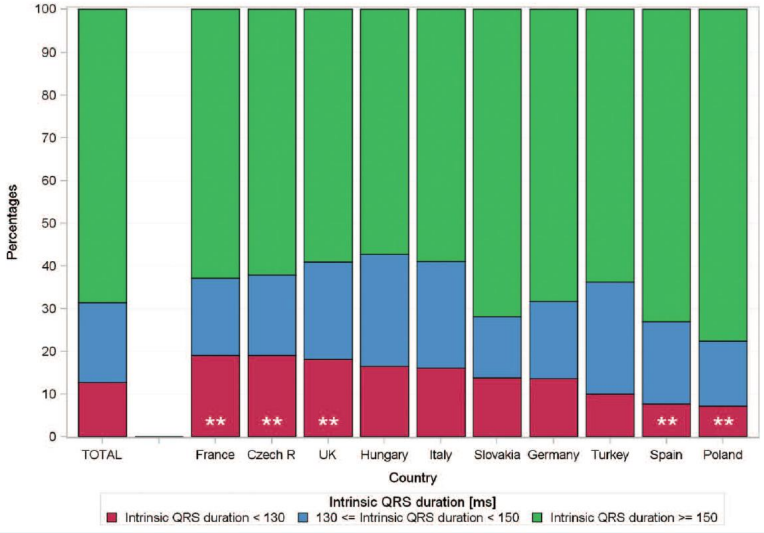


Figure 2d-Upgrades from a Previous Device

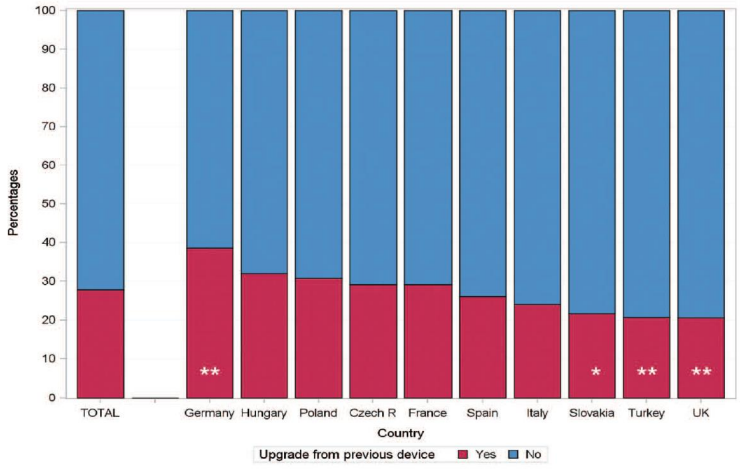
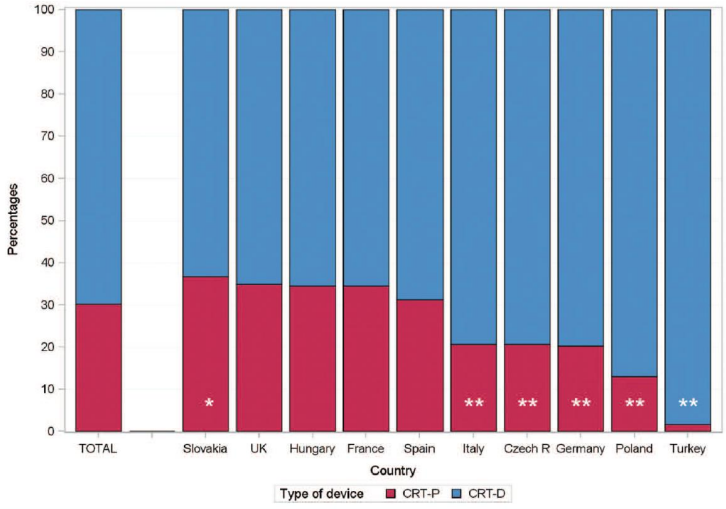


Figure 2e-Choice of Device Type (CRT-P vs. CRT-D)



The figures presents a comparison of selected characteristics across the top 10 recruiting countries. Asterisks demonstrate the level of statistical significance of the bottom red category for each country as compared to the total cohort. One asterisk denotes a *P*-value of <0.01 and two asterisks a *P*-value of <0.001.

3.3 Paper 3 – Cardiac Resynchronization Therapy Pacemaker or Cardiac Resynchronization Therapy Defibrillator: What Determines the Choice – findings from the ESC CRT Survey II?

This paper describes the choice of device type (CRT- P vs. CRT –D). This is an area where there is limited advice provide by guidelines because of sparse evidence. Of the 11 088 patients included in the survey, 10 692 had sufficient data collected to be included in the CRT-P vs. CRT-D analysis, and of these 3225 (30%) received a CRT-P device and 7467 (70%) a CRT-D device. Compared with those implanted with a CRT-D device, patients implanted with a CRT-P device were significantly older (mean age 75 vs. 68 years, $p < 0.001$), more often female (31% vs. 21%, $p < 0.001$) and were less likely to have ischaemic aetiology (33 % vs 49%, $p < 0.001$). They also had significantly more cardiovascular and non-cardiovascular comorbidities, including atrial fibrillation (50% vs. 37%, $p < 0.001$), valvular heart disease (30 % vs. 26%, $p < 0.001$), hypertension (67% vs 62%, $p < 0.001$), anaemia (18% vs. 14%, $p < 0.001$), and chronic kidney disease (35% vs. 29%, $p < 0.001$). Patients in the CRT-P group were more likely to be receiving an upgrade from a previous device either a permanent pacemaker or ICD (26% vs 21%, $p < 0.001$). (Table 8)

Table 8 - Clinical Characteristics of Patients Implanted with a CRT-P vs. CRT-D

	CRT-P ($n = 3225$)	CRT-D ($n = 7449$)	*P*-value
Demographics			
Age (years), median (IQR)	75 (67–80)	68 (61–74)	<0.00001
Age ≥75 (%)	51.2% (1652/3224)	23.6% (1758/7464)	<0.00001
Female gender	31.0% (998/3223)	21.3% (1592/7463)	
Currently enrolled in a clinical trial	6.5% (209/3218)	9.2% (684/7449)	<0.00001
Primary HF aetiology			
Ischaemic	32.9% (1054/3207)	49.4% (3668/7421)	<0.00001
Non-ischaemic	55.8% (1790/3207)	47.2% (3505/7421)	
Other	11.3% (363/3207)	3.3% (248/7421)	
Past history and major comorbidity			
Myocardial infarction	25.1% (804/3204)	40.8% (3022/7413)	<0.00001
PCI/CABG	27.7% (888/3203)	43.6% (3231/7413)	<0.00001
Valvular heart disease	30.3% (971/3209)	25.9% (1914/7402)	<0.00001
Valve surgery	35.9% (441/1229)	29.4% (709/2414)	0.00006
Hypertension	67.1% (2145/3195)	62.3% (4612/7399)	<0.00001
Diabetes	29.9% (959/3209)	31.8% (2352/7405)	0.05516
Obstructive lung disease	11.9% (383/3208)	12.0% (891/7406)	0.89359
Anaemia	17.8% (571/3207)	13.8% (1021/7402)	<0.00001
eGFR <60 mL/kg/min	35.4% (1135/3207)	29.2% (2159/7392)	<0.00001
HF hospitalization during last year	44.4% (1425/3209)	47.2% (3496/7399)	0.00699
Atrial fibrillation	49.8% (1597/3207)	36.8% (2724/7404)	<0.00001
Paroxysmal	30.1% (481/1597)	37.8% (1031/2724)	
Persistent	21.7% (346/1597)	23.0% (626/2724)	
Permanent	47.8% (763/1597)	38.5% (1048/2724)	
Previous device	25.8% (828/3214)	20.6% (1534/7461)	<0.00001
PM	25.3% (812/3214)	8.2% (614/7461)	
ICD	0.5% (16/3214)	12.3% (920/7461)	

CABG, coronary artery bypass grafting; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; PCI, percutaneous coronary intervention; PM, pacemaker.

A regression analysis to identify factors associated with implanting a CRT-P vs. a CRT-D showed that CRT-P was more commonly selected for patients with more severe symptoms of heart failure, more frequent comorbidities, advanced age, female gender, non-ischaemic heart failure aetiology, atrial fibrillation and evidence of AV block. Being implanted in a university hospital was also associated with being implanted with a CRT-P. (Table 9)

Table 9- Characteristics Associated with CRT-P vs. CRT-D Implantations- Regression Analysis

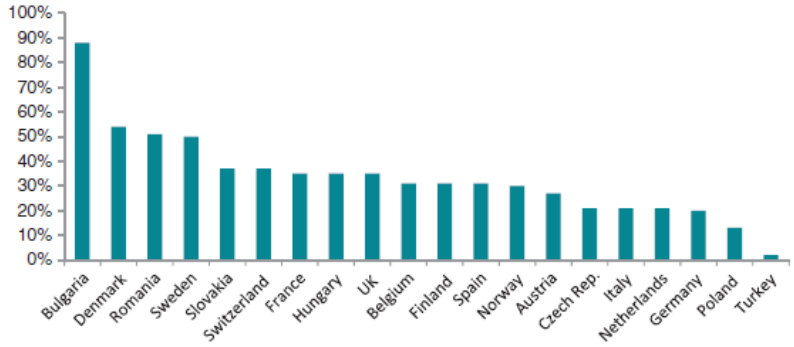
Characteristics	Odds ratios (95% confidence interval	*P*-value
Male gender	0.66 (0.58–0.66)	<0.0001
Age ≤75 years	0.27 (0.24–0.27)	<0.0001
Elective admission	0.86 (0.75–0.86)	0.0279
Ischaemic aetiology	0.45 (0.39–0.45)	<0.0001
Past medical history		
Hypertension	1.13 (1.00–1.13)	0.0478
Atrial fibrillation	1.42 (1.22 –1.42)	<0.0001
Pre-implant clinical evaluation		
NYHA functional class III/IV	1.37 (1.21–1.37)	<0.0001
LVEF ≤25%	0.50 (0.45–0.50)	<0.0001
Pre-implantation ECG		
Atrial fibrillation	1.45 (1.22–1.45)	<0.0001
AV block II/III	2.85 (2.37–2.85)	<0.0001
LBBB	0.84 (0.73–0.84)	0.0128
Hospital characteristic		
University hospital	2.11 (1.87–2.11)	<0.0001

AV, Atrioventricular; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ECG, electrocardiogram; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Furthermore, we demonstrated large inter-country variations in choice of CRT-P vs. CRT-D, ranging from 88% CRT-P (Bulgaria*)* to 2% (Turkey). Performing a linear regression analysis we were not able to link the percentage of CRT-P implanted in a country with their gross domestic

production (GDP). We therefore concluded that other national factors must be influencing the choice between CRT-P and CRT-D.

Figure 3 Percentage CRT-P per Country for Countries with >200 patients in CRT Survey



3.4 Paper 4 Adherence to ESC Cardiac Resynchronization Therapy Guidelines – Findings from the ESC CRT Survey II

In this paper we analysed adherence to ESC guidelines. 8021 patients with sufficient data were analysed for adherence to the ESC EHRA guidelines on CRT. Of these, 67% had a class I indication for CRT, 26% a class IIa and 5% a class IIb. Only 2% had a class III indication (contra-indicated). (Table 10)

Table 10 – Adherence to ESC EHRA 2013 CRT Guidelines

Recommendation Class	N	Percent of total
I	5358	67%
IIa	2126	26%
IIb	408	5%
III	129	2%

Details of patient characteristics for patients in the two largest groups (class I and IIa) are compared in Table 11.

Table 11– Patient Characteristics for CRT Indication Class (I vs. IIa) According to ESC EHRA 2013 Guidelines [27].

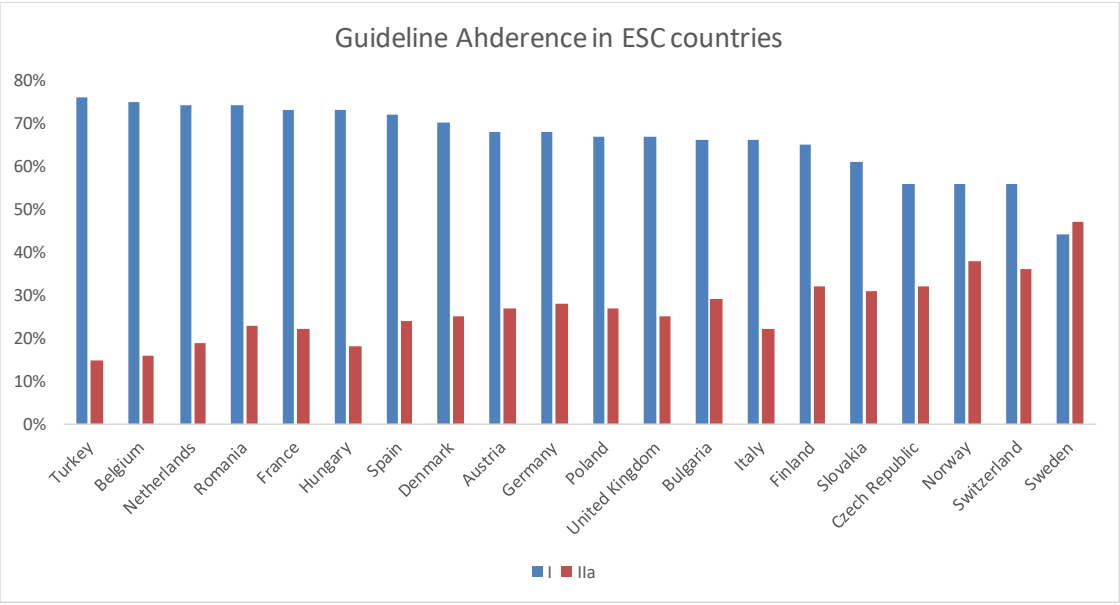
	Recommendation Class		
	I (n= 5358)	**IIa** (n= 2126)	**p-value**
Median age (year, IQR)	68 (61, 75)	72 (65, 78)	<.00001
Female (%)	28.5 % (1525/5354)	18.2 % (386/2126)	<.00001
Elective admission	82.6 % (4422/5355)	70.0 % (1487/2124)	<.00001
Ischaemic HF aetiology	43.0 % (2298/5349)	48.4 % (1029/2125)	0.01324
Past history and major comorbidity			
Myocardial infarction	35.3 % (1886/5350)	39.7 % (843/2124)	0.00033
Prior revascularization (PCI/CABG)	37.6 % (2014/5351)	41.7 % (883/2120)	0.00133
Hypertension	61.9 % (3306/5343)	66.5 % (1407/2116)	0.00019
Valvular heart disease	22.8 % (1218/5352)	35.5 % (755/2126)	<.00001
Obstructive lung disease	11.7 % (625/5353)	13.2 % (280/2124)	0.07160
Diabetes	31.1 % (1663/5351)	34.5 % (733/2125)	0.00431
Anaemia	13.0 % (697/5351)	18.8 % (400/2126)	<.00001
Chronic kidney disease (eGFR <60)	27.5 % (1466/5340)	40.8 % (867/2124)	<.00001
Dialysis	3.4 % (50/1460)	2.4 % (21/865)	0.17690
HF hospitalization during past year	48.5 % (2596/5354)	53.3 % (1133/2125)	0.00016
Pre-procedure ECG			
QRS duration (ms, median, IQR)	160 (150, 180)	160 (140, 174)	<.00001
Sinus Rhythm	93.3 % (4994/5355)	31.1 % (661/2123)	<.00001
Atrial fibrillation	4.5 % (239/5355)	66.1 % (1404/2123)	<.00001
Successful implantation	97.5 % (5285/5421)	97.1 % (2079/2141)	0.34227
Type of device			
CRT-P	19.6 % (1036/5282)	38.7 % (804/2076)	<.00001
CRT-D	80.4 % (4246/5282)	61.3 % (1272/2076)	<.00001

The majority of patients implanted with a class I indication for CRT were male (72%) and were a median of 4 years younger, had less comorbidity (including valvular heart disease, anaemia and renal failure) and fewer previous hospitalizations than those with a class IIa indication. They

were also more likely to receive a CRT-D (80%). For patients implanted with a class IIa indication, more were male (82%), more had ischaemic heart disease and additional cardiovascular comorbidities (atrial fibrillation, hypertension and valvular heart disease) and non-cardiovascular comorbidities (chronic kidney disease, diabetes and anaemia).

The results of the guideline analyses per country are shown in Figure 4. The percentage of patients implanted with a class I indication in countries with >200 patients recruited in the Survey varied from 44% (Sweden) to 76% (Turkey).

Figure 4 - Patients Implanted with Class I and IIa CRT Indications (for Countries with >200 Patients in the Survey)



Of the 11 088 patients included in the analysis, 7920 of 8021 had sufficient data entered to be included in the regression analysis. Multivariate analysis showed that women, patients <75 years, patients with non-ischaemic aetiology and those admitted electively were more likely to receive a CRT device with a class I indication. There were no significant differences in the proportions of patients with class I vs. class II CRT indications between high- and low-volume CRT implanting hospitals or between those associated with a university and those not associated with a university. The results are shown in table 12. Males, patients ≥75 years and patients admitted acutely are therefore more likely to be offered a CRT where the evidence level is lower.

Table 12 – Multivariate Regression Analysis - Characteristics Associated with Being Implanted Under Recommendation Class I

Characteristics	**Estimate**	**P-value**	**Odds Ratios (95% CI)**
Male gender	-0.5274	<.0001	0.59 (0.52-0.67)
Age ≥ 75 years	-0.4394	<.0001	0.64(0.58-0.71)
Elective admission	0.6280	<.0001	1.87 (1.68-0.90)
Ischaemic aetiology	-0.1983	<.0001	0.82 (0.74-0.90)
Implanted in University hospital	-0.0231	0.7330	
Implanted in High Volume Centre (≥100 per year)	-0.1471	0.0620	
University hospital Centre CRT implantation ≥100	-0.0816	0.4171	

About halfway through the CRT Survey II recruitment period another ESC society -the Heart Failure Association- released updated guidelines on heart failure treatment that included a section on CRT. [8] (Table 13). These included an increase in the lower limit of QRS duration from 120 ms to 130 ms and the lowering of the recommendation from class I to IIb for patients requiring an upgrade to a CRT from a pacemaker or ICD. The third major change was for patients with left ventricular dysfunction, a conventional indication for a pacemaker and expected high percentage of right ventricular pacing where the CRT recommendation was increased from class IIa to class I.

After the release of the ESC HFA guidelines there was a significant increase from 21% to 27% ($p < 0.001$) in the number of patients implanted with class I indication for avoidance of RV pacing. [8] In contrast, the percentage of patients upgraded to CRT due to worsening of heart failure remained unchanged at 5%. Following the lower limit for QRS duration for CRT implantation being raised to 130 ms there was a small but statistically significant increase in the number of patients implanted with a QRS duration between 120 -129 ms (7% before 2016 versus 10% after May 2016, $p<0.001$).

Table 13 European CRT Guidelines

European CRT Guidelines		
Year	2013	2016
Society	EHRA	HFA
Minimum recommended for CRT implantation	120 ms	130 ms
Upgrade to CRT from PM or ICD, recommendation class	I	IIb
RV pacing indication, recommendation level	IIa	I

4. Discussion

Randomised controlled trials provide the evidence that is reviewed by guideline task forces and incorporated into recommendations. Registries and surveys describe clinical practice, provide an opportunity to assess the implementation of guidelines and identify areas of practice requiring further research. [24] Good adherence to guideline-recommended HF medication therapy is associated with improved prognosis and several studies have analysed adherence to optimal medical therapy and the effect on clinical outcomes.[25] However, there is limited research on adherence to device therapy guidelines.

In this PhD thesis current international recommendations for CRT are compared and contrasted. Areas of inconsistency are identified and the evidence for CRT is reviewed in an attempt to explain why these variations are present.

Furthermore, using the population of CRT Survey II we have demonstrated variations in practice and guideline adherence in 42 ESC member states and attempted to explain why these exist based on guideline recommendation and the evidence behind these recommendations. The choice of device type between CRT-D and CRT-P was specifically selected as an area where no firm guidance is provided by the international cardiology societies and therefore hypothesized to be an area where large variations in practice are likely to occur.

4.1 Paper 1 – Indications for Cardiac Resynchronization Therapy: A Comparison of the Major International Guidelines.

In the international guideline comparison we demonstrated mainly consistency in the CRT recommendations. Such concordance in the guidelines was especially obvious for indications where the evidence is very strong, such as in patients in sinus rhythm, with LBBB, symptomatic heart failure and with QRS duration >150 ms. However, for several patient populations there exist inconstancies for how strongly CRT therapy is recommended. Many of these relate to QRS duration and morphology. One of the most striking is the difference between recommendation classes between the two ESC societies for patients with sinus rhythm, LBBB and a QRS duration between 120 ms and 129 ms. The ESC ERHA guidelines provide a recommendation class I (is recommended) and ESC HFA provide a class III recommendation (is not recommended). This inconsistency is likely due to the timing of release of these two guidelines. The ESC EHRA guidelines were published in 2013 and the ESC HFA guidelines were published in 2016. Between the publication of these two ESC guidelines the results of the Echo CRT trial were released showing no reduction in hospitalization or mortality rates for CRT in otherwise eligible patients with a QRS durations <130 ms. [18]

Another area where there are large inconsistencies in the international guidelines relates to class of recommendations awarded patients with sinus rhythm and non-LBBB ECG morphology. For patients in NYHA functional class II heart failure with non-LBBB, the recommendation classes vary from a strong recommendation A (Australian guidelines, their strongest recommendation) to IIa or IIb (all other guidelines reviewed). This, again, is assumed to be related to timing, as the oldest guidelines from Australia were published in 2011 and do not distinguish between LBBB

and non-LBBB when providing their recommendations. The evidence that led to a stronger recommendation class provided for LBBB came from subgroup analysis of the MADIT-CRT and the REVERSE trial, which showed greater benefit of CRT in LBBB. [15, 16] Therefore guidelines written after these publications differentiate LBBB from non-LBBB and provide a higher recommendation class for LBBB. However, these are subgroup analysis of RCTs with the majority of patients having LBBB. [15 16] So the evidence leading to this international weakening of the recommendation for CRT for patients with non-LBBB is not as strong as that which led to the QRS duration upper limit being raised to 130 ms.

However not all discrepancies were related to timing of evidence publication and guideline production. For patients with reduced LVEF and high degree AV block who are likely to be dependent on RV pacing the variations in guideline recommendations are more complex than simply due to timing. This indication was awarded a class IIa (should be considered) recommendation by both the 2013 ESC EHRA guidelines and the 2013 American guidelines. In 2013 the Block-HF trial was published and showed that biventricular pacing was superior to right ventricular pacing in patients with reduced LVEF, HF and AV block. [19] The 2016 ESC HFA guidelines raised the recommendation class to class I (is recommended). However, one year later the Canadian guidelines provided a class IIb recommendation (may be considered), evidence moderate for the same indication. Thus guideline task forces are providing varying degrees of recommendations while reviewing the same evidence.

4.2 Paper 2 - CRT Survey II: a European Society of Cardiology Survey of Cardiac Resynchronization Therapy in 11 088 Patients-Who is Doing What to Whom and How?

In the CRT Survey II we demonstrated that the majority of patients selected for CRT implantations in Europe had the clinical characteristics shown to be amenable to CRT and therefore recommended by the guidelines, such as sinus rhythm, wide QRS, LBBB, low ejection fraction and symptomatic heart failure. However, the survey also demonstrated that some CRTs were being implanted 'off label', that is, outside guideline recommendations such as in patients with asymptomatic heart failure (NYHA functional class I) and QRS duration <120 ms. None of the international guidelines recommend CRT in patients without symptomatic heart failure, however in CRT Survey II 3 % were classified in the NYHA I functional class. Regarding narrow QRS duration, our survey shows that 8% of implants were in patients with a QRS <120 ms. Again, none of the international guidelines recommend CRT implantation in patients with a CRT duration <120 ms. However, the median QRS duration was narrower (144 ms compared with 160 ms) for patients implanted only for the clinical indication 'pacemaker indicated and expected right ventricular pacing dependence' compared to the overall cohort. This indication does not specify the requirement for a wide complex, so this could partially explain why 8% of patients in our survey were implanted with a CRT despite having a QRS duration <120 ms. A total of 10% of the survey population was implanted with only this clinical indication and 22% of this group had a QRS duration <120 ms.

Furthermore, although by no means outside guideline recommendations, there was a large number of CRT implantations being undertaken in patient groups where there was a limited evidence base such as patients age >75 years, upgrades from a previous device (pacemaker or

ICD), patients with non-LBBB and patients with atrial fibrillation. These implantations suggest that clinicians continue to extrapolate data from RCT to patients who are not well represented in the evidence base. Clinical practice may be guided by clinical trials but differences in practice exist because clinicians have accumulated experience and try to offer the best treatment to individual patients, many of whom do not fulfil the selection criteria for the RCTs. Compared to patients enrolled in RCTs, patients in this survey were generally older, had more co-morbidities, were less likely to have ischaemic heart disease, had higher LVEF, narrower QRS complexes and more atrial fibrillation but a similar proportion were women. [28]

In the survey we also showed large inter-country variations in patient selection parameters. Country variations were particularly evident in areas where there was limited evidence base e.g. patients > 75 years, upgrades from a previous device (pacemaker or ICD) and choice of device (CRT-P vs. CRT-D).

4.3 Paper 3 – Cardiac Resynchronization Therapy Pacemaker or Cardiac Resynchronization Therapy Defibrillator: What Determines the Choice? - Findings from the ESC CRT Survey II

International guidelines do not provide firm recommendations regarding choice of device type (CRT-P vs. CRT-D). Most patients with an indication for a CRT device also have an overlapping indication for ICD implantation due to the risk of ventricular arrhythmias associated with the reduced ejection fraction. [8, 29] However no study has been designed or powered to directly compare CRT-P vs. CRT-D for clinical outcomes, limiting the ability of guidelines to advise on choice of device .[11] The ESC EHRA guidelines do list some factors in their guidelines that should be considered to weigh in favour of implanting a CRT-P versus a CRT-D; these include advanced heart failure, severe renal insufficiency or dialysis, and other major co-morbidities including frailty and cachexia. CRT-D is suggested for patients with a life expectancy >1 year, in NYHA functional class II, ischaemic heart disease, and no major co-morbidities. [27] The ESC HFA guidelines state that if the primary reason for implanting a CRT is to improve prognosis, most evidence lies with CRT-D in patients with NYHA functional class II and for CRT-P for patients in NYHA functional classes III to IV. However, if the primary reason for implanting the device is relief from symptoms, HFA guidelines propose that the clinician should choose between a CRT-P and a CRT-D, as he/she considers appropriate. [8] The NICE guidelines, specific to the UK, provide clear recommendations on type of device depending on NYHA Class and QRS duration and morphology but remain silent on the effects of co-morbidities and age on the relative benefit of CRT-D over CRT-P. [30] However, neither of these suggestions are accompanied by strength of recommendation or evidence level.

In CRT Survey II we showed that 70% of CRT recipients in Europe received a device with defibrillation capacity. The CRT-P recipients were significantly older, were more symptomatic of their heart failure, were more often female and more often had additional conduction tissue disease. They also had significantly more comorbidities including atrial fibrillation, valvular heart disease, hypertension, anaemia, and chronic kidney disease. Overall it appears possible that in patients selected for CRT-P, operators are appreciating the limited clinical effectiveness of ICD therapy in older and frailer patients. This is consistent with the limited guidance provided in the most recent EHRA ESC guidelines. On the other hand, patients implanted with a CRT-D device were more likely to have ischaemic heart failure aetiology, probably reflecting the stronger guideline levels of evidence for an ICD in patients with ischaemic aetiology than in those with non-ischaemic aetiology. [8]

The percentage of CRT-P vs. CRT-D varies greatly in different regions and countries. [31] In CRT Survey II the percentage of CRT-P devices ranged from as low as 2% to as high as 88 % (figure 3).[32] This variation could not be explained by economic factors alone, other factors like reimbursement policies may come into play as countries with comparable financial resources show markedly different implantation behaviour.

The limited advice provided by guideline task forces related to choice of device is likely due to the lack of studies comparing these two devices. Only one head-to-head study of CRT-D vs. CRT-P has ever been published. However, this study (COMPANION) was not designed to compare different CRT devices; rather, it focused on the overall concept of CRT versus optimal

medical therapy. It established the benefit of a CRT over medical therapy in eligible patients, but was underpowered to compare any difference between CRT-P and CRT-D.[7]

The majority of comparisons of CRT-P vs. CRT-D have been retrospective cohort studies and these have suggested that the benefit for a CRT-D over a CRT-P may be limited to those patients with ischaemic heart failure aetiology. [20,33,34]

The only recent RCT of defibrillator over standard care, the DANISH study, randomized 556 patients with heart failure of non-ischaemic aetiology with an LVEF ≤35% to either receive an ICD or usual clinical care. Despite the rate of sudden cardiac death being half in the ICD group (4.3%) compared with the control group (8.2%) this trial showed no significant difference in overall survival benefit between the two groups. There was, however, an age interaction suggesting that the benefits of ICD in patients with non-ischaemic aetiology were limited to the younger patients (<68 years of age). [35] In both the ICD and the control group 58% of the patients received a CRT device and these results were independent of whether or not the patients received a CRT. Therefore, this study enabled the direct comparison of 323 CRT-P patients versus 322 CRT-D patients with ischaemic heart failure aetiology. The DANISH study suggests that in patients ≥68 years of age with heart failure due to non-ischaemic aetiology the increased mortality rate is not due to sudden cardiac death but rather to another mode of death for which an ICD does not improve mortality rates.

In the French CeRtiTuDe registry, 1705 recipients of either a CRT-P or a CRT-D were followed rigorously for adjudicated causes of death over 2 years. [36] The CRT-P patients were older (mean

age 76 years), less often male, had more symptoms of heart failure, less often had heart failure of ischaemic aetiology and more patients had atrial fibrillation and other co-morbidities. Although in CeRtiTuDe mortality was double in the CRT-P vs the CRT-D group, this increased mortality rate was due to non-sudden cardiac death in the CRT-P group, thereby suggesting that the patients who are routinely selected for a CRT-P would not benefit from a CRT-D.

In short, CRT reduces but probably does not completely abolish the risk of sudden cardiac death. The likely mechanism is related to reverse remodelling following successful resynchronization. [37] Therefore, it has been speculated that a CRT-P may provide adequate protection from the increased mortality that these patients face and that they may not require the defibrillator part of the device.

Whether the patients actually required the defibrillator is important to consider, since the addition of the defibrillator component is not without potential adverse procedural complications including the risk of inappropriate shocks. [38, 39]

Perhaps providing implanters with a scoring system for patient selection would assist in appropriate patient selection. Several risk scores such as the Goldenberg risk score have been proposed to identify patients with a limited survival benefit from a CRT-D, who may therefore be implanted with a CRT-P rather than a CRT-D. [40 41] Such risk scores may prove useful in informing the selection of the most appropriate type of CRT device in the individual patient.

However, in order to properly resolve the P vs. D question, we would require a large, randomized controlled trial directly comparing the two types of CRT devices. Fortunately, the RESET-CRT

trial is underway in Germany (ClinicalTrials.gov number NCT03494933). In this study 2030 patients with both ischaemic and non-ischaemic HF aetiology will be randomized to a CRT-P or CRT-D. The primary endpoint of this study is all-cause mortality. Hopefully, the results of such a trial will shed more light on this important and clinically relevant issue, thereby allowing guidelines to provide a clearer recommendation in which patients to implant a CRT-P and in which to implant a CRT-D.

4.4 Paper 4 -Adherence to ESC Cardiac Resynchronization Therapy Guidelines – Findings from the ESC CRT Survey II

In this paper we examined adherence to guidelines and demonstrated that there is good adherence to the ESC EHRA CRT guidelines in the ESC countries surveyed. In CRT Survey II 67% of patients were implanted under recommendation class I and only 2% under recommendation class III.

We grouped the patients included in the survey according to which CRT indication they were implanted under and demonstrated that patients were more likely to be considered for a CRT under a weaker indication if they were male, age ≥ 75, had heart failure of ischaemic aetiology and were admitted to hospital acutely.

Patients admitted to hospital electively for CRT implantation were more likely to have class I indications than those admitted as an emergency, possibly due to a more systematic outpatient review. In contrast, non-elective admissions tended to be associated with prolonged hospital stays and these patients were more likely to receive a CRT device with a weaker indication. This may

be affected by a collaborative approach to therapeutic options in a hospital setting with more than one physician involved in the decision-making process.

We demonstrated large inter-country variations in the percentage of patients implanted under recommendation class I. These were mirrored by large variations in number of patients implanted under recommendation class IIa (should be considered). We postulated that a low percentage of patients implanted under recommendation class I does not necessary imply poor guideline adherence, but rather a willingness and ability to expand to implanting based on a wider indication and less evidence such as rapidly adopting new indications from trials like BLOCK HF. [19] These differences may reflect academic research interests or national culture. Certain countries are also highly dependent on strict recommendation class I guideline adherence in order to get reimbursement for the devices implanted, which likely accounts for some of the inter-country variation seen in our survey.

In this paper we also reported the results of an exploratory analysis of our data regarding the release of the ESC HFA 2016 guidelines. [8] We wished to identify whether the release of these guidelines half-way through the survey recruitment period affected clinical practice. The stronger recommendation for patients expected to be dependent on RV pacing was associated with a significant increase in the proportion of patients implanted with this indication. In contrast, the downgraded recommendation for upgrading to CRT due to worsening of heart failure did not have an impact, suggesting that physicians continued to believe that this indication is appropriate in clinical practice. The same was true of the stricter QRS duration criterion (>130ms), which did not appear to change practice as there was an increase in percentage of patients implanted with a QRS duration between 120 ms and 130 ms after the HFA guideline release. However, few

patients were implanted with a QRS of 120-130 ms. This could indicate that the higher QRS cut-off had already been implemented in many centres following the publication of the ECHO CRT trial in 2013 which clearly indicated increased mortality in patients with QRS duration ≤130ms. [18] Furthermore, although both the EHRA 2013 and HFA 2016 guidelines are endorsed by the ESC, they are written by two different associations representing electrophysiologists and heart failure physicians respectively. It could be expected that electrophysiologists were less likely to adhere to changes in guidelines produced by the HFA than if the guideline change had been produced by EHRA.

Several previous publications from registries have demonstrated under-utilization of CRT.[42-44] However, none of these studies assessed the adherence to ESC Guideline recommendations for CRT in patients implanted with a CRT device. A small retrospective study from the Netherlands in 2012 showed that 92% (45/49) of patients with a class I indication for a CRT underwent implantation (using the 2010 ESC focused update of ESC Guideline for Device Therapy in Heart Failure). [45] A larger study of 930 patients implanted with a CRT device reported that 61% had a class I indication and that these patients had lower mortality, fewer HF hospitalizations and more evidence of remodelling than those with other indications. [46] A recent survey of implanting centres' attitudes to guideline adherence indicated that in patients with class I indications and a QRS duration >150ms, 100% would implant a CRT device. However, with a QRS duration between 120 and 150ms, only 89% would recommend CRT.[47] 67% of centres said they would implant CRT devices for class IIa indications and only 17% for IIb indications. Interestingly, 2% of centres said they would implant CRT devices in patients with class III indications due to a QRS duration <120 ms, the same proportion as in this survey.

4.5 National Publications from CRT Survey II

Of the countries participating in CRT Survey II eleven have published national publications benchmarking their countries data against the total cohort. [48-58] Overall, patient selection and guideline adherence was similar in the 42 participating countries. However, these publications have highlighted some interesting differences. Georgia implanted few patients ≥ 75 years of age compared with the total cohort (13% vs. 32%, p<0.001) while France on the other hand had a much larger proportion of patients implanted ≥ 75 years (45%). [48, 49] Belgium implanted a significantly higher percentage of women with a CRT than the total cohort (33% vs. 24%, p<0.001) [50] In Spain there fewer percentage of patients with heart failure of ischaemic aetiology compared with the total cohort (38 % vs 45%, p<0.001). [51] A possible explanation offered for this finding was that Spain has a rather low national implantation rate and perhaps implanter are reserving CRT for patients for whom they believe the best benefit could be obtained. Croatia, Bulgaria, Poland, Switzerland and Germany all reported higher co-morbidities in their CRT population compared with the total cohort.[52, 54-57] Possible explanations for the higher rate of co-morbidities in patients in Germany is speculated to be a reluctance in other European countries to implant CRT in 'sicker' patients. In Bulgaria patients also appear to be referred later for a CRT device as more patients were in NYHA Class III or IV.[57] The Croatian population had a large number of patients implanted with LBBB (80%) and wide QRS complex (68% >150ms). Such large emphasis on QRS morphology and duration is believed to be due to health care budget restrictions in Croatia. [52] Bulgaria, Croatia and Switzerland had lower percentage CRT-D than the total cohort. [52, 55, 57] The Croatian and Bulgarian implanters attribute this lower percentage to budgetary restriction; in Bulgaria CRT-D is not fully reimbursed and patients are not always able to afford co-payments for these devices. Switzerland, on the other hand, has a reimbursement system that allows for easy access to available technology. They have attributed the higher rates

of CRT-P to the fact that their patients were older and that more often the CRT device was implanted by an electrophysiologist, who potentially would be more aware of the latest evidence suggesting that a CRT-P through reverse remodelling might reduce the need for a CRT-D. Therefore, despite not have the economic restraints of Croatia and Bulgaria, electrophysiologists in Switzerland preferentially select the less expensive CRT-P device with the primary goal of relief of heart failure symptoms. The Czech Republic reported a high percentage of patients implanted with a QRS duration <120 ms (13% vs. 7%, p<0.001) and linked this to their high percentage of patients with atrial fibrillation (47% had a past medical history of atrial fibrillation vs. 40%, p<0.001) and assume that these were likely to be implanted with a CRT prior to AV junction ablation. [53]

Scandinavia (Norway, Sweden and Denmark) reported a higher percentage of patients who had AV block or were pacing dependent (49% vs. 33%, p<0.001) with more patients implanted due to pacemaker indication and expected RV pacing dependence (36% vs. 22%, p<0.001). [58] The explanation offered for this higher rate in Scandinavia is that they are adopting the practice of implanting a CRT rather than a traditional pacemaker in patients with reduced LVEF and a high degree of AV block to avoid worsening of LVEF due to a high rate of RV pacing. This was demonstrated by the BLOCK HF trial and the HFA guidelines raised the recommendation class for this indication from a class IIa in the EHRA guidelines to a recommendation class I with evidence level A. [8, 19, 27]

Although there was mainly consistency in practice in Europe, several interesting differences are reported and many of these are attributed to economical differences between countries. Several of these national publications also highlight the difference between their countries' percentage of

CRT-P vs. CRT-D with that of the total cohort. These differences are often attributed to national spending patterns but may also be related to the imprecise recommendations provided by the guidelines.

4.6 Comparison of CRT Survey I vs. CRT Survey II

The inspiration for conducting CRT Survey II came from the success and findings of the first ESC CRT Survey (CRT Survey I) conducted in 2009. [59-63] CRT Survey I analysed data on 2438 patients implanted with a CRT device in 13 ESC member countries. At the start of the ESC CRT Survey, the most current guideline recommendations for a CRT were the 2008 HFA guidelines, which recommended implantation in patients with EF ≤ 35% in NYHA Class III and IV heart failure with a QRS duration >120 ms. [64] CRT Survey I found that that implanters were implanting a substantial number of devices outside the guideline recommendations, including 9% with QRS duration <120 ms, 20% in NYHA Class II , 2% in NYHA Class I and 23% of patients with AF. [60] Furthermore, 26% of patients implanted had a previous device and 31% were ≥75 years old. Although not outside guideline recommendations, both are patient groups for which there was and still is little RCT evidence of CRT effect.

All 13 countries participating in CRT Survey I also participated in CRT Survey II. These countries included Austria, Belgium, France, Germany, Ireland, Israel, Italy, Netherlands, Norway, Spain, Sweden, Switzerland and the United Kingdom. CRT Survey II collected data from 5313 patients in these 13 countries. In the years between the two surveys several large RCTs were performed with patients with milder heart failure (NYHA II): REVERSE, MADIT-CRT and RAFT [4-6]. These trials all concluded that the addition of a CRT device was associated with reduced rates for heart failure events in patients with NYHA Class II heart failure. RAFT

was also able to demonstrate a mortality benefit. This led to more recent ESC guidelines to include patients in NYHA class II in their CRT recommendations. [8,17,27] Our comparative analysis of CRT Survey I and II showed that clinical practice has evolved along with the guidelines with CRT Survey II including 40% patients in NYHA Class II compared with 20% in CRT Survey I.

Subgroups analysis of both the REVERSE and MADIT-CRT trials showed better response in patients with LBBB morphology than in those without, leading guidelines to divide their recommendations according to bundle branch morphology with a stronger recommendation awarded patients with LBBB. [8,15-17,27] Our comparative analysis of CRT Survey I and II has again shown that clinical practice has evolved in line with guideline recommendations; in CRT Survey II 73% patients had LBBB compared with 68% in CRT Survey I.

The most current guidelines at the start of CRT Survey I (2008 HFA guidelines) did not specify that the underlying rhythm be sinus for a recommendation class I for CRT and there was no mention of CRT in patients with atrial fibrillation. [64] Observational data and subgroup analyses showed conflicting results regarding the effectiveness of CRT in patients with atrial fibrillation. [65-67] The lack of firm evidence of effect of CRT in patient with AF has led the most recent ESC guidelines to provide patients with a lower recommendation class that those in sinus rhythm. [8,27] These less strong recommendations for patient with AF are reflected in clinical practice with 26% patients with AF in CRT Survey II and 23% in CRT Survey I.

CRT Survey II in line with CRT Survey I has further demonstrated that CRT is being implanted in patients for whom there is limited evidence from RCT, such as those ≥75 years of age (39% in II and 31% in I) and those upgraded from a previous device (25% in II and 26% in I).

CRT Survey I also found that high volume centres were more likely to explore newer indications in their CRT practice by implanting more patients with mild symptoms and narrow QRS duration [61] In CRT Survey II this was the case for narrow QRS duration (high volume centres 10% <120 ms vs 6% >120 ms for low volume centres). This finding could be partially explained by the large percentage of patients implanted with a pacemaker indication and expected RV pacing dependence (high volume centre 24% vs. 22% low volume). However, in CRT Survey II there was no difference in patients implanted in NYHA Class I or II for high versus low volume centres (41 % vs. 41%).

4.7 CRT in important subgroups

4.7.1 CRT in Women

International CRT guidelines do not categorize CRT recommendations based on gender. However, the ESC EHRA 2013 guidelines did suggest that women respond better to CRT therapy than men.[27]

In our primary publication of CRT Survey II we reported that only 24% of patients implanted with a CRT in Europe are women. [68] The women implanted in CRT Survey II had significantly less ischaemic heart failure aetiology (25%) than men (51%) with 20% of women having had a previous myocardial infarction compared with 42% of men. Despite achieving statistical significance, their median QRS durations (160 ms for both, $p<0.001$) and LVEF (30% for women, 28% for men, $p<0.001$) were similar. Therefore we found that apart from a substantial difference in percentage of patients with heart failure of ischaemic aetiology, men and women implanted with CRT in this survey had similar demographics and clinical characteristics.

In our CRT-P vs. CRT-D analysis (paper 3) we found that women were also less likely to receive a CRT-D [32]. In our guideline analysis paper (paper 4) we demonstrated that women appear to receive CRT implantation predominantly when the indication is very strong while men patients are more likely to undergo CRT implantation with less strong indications. This could represent a gender bias and may partially explain the low proportion of CRT implants in women. In another publication from CRT Survey II we demonstrated that female patients more often experienced

intra- and periprocedural complications such as pneumothorax, pericardial tamponade, coronary sinus dissection and lead dislodgment. [69]

The low percentage of women implanted with a CRT can partially be explained by the fact that women develop heart failure at older age than men. Women are also more likely to develop HF with persevered ejection fraction than heart failure with reduced ejection fraction and thereby not quality for a CRT.[70] This low percentage of women implanted with a CRT-D found in CRT Survey II is consistent with the findings from recent European Registry in which only 19% of primary preventive ICD recipients were female. [71]

The increased complication rate seen in women in CRT Survey II is consistent with observations from the Danish Cardiovascular Implantable Electronic Device Registry and the US National Cardiovascular Data Registry (NCDR) report which also found more device-related complications in women. [39, 72] The reasons for this increased risk of complications in women is unclear but it has been speculated that it is related to differences in body composition, including smaller vascular and cardiac dimensions, smaller body weight, and hormonal differences. This increased complication risk could be one of the factors limiting the implantation of these devices in women.

The underutilization of CRT in women is particularly unfortunate considering that there are several studies, including sub-analysis of RCTs, meta-analysis and registry data, suggesting that women have a greater benefit from CRT than men. [73-79] The mechanisms postulated to explain this increased benefit of CRT in women include greater reverse remodelling in women with

greater reduction in LV volumes and improvement in LVEF, more LBBB in women, LBBB at narrower QRS in women, and the fact that women more often have heart failure of non-ischaemic aetiology.[70, 73, 74, 80-82] In CRT studies patients with non-ischaemic HF aetiology have a better overall prognosis than patients with ischaemic aetiology in both the control arm and the CRT arm. [83] Post hoc analysis of the MADIT-CRT and COMPANION trials also showed that patients with LBBB had greater benefit of CRT than patients with non-LBBB. [15, 16] Finally, body size may be a factor which has been overlooked. In an individual patient meta-analysis of five RCTs with 3496 patients women were generally shorter than men but about a fourth of men were also 'short'. [84] In this meta-analysis with a composite outcome of mortality and HF-related hospitalizations, only height and QRS duration, but not sex, were independent predictors of CRT benefit. This meta-analysis generates the hypothesis that height may be a new factor to be considered in CRT implantation, in particular in patients with shorter QRS durations, and that other yet unidentified factors may predict CRT response.

Unfortunately, it is difficult to assess sex differences in CRT treatment because of the low number of women enrolled in HF trials including CRT trials. [85] In the pivotal CRT trials the percentage of women ranged from 19% to 33%. [1-7]

One of the most recent guidelines released by the ESC on the treatment of ST elevation myocardial infarction (STEMI) included in its key messages a section on gender aspects stating that 'Women tend to receive reperfusion therapy and other evidence-based treatments less frequently and/or in a delayed way than men. It is important to highlight that women and men

receive equal benefit from a reperfusion and other STEMI related therapies, and so both genders must be managed equally.' .[86] Unfortunately, the most recent ESC guidelines relating to CRT do not include such a statement. Perhaps this should be included in any future update of the guideline so that more eligible women are offered this treatment.

4.7.2 CRT in the Elderly

International guidelines do not suggest an upper age limit for CRT implantation. There is however some guidance regarding age and co-morbidities provided by a few of the international guidelines regarding the choice of device type. The Canadian guidelines state that CRT-P should also be considered in patients who are not candidates for ICD therapy because of limited life expectancy and significant co-morbidities.[87] ESC EHRA guidelines provide guidance on whether to place a CRT-P or a CRT-D depending on the co-morbidities of the patient. [27] The 2012 EHRA and Heart Rhythm Society Expert Consensus Statement on CRT in Heart Failure suggests performing a comprehensive assessment of comorbidities prior to selection of patients for CRT. [88] However, overall there is limited concrete advice in international guidelines regarding the impact on clinical decision-making of age and comorbidities in the individual patients.

In CRT Survey II 32% of patients included were ≥ 75 years of age. These patients were more frequently in NYHA Class III or IV (66% vs. 56%, $p<0.001$). The older patients had more comorbidity including hypertension (72% vs. 60%, $p<0.001$), atrial fibrillation (33% vs. 22%, $p<0.001$), anaemia (20% vs. 13%, $p<0.001$) and renal dysfunction (45% vs. 25%, $p<0.001$). They also had significantly higher median NT-pro BNP levels (3510 pg/ml vs. 1968 pg/ml, $p<0.001$) than younger patients. Despite substantially more patients ≥ 75 years of age having heart failure

of ischaemic aetiology (50% vs. 42%, p<0.001) compared with those <75 years of age, far fewer patients in the oldest group were implanted with a CRT-defibrillator (CRT-D) compared with those in the youngest group (52% vs. 78%, p<0.001).

Despite the fact that patients ≥75 years of age in CRT Survey II had greater comorbidities and experienced more symptoms from their heart failure, they suffered similar periprocedural complications (6% vs. 5%, p= 0.263) and adverse events (5% vs. 5%, p= 0.029) during the index hospitalization. Our findings suggest that CRT may safely be offered to elderly patients and that such patients should not be deprived of this treatment.

Although none of the pivotal CRT trials had an upper age limit for inclusion, the exclusion criteria of these trials limited the inclusion of elderly patients. The median age for patients included in the CRT landmark trials ranged from 62 to 68 years, therefore limited trial evidence exists for CRT in patients ≥ 75 years of age. [1-7] Only CARE-HF actually included some patients >75 years [89] Furthermore, several of the exclusion criteria for these trials, including the comorbidities – atrial fibrillation and inability to provide informed consent (due to significant cognitive dysfunction) - make the data difficult to extrapolate to elderly patients who often suffer from such co-morbidities. [90] However, both the prevalence of HF and LBBB increase with age. [91]

Whether CRT is more beneficial to different age groups is unclear since the evidence is conflicting. [90] In the MADIT CRT group there was a trend towards greater benefit in patients

≥ 65 years; the same was seen in the RAFT (2010) [5,6] The RESERVE trial (2008) showed an opposite trend, with greater response in patients <64 years of age. [4] However, none of these observations were significant.[90] The COMPANION trial found that patients aged ≥ 65 years had greater benefit from CRT-D than from CRT-P compared with younger patients but did not provide a p-value for this statement. [7,90] However, previous observational studies on elderly patients have been able to demonstrate benefit. An observational study with two-year follow-up comparing CRT in patients ≥ 75 years (107 patients) vs. those <75 years (159 patients) found similar improvements in quality of life, NYHA class and LVEF. The patients ≥ 75 years had a higher mortality rate. However, this was also non-significant. (35% vs 27%, p =0.36). [92] Another study with a similar 2 year follow-up compared CRT in patients ≥ 70 years (68 patients) with those <70 years (102 patients) and found that the two groups had similar quality of life and 6-minute walk distance improvements. [93] However, these were small single studies with small number of patients. A similar study of 49 patients ≥ 80 years found that although annualized mortality rates were significantly higher in this group (15% compared with 6% for those <70 years old) time to death or first heart failure admission was similar in these age groups. [94] Another study examined mortality data of 90 patients >80 years of age and found they had similar clinical benefits to younger patients. [95]

Regarding periprocedural complications in the elderly, a sub study of MADIT-CRT found no difference in 90 day-complication rate for CRT-D implantation in patients ≥ 75 year of age. [96] Such sub-analysis has not been performed for the other pivotal CRT trials. [90] However, observational data has provided some evidence suggesting that periprocedural complications are higher in the elderly. [97]

In a retrospective analysis of CRT in 177 patients >75 years of age there was no difference in mortality between he CRT-P and CRT-D groups in this elderly population. [98] A similar result was seen with a retrospective analysis of patients aged ≥75 years in Canada. Mortality data were compared for 128 patients with a CRT-D vs. 42 with a CRT-P and, again, there was no significant difference in mortality or cardiac hospitalization between these two groups. [99]

With a CRT-D device there is also the issue of end-of life care which is often more relevant in the elderly population. A study of 900 hospice providers found that although 97% admitted patients with an ICD only 10% of the hospice providers had a deactivation policy. [100]

However, if CRT can improve elderly patients' functional status, they are likely to require less intensive outpatient treatment and likely to spend less time in hospital, thereby reducing the cost of their HF treatment. [89] But CRT in itself is an expensive therapy for both the implantation and the follow-up. So careful considerations must be made in patient selection also in elderly patients as it is estimated that a patient must live for at least 4 years for a CRT implantation to be cost effective. [101]

4.7.3 CRT in Patients with Atrial Fibrillation

Both the ESC, the Canadian and the American guidelines provide either a class IIa or IIb recommendation for CRT in patients with systolic heart failure and AF. [8, 27, 87, 102] European guidelines specify that patients must have LVEF ≤ 35% and NYHA Class III or IV HF. Again, the ESC associations disagree on QRS duration (≥130 ms for HFA and ≥120 ms for EHRA). While the ACC/AHA/HRS and CCS guidelines simply state that eligible patients must be

otherwise suitable for a CRT, the Australian and New Zealand guidelines do not discuss patients with atrial fibrillation. [103]. In the guidelines that provide recommendations for CRT in patients with atrial fibrillation there is consensus that ventricular rate must be adequately controlled by pharmacologic intervention or atrioventricular nodal ablation in order to ensure a high degree of CRT pacing.

In CRT Survey II 41% of patients had a past medical history of atrial fibrillation and 26% had documented atrial fibrillation on their ECG at the time of implantation. Patients with atrial fibrillation and without atrial fibrillation at implantation had similar heart failure aetiologies, with 44% of patients with atrial fibrillation and 45% ($p = 0.023$) of those without atrial fibrillation having heart failure of ischaemic aetiology. However, patients with atrial fibrillation were older (median age 72 years vs. median age 68 years, $p<0.001$), had more advanced heart failure (66% NYHA functional class III and IV in the AF group vs. 54% in the non-AF group, $p<0.001$) and more co-morbidities than patients without atrial fibrillation. However, periprocedural complications (5% in the AF groups vs. 6% in the non-AF group, $p=0.135$) and adverse events (5% for those with AF vs. 4% without AF, $p=0.010$) were similar in the two groups.

No substantial sized trial has compared CRT to a pharmacological control group for patients with atrial fibrillation. Most of the large trials on CRT excluded patients with atrial fibrillation and the trials that included patients with atrial fibrillation were small. [104, 105] At least two trials have compared CRT to RV pacing after AV node ablation. These suggest that CRT is superior. [106, 107]

However, whether this reflects a benefit from CRT or simply avoiding the harm of RV pacing is unclear.

However, atrial fibrillation is common in the heart failure population with as many as 10-50% of patients with moderate or severe heart failure having concomitant atrial fibrillation. [108] A large proportion of these heart failure patients with atrial fibrillation also have wide QRS complexes.[109] Patients with atrial fibrillation should also benefit from CRT if a high rate of biventricular pacing dependence is maintained by slowing AV conduction either by pharmacological treatment or by assuring total dependence AV node ablation. Observational data and subgroup analyses demonstrate conflicting results regarding effectiveness of CRT in patients with atrial fibrillation. [65-67] Clearly, the benefits of CRT in atrial fibrillation patients should be further investigated in a well-designed prospective RCT.

4.7.4 CRT in Patients with Non-LBBB

For patients with non-LBBB there is considerable variation in international guideline recommendations. If the patients has a QRS duration >150 ms and is in NYHA class III/ IV then both the two ESC guidelines and the American guidelines suggest that a CRT should be considered (recommendation class IIa). The Canadian guidelines provide a 'may be considered' (class IIb) recommendation for the same indication.

However, where the inconsistency between guidelines is greatest is for patients with non-LBBB and a QRS <150 ms with recommendations varying from the strongest recommendation class (A

from the Australian guidelines to the weakest III from the American guidelines for NYHA functional class II). This large discrepancy mainly relates to the Australian guidelines not distinguishing based on type of bundle branch block in their CRT recommendations. The Canadian guidelines do not provide a formal recommendation for this patient group; instead, they simply state that there is no clear evidence of benefit from CRT for patients with QRS duration <150 ms because of non-LBBB conduction.

In CRT Survey II, 73% of patients had LBBB. The patients with LBBB and non-LBBB were similar in NYHA functional class grouping and LVEF. However, patients with non-LBBB were more often male (83% vs. 73%, $p<0.001$), had more often heart failure of ischaemic aetiology (51% vs. 42%, $p<0.001$) and narrower median QRS duration (140 ms vs. 160 ms, $p<0.001$) than those with LBBB.

Although none of the large RCTs evaluating CRT specified LBBB as selection criteria, most of the patients included in these trials had LBBB. Subgroup analyses of RCTs have strongly suggested that LBBB morphology was associated with substantially better outcome and therefore a stronger recommendation class is provided in the guidelines for patients with LBBB. [15, 16] However, patients with LBBB tend to have a wider QRS and the data is conflicting as to whether LBBB is a predictor of CRT success or whether it is just a surrogate marker for a wide QRS. [15, 16, 110, 111]

4.7.5 Right Ventricular Pacing Dependence and Upgrades from a Previous Device

Patients with a high degree of AV block implanted with a traditional two lead-pacemaker can display pacing dependence with high amounts of RV pacing. RV pacing has been shown to lead to adverse LV remodelling and deterioration of systolic function. [112-115] Mechanistically, RV pacing resembles LBBB and, therefore, patients with HF and AV block should benefit from CRT therapy. In such patients, biventricular pacing rather than RV pacing alone prevents further progression of systolic dysfunction and LV dilatation. [19] However, the benefit of prophylactic implantation of CRT device remains unclear and guidelines provide varying recommendation for this indication. [11]

Interestingly, the avoidance of RV pacing by using a CRT-P rather than a pacemaker was already mentioned in the 2008 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure, under a contraindication to a pacemaker with a recommendation class III, level of evidence C. These guidelines state 'In HF patients with concomitant indication for permanent pacing (first implant or upgrading of a conventional pacemaker) and NYHA class II–IV symptoms, low LVEF ≤35%, or LV dilatation, CRT with pacemaker function (CRT-P) should be considered. In these patients, the use of right ventricular pacing may be deleterious and may cause or increase dyssynchrony. [64] In the 2012 ESC HFA heart failure guidelines patients with an indication for conventional pacing and no other indications for CRT were provided with a recommendation class IIa or IIb for a CRT depending on their NYHA functional class. Both these recommendations were provided with an evidence level C. There was no mention of upgrading from a previous device. [17] The ESC EHRA (2013) guidelines also provided a class IIa recommendation for a CRT to avoid RV pacing dependence. However, a Class I recommendation

was provided for upgrading to a CRT from either a pacemaker or an ICD if the patient had a high percentage of ventricular pacing. [27] The ESC HFA guidelines released three years later provided the opposite recommendations class I for prophylactic insertion of a CRT device to avoid deterioration of LV function with chronic pacing and a IIb for an upgrade from a previous device.[8] While the Canadian guidelines released the following year lowered the recommendation for patients with a high degree of AV block likely to be RV pacing dependent to a class IIb. [87]

In CRT Survey II 23% of patients were upgrade from a previous device (pacemaker of ICD). Of these patients 44% had AV block type I and II and 39% had the clinical indication of implantation of a CRT -pacemaker indication and expected RV pacing dependence. These findings suggests that despite the imprecise nature of the evidence and the guidelines, implanters continue to appreciate the value of avoiding RV pacing either by prophylactically inserting a CRT device or by later upgrading to one. In our survey, patients upgraded from a previous device and those implanted de novo were equally frequently successfully implanted and the patients had similar complication rates. [116] Interestingly, these similar successes and complication rates were present despite the upgraded patient population being older, having greater co-morbidities and worse heart failure disease state.

The decision to prophylactically implant a CRT or later upgrade is difficult to make due to the limited evidence available in this area. Patients with a previous pacemaker were excluded from the landmark CRT trials (expect for MUSTIC-AF and RAFT) and, therefore, trial evidence to support upgrading to a CRT remains lacking. Registry data from both Denmark and the US

reported more complications with patients who were upgraded from a previous device compared with those implanted de-novo. [39, 117] Furthermore, an observational study comparing 233 patients with an upgraded CRT device found that these patients had inferior long term outcomes compared with those implanted de-novo. [118] In contrast, a large meta-analysis analysis of 21 363 patients upgraded to a CRT found that they had similar all-cause mortality to patients implanted de-novo. [119] Therefore, the evidence is unclear as to what is the best treatment for patients with AV block who are likely to be have a high degree of RV pacing. Fortunately, there is currently a RCT ongoing called the BUDAPEST-CRT upgrade study, which will randomize patients to a CRT-D or ICD upgrade. Hopefully, this study will be able to help guideline task forces to determine whether CRT should be upgraded prophylactically in these patients or whether they should wait until either their systolic function deteriorates or their QRS duration lengthens? [120]

4.8 Factors Influencing Health Care Resources Utilization

We split the 42 countries participating in CRT Survey II into three groups according to how high their current health expenditure was per capita: high (3493 patients), medium (6355 patients) and low (848 patients) and compared these three groups. The countries with the lowest health care expenditure were more likely to implant CRT in patients that had strong guideline recommendations for implantation such as symptomatic heart failure – NYHA Class II-IV (99% vs. 95%, $p<0.001$), LVEF$\leq$ 35% (95% vs. 84%, $p<0.001$), sinus rhythm (81% vs 67%, $p<0.001$), QRS duration $\geq$150 ms (73% vs. 66%, $p<0.001$) and LBBB (84% vs. 74%, $p<0.001$). Patients with all the above characteristics have a recommendation class I, evidence level A indication for CRT in both the ESC CRT guidelines from the HFA and EHRA. [8, 27] Overall, 78% of patients

were implanted with indications with recommendation class I, evidence level A in the lowest healthcare spending per capita countries vs. 56 % in the highest spending group. These countries were also less likely to implanted patients under lower recommendation class such as those with atrial fibrillation (16% vs. 27%, p<0.001).

Regarding CRT indication with different recommendation strength in the ESC EHRA and ESC HFA guideline such as upgrades from a previous device and pacemaker indication with expected RV pacing dependence, these indications were also much less frequent in countries with the lowest expenditure on health care (14% vs.28%, p<0.001 and 11% vs. 27%, p<0.001 respectively), thereby suggesting that the high guideline adherence may not be related to compliance but rather to the limited resources to explore indications with less strong guideline recommendations. Our data also suggest that countries with lower health care expenditure are limiting CRT devices not only to those with the strongest recommendation class but also to the most symptomatic patients, with 56% vs. 45%, p<0.001 having been hospitalized for HF during the past year and 61% vs. 56%, p<0.001 being in NYHA Class III or IV.

The countries with the lowest health care expenditure were also less likely to implant CRT in elderly patients (median age 65 years vs. 72 year, p<0.001 with 15% vs. 39%, p<0.001 of patients ≥75 years of age), thereby perhaps actively limiting these devices to younger patients. The percentage of females implanted with device on the other hand was high in the low expenditure countries (31% vs. 25%, p<0.001). This finding fits with the conclusion of paper 4 that women are more likely to be implanted under strong recommendation class compared with men. The ratio of CRT-P to CRT-D implants were similar in all three of the spending groups with CRT-P

percentages being 28% in the lower health care spending group, 30% in the moderate and 32% in the highest spending group.

We have also analysed our data to compare countries with a higher CRT implantation rate per capita (≥ 0.011%, 13 countries) compared to those with a lower implantation rate (<0.011%, 29 countries). Again we found differences in percentage of the following characteristics associated with high recommendation class in ESC guidelines. Countries with the lowest implantation rates had greater percentage of patients who had strong guideline recommendations for implantation such as symptomatic heart failure – NYHA Class II-IV (98% vs. 95% p<0.001), LVEF≤ 35% (89% vs. 85%, p<0.001), sinus rhythm (71% vs 68%, p<0.001), QRS duration ≥150 ms (75% vs. 63%,p<0.001) and LBBB (78% vs. 73%, p<0.001). However these differences between the groups were not as large as those seen in the healthcare expenditure analysis. Overall, 66 % of patients were implanted with indications with recommendation class I, evidence level A in the countries with lower implantation rate vs. 56 % in the countries with higher implantation per capital group.

The countries with the lowest implantation rates also had slightly lower rates of implantation of patient groups with weaker recommendations (AF, 25% vs. 27%, p<0.001). Regarding the indications with varying degrees of recommendation in the EHRA and HFA guidelines, they were slightly lower for the upgrades (21 % vs. 26%, p<0.001) and similar in the patients implanted with pacemaker indication and high degree of RV pacing dependence 24% vs. 23%, p=0.262).

Median age of the patients was lower for the countries with the lowest implantation rate (68 years vs. 72 years, p<0.001) and so was the percentage of female patients (23% vs. 25%, p=0.144). Our data suggest that European countries with a lower implantation rate may be more likely to limit CRT implantation to patients with the strongest recommended indication for CRT.

Comparing centres that where only funded by public healthcare with those totally or partially privately funded there was no major differences in NYHA Class II-IV (97% vs. 97%, p=0.301), LVEF≤ 35 (87% vs. 87%, p=0.081), sinus rhythm (69% vs 69%, p=0.444), QRS duration ≥150 ms (69% vs. 69%,p=0.162) and LBBB (75% vs. 75%, p=0.562). Overall 61 % of patients implanted in centres only funded by public healthcare were implanted with indications with recommendation class I, evidence level A vs. 62 % implanted in centres totally or partially privately funded. Thus, how the centre was funded did not appear to highly influence how many patients are implanted under the strongest guideline recommendations.

Regarding the indications with weaker recommendation classes such as patient with AF, there was also no difference (26% vs. 25%, p=0.443). The indications with varying degrees of recommendation in the EHRA and HFA guidelines were slightly lower in the publically funded group (upgrades 23% vs. 26%, p<0.001 and patients implanted with pacemaker indication and high degree of RV pacing dependence 22% vs. 28%, p<0.001). Median age of the patients (70 years vs. 71 years, p=0.051) and percentage females (24% vs. 24%, p=0.683) were also similar. Again percentage of CRT-P and CRT-D were similar in the two groups. Our data suggest that in Europe the way the centres are funded does not appear to have a large effect on guideline adherence.

CRT Survey II has thus demonstrated unwarranted variation in CRT delivery. The term 'unwarranted variation' has been coined to describe variations in medical practice between geographical regions or provider groups (hospitals or physicians) that cannot be explained by the patient's morbidity, risk factors or preferences. [121, 122] Such ununiformed delivery of healthcare demonstrated in CRT Survey II is unfortunately not unique; previous studies have shown that patients' morbidity is not the main determinant of healthcare utilization and expenditure; rather, it is geography.[123, 124 121] Previous evidence suggests that the problem of unequal health delivery is not only related to differences in individual countries but that there also exists uneven healthcare delivery between centres and physicians for similar medical conditions. [121] In Europe, a collaboration has been initiated to understand and address these variations in medical practice – the European Collaboration for Healthcare Optimization. [124]

CRT is an example of 'supply-sensitive care' where the supply of a specific resource has also an influence on the implantation rates. However, CRT is also an example of 'preference-sensitive care' where different choices are available for patient care that include different risks and benefits and thus patients' attitudes towards the treatment is likely to vary. [124] Such preference could influence the implantation of a CRT-P vs. a CRT-D or CRT implantation vs. intensifying optimal medical therapy. In preference-sensitive care the correct CRT implantation rate reflects the choice of correctly informed patients. [124]

Global comparison analysis of heart failure treatment has been performed in the ASCEND-HF, ASTRONAUT trial and PARADIGM- HF trials. All these comparisons showed large differences in percentage of HF patients that were implanted with CRT and ICD/CRT-D between continents (table 14, 15 and 16). [125 126, 127]

Table 14- Global Variation in ASCEND-HF Trial,

% Adherence	Total Trial Cohort (n=7007)	North America (n=3149)	Latin America (n=658)	Asia Pacific (n=1744)	Central Europe (n=966)	Western Europe (n=490)	*P* Value
CRT with/without ICD therapy	(353/1362) 25.9%	(289/675) 42.8%	(7/115) 6.1%	(11/301) 3.7%	(13/179) 7.3%	(33/92) 35.9%	<0.001

Table adapted from ASCEND-HF trial 2013.[126]

Table 15- Geographic Variations in the ASTRONAUT Heart Failure Trial

	North America	Latin America	Western Europe	Eastern Europe	Asia/ Pacific	*P*-value
CRT	14 (11.4)	6 (3.7)	48 (12.2)	25 (5.1)	16 (3.6)	<0.001

Adapted from ASTRONAUT trial. 2015 [127]

Table 16- Geographic Variations in the PARADIGM-HF Heart Failure Trial

	North America	Western Europe	Central/Eastern Europe/Russia	Latin America	Asia-Pacific	*P*-value
Any CRT	130 (22%)	207 (12%)	113 (4%)	29 (2%)	42 (3%)	<0.0001
ICD or CRT-D	327 (54%)	559 (33%)	193 (7%)	61 (4%)	26 (2%)	0.0033

Adapted from PARADIGM-HF 2016.[125]

An important explanation for the large variations in CRT delivery demonstrated in CRT Survey II and worldwide is that these devices are not reimbursed in all countries. Implementation of CRT requires a large infrastructure to select, implant and follow-up CRT devices and thus implantation rates per capita are usually higher in well-resourced healthcare systems. [126]

4.9 CRT Response and Underutilization of CRT

This PhD thesis focuses on patient selection for CRT. However, in order for a CRT device to result in morbidity and mortality improvement it is essential that the device is optimally implanted and that the patient is adequately followed up. Further discussion on this topic is beyond the scope of this PhD.

The main obstacle to a successful treatment with CRT remains underuse. A study in Sweden showed that although 25–30% of patients with heart failure had a strong indication for a CRT device, only 7% had a device implanted. [128] Factors associated with underuse included inadequate referral, female sex, and being older than 75 years. [128] Therefore, not only is it important to select the correct patient for a CRT, it is also essential that awareness of the benefits of this device are made clear to physicians so that more patients can be referred for a CRT.

5. Limitations

The ability of a survey to describe practice is related to the strength of its methodology, its representativeness and size. Although the number of patients enrolled in CRT Survey II was large, there were substantial differences in recruitment between countries. Overall, we estimate that about 11% of patients implanted with CRT devices in participating countries during the recruitment period were enrolled in the survey. We cannot assess the degree of selection bias in the choice of enrolled patients. Although we requested enrolment of consecutive patients, it was not possible to verify this, and sites may have been less likely to report unsuccessful implants or cases with a poor outcome. It is also possible that centres may have been less likely to report implants in patients without class I or II guideline indications, resulting in low reported numbers with class III indications. Furthermore, the eCRF was designed to be as user-friendly as possible in order to maximize the number of patients enrolled and the interpretation of questions was up to the discretion of the investigator.

Finally, as in all non-mandatory registries or surveys we are only able to comment on the patients who received a CRT device. We do not know how many patients with a class I indication did not receive a CRT device. It should also be noted that in our comparison of CRT Survey I and CRT Survey II the eCRFs were not identical; furthermore, CRT Survey I included patient follow-up while CRT Survey II did not. CRT Survey I contains far fewer patients, and although the same countries were compared in this analysis, the centres participating each time were not the same.

Although the survey appears to demonstrate that evidence defines guidelines, which then in turn define practice, we cannot firmly conclude that this is the case. We can merely state that these three factors appear to be related.

6. Conclusion

In patients with indications for CRT where there is firm evidence of treatment benefit, the international guidelines all provide strong recommendations for this treatment. However, in patients where the evidence of effect of CRT is limited, such as those with non-LBBB, atrial fibrillation or a high degree of AV block and presumed RV pacing dependence, international guidelines provide imprecise and inconsistent recommendations.

In CRT Survey II we demonstrated that most patients implanted with a CRT device had a guideline recommendation class I indication for a CRT and therefore adherence to CRT guidelines in Europe is high. However, particularly for the patients with CRT indications where there is limited evidence of benefit and international recommendations are inconsistent, variations in European practice are evident.

Such variations in clinical practice were also found in the choice of device type (CRT-P vs. CRT-D), which is also an area where trial evidence is lacking and international guidelines provide imprecise recommendations. We demonstrated large variations in percentage of CRT-P vs. CRT-D in our cohort between patient subgroups and between countries.

We also found that countries with both the lowest healthcare expenditure and the lowest implantation rate per capita were more likely to implant patients with indications associated with strong recommendation classes. These findings suggest that this high guideline adherence may not be related to compliance but rather to the limited resources to explore indications with less strong guideline recommendations. Such limitations of CRT implantations to patients with

strong indications were also evident in certain patient subgroups including women and younger patients.

These variations in CRT practice are likely to decrease when the data from trials on patient with lacking evidence of CRT benefit are published and can be reviewed by guideline task forces.

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Errata

Page 34 Incorrect number: “CRT-D (n=**7449**)”. Text should read: “CRT-D (n=**7467**)”

Page 47 Misspelling: “should be considered to **weight** in favour of” – corrected to “should be considered to **weigh** in favour of”

Page 68 Incorrect word: “73% of patients had **non-LBBB**” – corrected to “73% of patients had **LBBB**”

Page 72 Incorrect words: “expected **high degree of AV block**” – corrected to “expected **RV pacing dependence**”

Page 75 Misspelling: “hospitals **of** physicians” – corrected to “hospitals **or** physicians”

Paper III, Page 919 Incorrect number: “the cohort of **7305** patients”. Text should read: “the cohort of **7246** patients”

Paper III, Page 921 Table 1 Incorrect number: “CRT-D (n=**7449**)” should read “CRT-D (n=**7467**)”

Paper IV, Page 4 Incorrect word: “implanted under **other** indications” – corrected to “implanted under **Level I** indications”

Paper IV, Page 9 Incorrect numbers: “**4891** were de novo implantations, **493** were upgrades” – corrected to “**4623** were de novo implantations, **735** were upgrades”

Paper IV, Page 9 Incorrect number: “**1203** had atrial fibrillation (AF)” – corrected to “**1404** had atrial fibrillation (AF)”

PAPER 1

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CLINICAL RESEARCH

Indications for Cardiac Resynchronization Therapy

A Comparison of the Major International Guidelines

Camilla Normand, BM BCH,[a,b] Cecilia Linde, MD, PHD,[c] Jagmeet Singh, MD, PHD,[d] Kenneth Dickstein, MD, PHD[a,b]

JACC: HEART FAILURE CME/MOC

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CME/MOC Objectives for This Article: Upon completion of this activity, the learner should be able to: 1) discuss the indications for cardiac resynchronization therapy (CRT) in patients with heart failure; and 2) identify differences in international guidelines with respect to indications for CRT.

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From the [a]Cardiology Department, Stavanger University Hospital, Stavanger, Norway; [b]Institute of Internal Medicine, University of Bergen, Bergen, Norway; [c]Department of Cardiology, Karolinska University Hospital, and Karolinska Institutet Stockholm, Stockholm, Sweden; and the [d]Division of Cardiology, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts. Drs. Normand, Linde, Singh, and Dickstein have received research support from Biotronik, Boston Scientific, Medtronic, LivaNova, and Abbott. Dr. Linde has received research support from Astra Zeneca, Swedish Heart-Lung Foundation, and the Stockholm County Council. Dr. Singh is a consultant for Impulse Dynamics and Respicardia.

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Indications for Cardiac Resynchronization Therapy

A Comparison of the Major International Guidelines

Camilla Normand, BM BCh,[a,b] Cecilia Linde, MD, PhD,[c] Jagmeet Singh, MD, PhD,[d] Kenneth Dickstein, MD, PhD[a,b]

ABSTRACT

OBJECTIVES This study compares and contrasts the recommended indications for cardiac resynchronization therapy (CRT) according to the most recent guidelines from international cardiology societies.

BACKGROUND CRT has been shown to reduce morbidity and mortality in selected patients with systolic heart failure. Cardiology societies provide guidelines regarding the indications for CRT. As evidence evolves, it is challenging for the guideline committees to review the impact of newer evidence in a timely fashion.

METHODS Six of the most recent international guidelines providing recommendation concerning CRT implantation ranging from 2011 to 2017 were reviewed. These included guidelines from 2 European, 1 North American, 1 Canadian, and 1 Australian/New Zealand societies and the National Institute for Health and Care Excellence guidelines, specific to the United Kingdom.

RESULTS Although international societies provide consistent recommendations for most CRT indications, differences are found in recommendations for several important patient populations. Specifically, divergent recommendations exist regarding QRS duration, bundle branch morphology, patients in atrial fibrillation, choice of device type (CRT pacemakers vs. CRT defibrillators), and selected patients who are likely to be dependent on right ventricular pacing. The timing of publication of specific guidelines appears to play an essential role in explaining these disparities.

CONCLUSIONS Despite general consistency in international guideline recommendations, there remain certain patient populations for whom there are variations in recommendations concerning eligibility for CRT and selection of the most appropriate device in the individual patient. (J Am Coll Cardiol HF 2018;6:308–16) © 2018 by the American College of Cardiology Foundation.

The benefits of cardiac resynchronization therapy (CRT) have been firmly established in heart failure (HF) patients who remain in New York Heart Association (NYHA) functional classes II and III, despite optimal medical therapy with a wide QRS complex and reduced left ventricular ejection fraction (LVEF) (≤30% to 35%) (1–7).

This review compares and contrasts the most recent international guidelines for CRT implantation from 2011 to 2017. It includes guidelines from 2 European, 1 North American, 1 Canadian, and 1 Australian/New Zealand society. Also included are the National Institute for Health and Care Excellence (NICE) guidelines, specific to the United Kingdom. Details of these guidelines are outlined in **Table 1**.

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for the management of HF published in 2013 were harmonized with the ACCF/AHA/Heart Rhythm Society (HRS) 2012 focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities (8). For simplicity, these documents were considered together and referred to as the ACC/AHA/HRS guidelines. Furthermore, since publication of the 2013 guidelines, several focused updates of HF have been published by ACC/AHA/Heart Failure Society of America (HFSA). These updates do not propose changes to CRT recommendations and, therefore, will not be discussed further (9,10). HFSA produced their latest CRT recommendations in their 2010 guidelines and 2011 guideline update (11,12). They have since been involved in publication of the above-mentioned focused updates and collaborated with ACC/AHA/HRS in both their 2012 focused update on CRT and the ACCF/AHA 2013 guidelines. We have, therefore, decided not to include the 2010 HFSA guidelines in the review as these no longer represent the latest recommended HF treatments from the HFSA.

Guideline recommendations are based on the inclusion criteria in randomized controlled studies

JACC: HEART FAILURE VOL. 6, NO. 4, 2018
APRIL 2018:308–16

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy-defibrillator

CRT-P = cardiac resynchronization therapy-pacemaker

HF = heart failure

ICD = implantable cardioverter-defibrillator

LBBB = left bundle branch block

LV = left ventricular

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

RBBB = right bundle branch block

RV = right ventricle

and their year of publication (Online Table 1) (13). These criteria included severity of HF despite optimal medical therapy, reduced LVEF, electrical dyssynchrony, and atrial rhythm.

GENERAL OVERVIEW OF THE GUIDELINES CONSTRUCTION

LEVEL OF RECOMMENDATIONS AND GRADING OF EVIDENCE. The 2 European Society of Cardiology (ESC) guidelines and the ACC/AHA/HRS guidelines use similar predefined scales to grade their recommendations and levels of evidence, with recommendations ranging from Classes I to III and evidence levels from A to C. Classes of recommendation and levels of evidence used in the ESC guidelines are presented in Online Tables 2A and 2B (14,15).

Regarding the recommendation categories, rather than providing numerical values, the Canadian Cardiovascular Society (CCS) uses only text such as: "*is recommended, should be considered, may be considered, and is not recommended*." For simplicity of comparison and presentation, we have divided the text categories into I, IIa, IIb, and III, respectively. Furthermore, rather than use evidence levels A to C, the Canadian guidelines grade the quality of evidence as "High," "Moderate," "Low," or "Very Low," according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) standards (16,17). These are shown in Online Table 3.

The Australian guidelines use the National Health and Medical Research Council (NHMRC) guidelines, "A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines" (18), to grade their evidence levels and recommendations. In these guidelines, the level of evidence is stated numerically and the grade of recommendation alphabetically, which is the reverse of the other guidelines reviewed. These are shown in Online Tables 4 and 5.

The NICE guidelines, on the other hand, do not provide levels of evidence or grades of recommendations. They are different in presentation as they specifically address which type of device therapy is indicated (CRT-pacemaker [CRT-P], CRT-defibrillator [CRT-D], or implantable cardioverter-defibrillator [ICD]) based on NYHA functional class and QRS duration and morphology.

COMPARISON OF GUIDELINES RECOMMENDATIONS FOR CRT THERAPY IN PATIENTS IN SINUS RHYTHM

PATIENTS WITH LEFT BUNDLE BRANCH BLOCK. Table 2 compares recommendations for patients with left bundle branch block (LBBB). In patients with LBBB and a QRS duration >150 ms, all guidelines reviewed provide strong recommendations for CRT.

For a QRS duration between 120 and 129 ms, there are inconsistencies particularly between the 2 ESC associations. ESC European Heart Rhythm Association (EHRA) (2013) provides a Class I recommendation ("*is recommended*"), whereas the ESC Heart Failure Association (HFA) (2016) states a Class III recommendation ("*is not recommended*")! The CCS guidelines (2017) also clearly state that CRT should not be used for patients with QRS <130 ms. QRS duration with the cutoff set to >120 ms in the EHRA guidelines reflects the inclusion criteria in many trials such as COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) and CARE-HF (Cardiac Resynchronization–Heart Failure) (3,7). After publication of the ECHO CRT study, which indicated increased cardiovascular mortality with CRT in patients with QRS <130 ms, the HFA 2016 and CCS 2017 guidelines set the cutoff for CRT to >130 ms (19).

PATIENTS WITH NON-LBBB. For patients with non-LBBB, ACC/AHA/HRS and ESC guidelines agree that if a patient has a QRS duration >150 ms and is in NYHA functional class III or ambulatory IV, then a CRT "*should be considered*" (Class IIa). CCS provides a "*may be considered*" (Class IIb) recommendation for the same indication (**Table 3**).

There is considerable inconsistency in the guidelines for patients with non-LBBB and a QRS <150 ms, with recommendations varying from Classes IIb to III. The CCS guidelines do not provide a formal recommendation for this patient group; instead, they simply state that there is no clear evidence of benefit with CRT among patients with QRS duration <150 ms because of non-LBBB conduction. Furthermore, the levels of evidence provided for this patient group vary even for similar classes of recommendation.

AUSTRALIA (2011). The Guidelines for the Prevention, Detection and Management of Chronic HF in Australia, published by the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand in 2011, do not distinguish between LBBB and non-LBBB when providing their recommendations for CRT in patients in sinus rhythm (20).

TABLE 1 Recent International Guidelines on CRT Implantation Recommendations and Indications

Society	Guideline (Ref. #)	Year
ESC Heart Failure Association	Guidelines for the diagnosis and treatment of acute and chronic HF (15)	2016
ESC European Heart Rhythm Association	Guidelines on cardiac pacing and CRT (14)	2013
American College of Cardiology Foundation/ American Heart Association	Guidelines for the management of HF (37)	2013
Canadian Cardiovascular Society	Comprehensive update of the Canadian Cardiovascular Society Guidelines for the Management of HF (16)	2017
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand	Update to guidelines for the prevention, detection and management of chronic HF in Australia, 2006 (20)	2011
National Institute of Health and Care Excellence	ICD and CRT for arrhythmia and HF (38)	2014

CRT = cardiac resynchronization therapy; ESC = European Society of Cardiology; HF = heart failure; ICD = implantable cardioverter-defibrillator.

NICE GUIDELINES (2014). NICE guidelines recommend placement of a CRT device in patients with LBBB with a QRS duration ≥120 ms and in those with non-LBBB, if the QRS duration is ≥150 ms for patients in NYHA functional classes II, III, and IV. This is generally consistent with other guidelines reviewed.

For patients with non-LBBB who have a QRS between 120 and 149 ms, NICE guidelines only recommend placing a CRT pacemaker without ICD in patients in NYHA functional class IV. In contrast to the other guidelines reviewed, NICE guidelines do not specify that NYHA functional class IV patients must be ambulatory. They also recommend implantation in NYHA functional class I provided the patients have a QRS >150 ms. NICE guidelines also differ from most of the other guidelines reviewed in that they provide clear guidance on whether to implant a CRT-P or a CRT-D. However, in contrast to the other guidelines, NICE does so without providing classes of recommendation or levels of evidence.

SUMMARY OF INTERNATIONAL RECOMMENDATIONS FOR LBBB AND NON-LBBB. All cardiac societies' guidelines reviewed agree that patients with LBBB and a QRS duration ≥150 ms should be offered a CRT device provided they are in NYHA functional class III.

There also appears to be general consensus among the international guidelines for CRT implantation in patients with LBBB and a QRS duration ≥150 ms in NYHA functional class II and ambulatory IV.

In LBBB patients with narrower QRS duration (120 to 149 ms), there is less agreement, especially in patients with a QRS duration <129 ms and NYHA functional class II symptoms. The most striking discrepancy is between the ESC guidelines, with EHRA providing a Class I recommendation for QRS duration between 120 and 129 ms and HFA class III.

With non-LBBB there is a wide discrepancy among the guidelines, again especially concerning the narrower QRS and patients with less symptomatic HF, due to year of publication. Since 2011, increasing evidence has shown better prognosis for CRT implantation in LBBB patients versus non-LBBB patients in subgroup analysis of randomized control trials (21,22). These analyses have greatly influenced the guidelines. LBBB was not a selection criteria in any of

TABLE 2 Comparison of Recommendations for LBBB

	QRS ≥150 ms		QRS 130–149 ms		QRS 120–129 ms	
Guideline (Year)	NYHA Functional Class III/IV	NYHA Functional Class II	NYHA Functional Class III/IV	NYHA Functional Class II	NYHA Functional Class III/IV	NYHA Functional Class II
ESC HFA (2016)*	I, A	I, A	I, B	I, B	III, A	III, A
ESC EHRA (2013)	I, A	I, A	I, B	I, B	I, B	I, B
ACC/AHA/HRS (2013)	I, A	I, B	IIa, B	IIa, B	IIa, B	IIa, B
CCS (2017)	I, High	I, High	I, High	I, High	III, Moderate	III, Moderate
Australian Guidelines (2011)	A		A		A	
NICE (2014)	CRT-P or CRT-D†	CRT-D	CRT-P or CRT-D†	CRT-D	CRT-P or CRT-D†	CRT-D

Values are Class of Recommendation, Level of Evidence, unless otherwise indicated. Australian guidelines provide only grade of recommendation (A), not evidence level for these recommendations. NICE guidelines provide guidance on type of device rather than recommendation or evidence level. *The ESC HFA guidelines do not specify NYHA functional class, rather they state that the guidelines refer to symptomatic patients with heart failure. †Not for NYHA functional class IV.

ACC/AHA/HRS = American College of Cardiology/American Heart Association/Heart Rhythm Society; CCS = Canadian Cardiology Society; CRT-D = cardiac resynchronization therapy-defibrillator; CRT-P = cardiac resynchronization therapy-pacemaker; ESC EHRA = European Society of Cardiology European Heart Rhythm Association; ESC HFA = European Society of Cardiology European Heart Rhythm Association; LBBB = left bundle branch block.

JACC: HEART FAILURE VOL. 6, NO. 4, 2018
APRIL 2018:308–16

TABLE 3 Comparison of Recommendations for Non-LBBB

Guidelines (Year)	QRS ≥150 ms		QRS 130–149 ms		QRS 120–129 ms	
	NYHA Functional Class III/IV	NYHA Functional Class II	NYHA Functional Class III/IV	NYHA Functional Class II	NYHA Functional Class III/IV	NYHA Functional Class II
ESC HFA (2016)*	IIa, B	IIa, B	IIb, B	IIb, B	III, A	III, A
ESC EHRA (2013)	IIa, B	IIa, B	IIb, B	IIb, B	IIb, B	IIb, B
ACC/AHA/HRS (2013)	IIa, A	IIb, B	IIb, B	III, B	IIb, B	III, B
CCS (2017)	IIb, Low	IIb, Low			III, Moderate	III, Moderate
Australian Guidelines (2011)	A		A		A	
NICE (2014)	CRT-P or CRT-D†	CRT-D	CRT-P‡		CRT-P‡	

Values are Class of Recommendation, Level of Evidence, unless otherwise indicated. Australian guidelines provide only grade of recommendation (A), not evidence level for these recommendations. NICE guidelines provide guidance on type of device rather than recommendation or evidence level. *The ESC HFA guidelines do not specify NYHA class, rather they state that the guidelines refer to symptomatic patients with heart failure. †Not for NYHA functional class IV. ‡Only for NYHA functional class IV.

Abbreviations as in Table 1 and 2.

the CRT trials; however, a wide QRS duration in these trials (average, 168 ms) in CARE-HF, MUSTIC, MIRACLE, and COMPANION trials was most often accompanied by LBBB (1–3,7). In contrast, in the later trials including mild to moderate heart failure, average QRS durations were smaller at 158 ms, and in these subgroups, analyses revealed a greater benefit in cases of LBBB than in other bundle branch morphologies (21,22). It should be noted, however, that there are mixed views of the value of LBBB in determining response to CRT. A meta-analysis of 5 randomized trials showed QRS duration to be a powerful predictor of CRT effect with QRS morphology not providing any additional information about clinical response (23).

GUIDELINE RECOMMENDATIONS FOR PATIENT GROUPS WITH LESS CONVENTIONAL INDICATIONS FOR CRT

ATRIAL FIBRILLATION. The two ESC and the ACC/AHA/HRS guidelines provide a Class IIa recommendation for CRT implantation in patients with systolic HF and AF (**Table 4**). CCS provides a "*may be considered*" (Class IIb) for these patients. European guidelines specify that patients must have LVEF ≤35% and NYHA functional class III or IV HF. Again, the ESC associations disagree on QRS duration. The ACC/AHA/HRS and CCS guidelines simply state that eligible patients must otherwise qualify for a CRT device. The Australian guidelines do not discuss patients with AF.

TABLE 4 Less Conventional Indications for CRT

Guidelines (Year)	Atrial Fibrillation and HF	Expected High % of Ventricular Pacing With Reduced LVEF and Symptomatic HF
ESC HFA (2016)	IIa, B	I, A
ESC EHRA (2013)	IIa, B	IIa, B
ACC/AHA/HRS (2013)	IIa, B	IIa, C
CCS (2017)	IIb, Low	IIb, Moderate

Values are Class of Recommendation, Level of Evidence.

Abbreviations as in Tables 1 and 2.

There is, therefore, general consistency in the guidelines that patients with AF may be considered for a CRT but that the evidence for this is limited. Most randomized control trials of CRT excluded patients with AF, and those trials that did include patients with AF were small (Online Table 1) (6,24,25). This is unfortunate as 10% to 50% of patients with moderate or severe HF have concomitant AF (24,26). In the guidelines that provide recommendations for CRT in patients with AF there is consensus that ventricular rate must be adequately controlled by pharmacologic intervention or atrioventricular nodal ablation in order to ensure a high degree of CRT pacing (27).

CONVENTIONAL PACEMAKER INDICATION AND HF. In patients with systolic HF and conventional indications for pacemaker that are likely to be dependent on chronic right ventricular (RV) pacing, the strongest recommendation comes from the ESC. HFA guidelines (2016) provide a Class I recommendation, Level of Evidence: A for patients with an indication for ventricular pacing and high-degree atrioventricular block and include patients with AF. These guidelines were published after the publication of the BLOCK-HF trial, which showed that biventricular pacing was superior to RV pacing in patients with HF and atrioventricular block (28). The EHRA and ACC/AHA/HRS guidelines provide a Class IIa recommendation. The ACC/AHA/HRS guidelines specify that the degree of anticipated RV pacing must be >40%. This figure is based on the DAVID (Dual Chamber and VVI Implantable Defibrillator) trial, which suggested a worse outcome in patients who were paced at >40% (29). None of the other

guidelines specify the exact degree of anticipated pacing for this recommendation.

The CCS guidelines provide a Class IIb recommendation for patients who require chronic RV pacing in the setting of HF symptoms and reduced LVEF, with moderate quality evidence. Interestingly, these guidelines, like the HFA guidelines, were produced after BLOCK-HF. However, HFA guidelines provide a recommendation level I and CCS only a level IIb. This indication is not discussed in the Australian guidelines.

Choice of device—a conventional pacemaker or a CRT—is a rapidly evolving issue, and guidelines concerning the patient categories likely to benefit from CRT are not yet clearly defined. Evidence suggests that chronic RV pacing in patients with symptomatic HF or left ventricular (LV) dysfunction may lead to deterioration in LV systolic function accompanied by an increase in LV volumes (30,31). Although the complication rate is greater with an increasing number of leads implanted, a later upgrade from a permanent pacemaker to a CRT is also associated with added risk.

PATIENTS WITH HF AND AN ICD INDICATION. The ESC EHRA and CCS guidelines provide a Class I recommendation for a CRT-D in patients requiring an ICD if a CRT is indicated. The HFA guidelines state that if a patient is due to receive an ICD and has a QRS duration between 130 and 149 ms, a CRT-D should be considered, and if the QRS is ≥150 ms, a CRT-D is recommended. The Australian guidelines provide a grade A recommendation for CRT for patients requiring an ICD in NYHA functional class II, provided they are in LBBB with a QRS ≥150 ms and an LVEF ≤30%. The NICE guidelines provide clear guidance concerning the choice between CRT-P and CRT-D. If an ICD is required in a patient with overlapping CRT indications, perhaps an unnecessary later upgrade from an ICD to CRT-D could be avoided.

CRT-P VERSUS CRT-D. EHRA guidelines also provide guidance as to whether to implant a CRT-P or a CRT-D. EHRA guidelines favor CRT-P implantation in patients with advanced HF, severe renal insufficiency or dialysis, and other major co-morbidities including frailty and cachexia. CRT-D, on the other hand, is recommended if the life expectancy is >1 year in patients with NYHA functional class II, ischemic heart disease, and no major co-morbidities. HFA guidelines state that, if the primary reason for implanting a CRT is to improve prognosis, most evidence lies with CRT-D in patients with NYHA functional class II and for CRT-P for patients in NYHA functional classes III to IV. If the primary reason for implanting the device is relief from symptoms, HFA guidelines propose that the clinician should choose between a CRT-P and a CRT-D, as he/she considers appropriate. CCS guidelines suggest that a CRT-P be considered in patients who are not candidates for ICD therapy, such as those with a limited life expectancy because of significant comorbidities. NICE guidelines also clearly provide advice concerning the choice of device.

No randomized study was powered to compare CRT-D versus CRT-P, but one study compared these devices to optimal medical therapy (7). It is likely to be this lack of evidence which leads most associations to leave the choice of device to the implanting physician.

UPGRADES. HFA guidelines state that patients who have received a conventional pacemaker or an ICD and develop worsening HF and who have a high proportion of RV pacing may be considered for an upgrade to a CRT. This is a Class IIb recommendation with Level of Evidence: B. EHRA guidelines, on the other hand, provide a Class I recommendation with a Level of Evidence: B for an upgrade from both a pacemaker and an ICD, providing the patient has a high degree of ventricular pacing and is in NYHA functional class III or ambulatory IV. The ACC/AHA/HRS guidelines provide a recommendation Class IIa, Level of Evidence: C, for patients with LVEF ≤35% who are undergoing implantation of a replacement device with anticipated requirement for significant (>40%) ventricular pacing.

The CCS guidelines do not provide recommendations for upgrading previous devices, and there is no mention of upgrades in the Australian guidelines. CRT survey II found that 28% of CRT devices implanted were upgrades from either a permanent pacemaker or an ICD (35). Despite this large number of upgrades implanted, the evidence in this area is limited to small trials and observational studies. Upgrades have become increasingly common in view of heightened awareness that RV pacing >40% may aggravate LV function and cause HF. It was demonstrated that patients upgraded to CRT with prior RV pacing respond to CRT at least as well as, if not better than, HF patients eligible for CRT by wide QRS complex (36).

NYHA FUNCTIONAL CLASS I. None of the ESC guidelines, CCS, or Australian guidelines provide recommendations for patients in NYHA functional class I. The ACC/AHA/HRS guidelines, on the other hand, provide a Class IIb recommendation, evidence level C, on condition that the patients have LBBB with a QRS ≥150 ms, HF caused by ischemia, and an LVEF ≤30% on guideline-directed medical therapy. They do not recommend CRT implantation in NYHA

JACC: HEART FAILURE VOL. 6, NO. 4, 2018
APRIL 2018:308–16

functional class I patients if they do not have LBBB and a QRS ≤150 ms, providing this indication with a Class III recommendation. NICE guidelines recommend implantation in patients with a QRS ≥150 ms in NYHA functional class I, regardless of the morphology of the bundle branch block. CCS guidelines state that there is insufficient evidence to recommend CRT to patients with NYHA functional class I status.

Thus, most of the guidelines do not discuss patients with NYHA functional class I. Those that do, either provide a III recommendation or a weak recommendation for a wide QRS. Although both the MADIT CRT and REVERSE studies included NYHA functional class I patients, the total number of these patients included was small, and the subgroup analysis was not meaningful (4,5).

NARROW QRS. EHRA guidelines provide a Class III recommendation, Level of Evidence: B, for a QRS duration <120 ms; whereas the HFA provides a III recommendation, Level of Evidence: A, for QRS duration <130 ms; and CCS clearly states that CRT should not be used in patients with QRS duration <130 ms. NICE guidelines clearly state that a CRT is not indicated in NYHA functional class IV with a QRS <120 ms. The other guidelines only provide guidance for patients with QRS >120 ms rather than specifically mentioning not to implant in cases with a narrower QRS.

There is increasing evidence that patients with a narrow QRS do not benefit from a CRT device. The Echocardiography CRT and the LESSER EARTH trials were designed to compare effects of active versus inactive CRT therapy in patients with a QRS >130 ms and QRS >120 ms, respectively (19,32). Both trials were stopped as they were deemed futile. Following the publications of those trials, 2 meta-analyses have been published showing that CRT implantation in narrow QRS is associated with a poor prognosis (33,34).

AGE AND CO-MORBIDITIES. CCS guidelines state that CRT-P should also be considered in patients who are not candidates for ICD therapy because of limited life expectancy and significant co-morbidities. EHRA guidelines provide guidance on whether to place a CRT-P or a CRT-D depending on the co-morbidities of the patient. Remarkably, there is limited concrete advice in the other guidelines regarding the impact on clinical decision making of age and comorbidities in the individual patient.

DISCUSSION

This review is the most currently available comparison of international guidelines on CRT. It demonstrates areas of consistency and inconsistency in recommendation for CRT.

POTENTIAL EXPLANATIONS AND CONSEQUENCES FOR INCONSISTENCIES AMONG GUIDELINES. Guideline development is a rigorous process. Evidence produced by randomized control trials must be peer reviewed and published before it is interpreted by the guideline task forces and specific recommendations are formed. Therefore, there is a time lag between production of evidence and its incorporation into guidelines, and some pivotal studies may, as a result, only be available for the next guidelines. If these guidelines are those of another society or association, this will result in guideline inconsistencies. A recent example is the inconsistency between the EHRA ESC guidelines (2013), which recommended implantation of CRT in appropriate patients with a QRS duration >120 ms and the ESC HFA, published 3 years later, which emphasized new evidence that emanated from ECHO-CRT, showing no CRT benefit in otherwise eligible patients with a QRS durations <130 ms (19).

When guidelines provide a Class IIa or IIb recommendation, it reflects insufficient scientific evidence and uncertainty concerning the efficacy of CRT in a particular clinical scenario. In these situations, it is not surprising that there may be different interpretations between different guideline task forces. For example, regarding permanent AF, some guideline committees interpret the existing scientific evidence as supporting the use of CRT in order not to withhold a potentially beneficial therapy in a particular patient with permanent AF and symptomatic HF. Whereas other committees may be less persuaded by the available evidence which to date has not convincingly demonstrated efficacy in this population.

The International Cardiology Societies reviewed here appear to differ in the ways in which they evaluate the strengths and weaknesses of a study. This is apparent by their choice of different grading systems and also by the fact that the same evidence is graded with different strengths. Most of the guidelines reviewed provide guidance for a single country; however, the ESC guidelines by EHRA and HFA provide recommendations for all 56 member states. Applicability of the recommendations in all these countries must therefore be considered by the task forces. Furthermore, although all guideline taskforces are well aware of the high initial costs of CRT implantation, only NICE formally considers health economics when providing their guidelines.

There are important consequences of these inconsistencies in guidelines for patients, clinicians, policy makers, and stakeholders. Clearly, the variations in recommendations, especially among societies responsible for the same health care geographical area, such as ESC EHRA and ESC HFA,

may contribute to some confusion among those delivering the care.

Furthermore, these inconsistencies make it difficult to accurately assess CRT adoption rate in different countries; therefore, identifying whether appropriate and evidence-based patient care is being delivered uniformly is challenging.

CLINICAL AND HEALTH POLICY IMPLICATIONS OF THIS REVIEW. For clinicians and health care providers, demonstration of consistency across guidelines in this review is reassuring since it identifies populations where there is agreement on CRT efficacy. In contrast, the areas where this review identified inconstancies will serve to make clinicians less enthusiastic about implanting a CRT in the patient populations in which the evidence is insufficient.

This review should inform future clinical research by highlighting the areas in which evidence is scarce or open to interpretation. Areas which require more research include CRT in patients with AF, non-LBBB, and those dependent on RV pacing. The guidelines are also inconsistent with regard to recommendation for device upgrades and the choice of CRT-P versus CRT-D in a particular patient.

Furthermore, considering the length of time required to produce a complete update of the guidelines on HF, perhaps a sensible approach is to release specific, focused updates on HF regularly, concentrating on areas where there is new evidence. Such updates have been produced by several of the associations reviewed.

Finally, this review encourages clinicians and health care providers to consult the most recent international guidelines as these guidelines may include the most current evidence and contain the most appropriate recommendations.

CONCLUSIONS

Generally, there is strong consistency in the international guidelines on CRT implantation. However, there remain certain patient populations for whom there are divergent recommendations considering eligibility and selection of the most appropriate device in a particular clinical scenario. Guidelines are a documentation of best practice in a particular environment at a certain moment in time and clinicians, when reviewing these, should take a critical view, especially as newer evidence accumulates.

ADDRESS FOR CORRESPONDENCE: Dr. Camilla Normand, Cardiology Department, Stavanger University Hospital, Gerd-Ragna Bloch Thorsens gate 8, 4011 Stavanger, Norway. E-mail: Camilla.normand@doctors.org.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Guidelines are updated as new evidence of best clinical practice emerges. However, as publication of clinical trial results may be delayed and guideline task-force review of this new evidence is time consuming, guideline recommendation may not always reflect the latest evidence. This review of international guidelines has identified certain discrepancies in CRT recommendations, suggesting that clinicians may wish to review the most recent guidelines available.

TRANSLATIONAL OUTLOOK: This review of current international guidelines identifies several patient groups where there are inconsistencies in guideline recommendations for CRT indication. One of the explanations for these inconsistencies is likely due to limited evidence of CRT benefit in these patients. This review specifically identifies two important clinical areas in which trial evidence is clearly lacking. These include management of patients with atrial fibrillation and the choice of the most appropriate device (pacemaker CRT vs. defibrillator CRT) for individual patients.

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KEY WORDS CRT, guidelines, heart failure

APPENDIX For supplemental tables, please see the online version of this paper.

PAPER 2

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RESEARCH ARTICLE

CRT Survey II: a European Society of Cardiology survey of cardiac resynchronisation therapy in 11 088 patients—who is doing what to whom and how?

Kenneth Dickstein[1,2]*, Camilla Normand[1,2], Angelo Auricchio[3], Nigussie Bogale[1], John G. Cleland[4], Anselm K. Gitt[5,6,7], Christoph Stellbrink[8], Stefan D. Anker[9,10], Gerasimos Filippatos[11], Maurizio Gasparini[12], Gerhard Hindricks[13], Carina Blomström Lundqvist[14], Piotr Ponikowski[15], Frank Ruschitzka[16], Giovanni Luca Botto[17], Alan Bulava[18,19,20], Gabor Duray[21], Carsten Israel[22], Christophe Leclercq[23], Peter Margitfalvi[24], Óscar Cano[25], Chris Plummer[26], Nedim Umutay Sarigul[27,28], Maciej Sterlinski[29], and Cecilia Linde[30]

[1]Cardiology Division, Stavanger University Hospital, Stavanger, Norway; [2]Institute of Internal Medicine, University of Bergen, Bergen, Norway; [3]Division of Cardiology, Fondazione Cardiocentro Ticino, Lugano, Switzerland; [4]Robertson Centre for Biostatistics and Clinical Trials, University of Glasgow and National Heart & Lung Institute, Imperial College London, UK; [5]Stiftung Institut für Herzinfarktforschung Ludwigshafen, Ludwigshafen, Germany; [6]Medizinische Klinik B, Klinikum der Stadt Ludwigshafen, Ludwigshafen, Germany; [7]University of Cyprus, School of Medicine, Cyprus; [8]Department of Cardiology, Klinikum Bielefeld, Germany; [9]Division of Cardiology and Metabolism; Department of Cardiology (CVK); Berlin-Brandenburg Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany; [10]Department of Cardiology and Pneumology, University Medicine Göttingen (UMG), and German Centre for Cardiovascular Research (DZHK), Göttingen, Germany; [11]National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Athens University Hospital Attikon, Athens, Greece; [12]Humanitas Research Hospital IRCCS, Rozzano, Italy; [13]Department of Cardiac Surgery, HELIOS Heart Center Leipzig, Leipzig, Germany; [14]Department of Cardiology, Institution of Medical Science, Uppsala University, Uppsala, Sweden; [15]Department of Heart Diseases, Medical University Wroclaw, Wroclaw, Poland; [16]Department of Cardiology, University Hospital Zurich, Zurich, Switzerland; [17]Sant'Anna Hospital, Como, Italy; [18]Department of Cardiology, Ceske Budejovice Hospital, Ceske Budejovice, Czech Republic; [19]Faculty of Health and Social Sciences, University of South Bohemia, Ceske Budejovice, Czech Republic; [20]Faculty of Medicine and Dentistry, Palacky University, Olomouc, Czech Republic; [21]Clinical Electrophysiology, Department of Cardiology, Medical Centre, Hungarian Defence Forces, Budapest, Hungary; [22]Klinik für Innere Medizin - Kardiologie, Diabetologie & Nephrologie, Evangelisches Krankenhaus Bielefeld, Bielefeld, Germany; [23]Rennes University Hospital, University of Rennes, France; [24]The National Institute of Cardiovascular Diseases, Bratislava, Slovak Republic; [25]Unidad de Arritmias, Hospital Universitari i Politècnic La Fe, Valencia, Spain; [26]Department of Cardiology, Freeman Hospital, Freeman Rd, Newcastle upon Tyne, UK; [27]Department of Cardiology, Medicalpark Goztepe Hospital, Istanbul, Turkey; [28]Kardio Bremen, Bremen, Germany; [29]Heart Rhythm Department, Institute of Cardiology, Warsaw, Poland; and [30]Heart and Vessels Theme, Karolinska University Hospital, Stockholm, and Karolinska Institutet, Stockholm, Sweden

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Background Cardiac resynchronisation therapy (CRT) reduces morbidity and mortality in appropriately selected patients with heart failure and is strongly recommended for such patients by guidelines. A European Society of Cardiology (ESC) CRT survey conducted in 2008–2009 showed considerable variation in guideline adherence and large individual, national and regional differences in patient selection, implantation practice and follow-up. Accordingly, two ESC associations, the European Heart Rhythm Association and the Heart Failure Association, designed a second prospective survey to describe contemporary clinical practice regarding CRT.

Methods and results A survey of the clinical practice of CRT-P and CRT-D implantation was conducted from October 2015 to December 2016 in 42 ESC member countries. Implanting centres provided information about their hospital and CRT service and

*Corresponding author. Cardiology Division, Stavanger University Hospital, Gerd Ragna Block Thorsensgate 8, 4003 Stavanger, Norway. Tel: +47 51 518000, Fax: +47 51 519921, Email: trout@online.no

The list of CRT Survey II implanters is provided in the supplementary material online, *Appendix S1*.

were asked to complete a web-based case report form collecting information on patient characteristics, investigations, implantation procedures and complications during the index hospitalisation. The 11 088 patients enrolled represented 11% of the total number of expected implantations in participating countries during the survey period; 32% of patients were aged ≥75 years, 28% of procedures were upgrades from a permanent pacemaker or implantable cardioverter-defibrillator and 30% were CRT-P rather than CRT-D. Most patients (88%) had a QRS duration ≥130 ms, 73% had left bundle branch block and 26% were in atrial fibrillation at the time of implantation. Large geographical variations in clinical practice were observed.

Conclusion CRT Survey II provides a valuable source of information on contemporary clinical practice with respect to CRT implantation in a large sample of ESC member states. The survey permits assessment of guideline adherence and demonstrates variations in patient selection, management, implantation procedure and follow-up strategy.

Keywords Heart failure • Cardiac resynchronisation therapy • Demographics • Cardiac devices • Health care utilisation •

Introduction

Randomised controlled trials (RCTs) and meta-analyses have demonstrated that cardiac resynchronisation therapy (CRT) reduces morbidity and mortality in appropriately selected patients with symptomatic heart failure (HF), reduced left ventricular ejection fraction (LVEF) and QRS prolongation on the electrocardiogram.[1–7] Accordingly, the benefits of CRT for such patients were accorded high levels of evidence and strong recommendations in European Society of Cardiology (ESC) and other international guidelines.[8–12]

The first ESC CRT survey, performed in 2008–2009 in 13 ESC countries, demonstrated that implanters often extrapolated the benefits of CRT to a broader population including patient groups that were not well represented in RCTs, such as patients aged >75 years or with a QRS duration <120 ms, atrial fibrillation (AF), or requiring an upgrade from an existing permanent pacemaker (PPM) or implantable cardioverter defibrillator (ICD). The first CRT survey also showed considerable regional and national differences in implantation practices.[13] Since this survey was published, several important modifications of ESC guideline recommendations concerning CRT indications have been made by both the Heart Failure Association (HFA) and European Heart Rhythm Association (EHRA).[8,9,12] Therefore, these two ESC Associations decided to collaborate and undertake a pan-European survey designed to describe current clinical practice regarding implantation of CRT devices in a larger sample of patients and greater number of ESC member countries. CRT Survey II was not designed to compare results with the first survey. There was limited overlap between the cohorts of the two surveys and substantial differences in the data collected precluding valid comparison. Lessons learned from conducting the first survey were used to improve both the design and performance of CRT Survey II, which involved many more countries. CRT Survey II provides insights into contemporary clinical practice that is useful for patients, clinicians, administrators, the pharmaceutical and device industry as well as for parties who fund health care. Further analyses confined to the subset of countries participating in both surveys are planned.

Methods

Survey infrastructure

The survey was designed as a joint initiative between the EHRA and HFA. These two ESC Associations co-coordinated the survey with sponsorship from all five companies that manufacture CRT devices as well as from several pharmaceutical and diagnostic companies (see Acknowledgements). The design and rationale of CRT Survey II, along with the detailed contents of the electronic case report form (eCRF) have been published previously.[14]

A Scientific Committee was established, composed of equal number of members from each Association, together with non-voting representatives from each of the five CRT device companies. The Scientific Committee regularly monitored the progress of the survey and agreed on logistical adjustments during the period of data collection.

Recruitment

The 47 ESC member states detailed in the 2014 EHRA White Book, which provided information on the number of sites implanting CRT and volume of activity in these countries, were invited to participate.[15] Each participating ESC member country was represented by a National Coordinator who was nominated by the President of their National Cardiology Society. The National Coordinators were responsible for obtaining national Institutional Review Board approval if required, recruiting centres in their country and distributing information from the Scientific Committee to their implanters. Of the 47 invited ESC member countries, 42 agreed to participate. The National Coordinators were requested to contact CRT implanters in their countries and invite them to participate in the survey. Sites were then asked to enter consecutive patients implanted with a CRT during the inclusion period. Overall, 288 individual centres participated in CRT Survey II.

Data collection, management and analyses

For the first ESC CRT survey, the web-based eCRF used for data collection was developed by Institut für Herzinfarktforschung Ludwigshafen

(IHF),[16] which also conducted data management and statistical analyses. Therefore, the Associations decided that IHF should support similar functions for CRT Survey II. Together with the Scientific Committee, the IHF revised the eCRF, developed the statistical analysis plan and was responsible for data monitoring and verification. No imputation for missing data was done. All percentages are relative to the total number of patients with available information.

Each participating country had their data-points collected in the eCRF benchmarked against the total cohort. The day-to-day operational running of the survey was conducted by Tessa Baak at Stavanger University Hospital, University of Bergen, Norway.

Survey population

Any patient in the 42 participating countries was eligible for inclusion if he/she was implanted with either a CRT with pacemaker function (CRT-P) or a CRT with an incorporated defibrillator (CRT-D). This included both successful and unsuccessful implantations as well as both de-novo CRT devices and upgrades from a PPM or ICD. Generator replacements or revisions of existing CRT devices were excluded as the survey was designed to capture only new CRT implantations.

The one-time site questionnaire

Each implanting centre was requested to complete a one-time site questionnaire, which provided information on hospital type, size, population served, operator speciality, infrastructure, facilities and implantation routines for their CRT device programme. The data collected also provided useful information related to health care resource utilisation.[14]

The electronic case report form

Implanting centres were asked to complete a web-based eCRF of consecutive patients scheduled to receive a CRT device. The eCRF collected information on patient characteristics, investigations, indications for CRT, implant procedures and short-term outcomes including adverse events and complications during the index hospitalisation.[14] Information on longer-term outcome was not collected. The eCRF was reviewed by ESC data protection consultants to ensure patient anonymity. This, together with the fact that the survey did not include follow-up data after discharge, obviated the necessity for formal Institutional Review Board approval in most countries. Most centres were simply required to notify their local or national ethics committee of their participation in the survey.

Timelines

The first patient was included on 1 October 2015. The survey was initially planned to run for 9 months. However, the Scientific Committee decided to extend the enrolment by 6 months to 31 December 2016 in order to increase sample size and improve representativeness and therefore the ability to compare differences in practice amongst participating countries.

Results

The CRT Survey II recruited 11 088 patients from 42 ESC countries. The number of patients included per country is shown in *Table 1*. Using data from the EHRA White Book 2015 on national implantation rates we estimated representativeness,[17] that is the number of patients enrolled compared with expected total implants in that country. This metric was updated continuously and permitted us to estimate how representative of the predicted national implantation rates was the data collected in the survey.

Overall, the survey collected data on 11% of expected implantations during the enrolment period of the survey. Of the 42 countries, 34 (81%) had >10% of the expected total number of implants for that country.

Tables 2–6 report key findings from the total cohort and the number of patients contributing to each data-point.

Hospital demographics

University hospitals accounted for 59% of participating centres. The median (interquartile range, IQR) number of CRT implants per hospital per year was 52 (30–96) and 76% of centres were participating in a national device registry. Device remote monitoring was employed by 59% of centres and 99% of centres had either partial or total reimbursement from public health providers (*Table 2*).

Patient characteristics

The median (IQR) age at implantation was 70 (62–76) years, 32% of patients were aged ≥75 years and 24% were women. Half of the patients had ischaemic heart disease, 41% had a prior history of AF of which 42% of these were permanent AF, 31% had diabetes mellitus, and 47% had a HF hospitalisation during the previous year (*Table 3*).

Pre-implant clinical evaluation

Most patients were in New York Heart Association (NYHA) functional class III or IV (60%) and the natriuretic peptide levels were generally substantially elevated. The ECG at the time of implantation showed AF in 26%, a QRS duration of <130 ms in 13% and ≥150 ms in 69% of patients and 73% had left bundle branch block (LBBB). On imaging, 13% of patients had an LVEF >35%, the median (IQR) left ventricular end-diastolic diameter was 63 (58–69) mm and 34% had either moderate or severe mitral regurgitation. The clinical indication for CRT implantation was HF with a wide QRS in 60% of cases, HF or left ventricular dysfunction and indication for an ICD in 48%. In 10% of patients the sole clinical indication for CRT was HF and a PPM indication with expected right ventricular pacing dependence (*Table 4*).

Cardiac resynchronisation therapy implant procedure

Hospital admission was elective for 77% of implants, 77% of which were performed by electrophysiologists; 97% of procedures were successful, 70% of devices implanted were CRT-D and only 25% were referrals from other centres. The median (IQR) duration of

Table 1 CRT Survey II total cohort

Country	National coordinator	Patients entered
Algeria	Seddik Ait-Messaoudene	66
Armenia	Svetlana Grigoryan	2
Austria	Marianne Gwechenberger	407
Belgium	J.B. le Polain de Waroux	262
Bulgaria	Svetoslav Iovev	264
Croatia	Sandro Brusich	115
Czech Republic	Alan Bulava	931
Denmark	Helen Høgh Petersen	254
Egypt	Mostafa Nawar	22
Estonia	Jüri Voitk	58
Finland	Sami Pakarinen	351
France	Christophe Leclercq	754
Georgia	Giorgi Papiashvili	24
Germany	Carsten W. Israel	675
Greece	Antonis Sideris	137
Hungary	Gabor Duray	467
Iceland	Sigfús Gizurarson	19
Ireland	Ricky Sheahan	85
Israel	Michael Geist	39
Italy	Giovanni Luca Botto	526
Kazakhstan	Roin Rekvava	34
Latvia	Oskars Kalejs	79
Lebanon	Marwan M. Refaat	30
Lithuania	Germanas Marinskis	173
Luxembourg	Laurent Groben	36
Macedonia FYR	Nikola Gjorgov	70
Malta	Mark Sammut	26
Montenegro	Ljilja Music	6
Marocco	Salima Abdelali	12
Netherlands	Alexander Maass	202
Norway	Torkel Steen	370
Poland	Maciej Sterlinski	1241
Portugal	Francisco Morgado	58
Romania	Dan Dobreanu	214
Russian Federation	Amiran Revishvili	71
Slovakia	Peter Margitfalvi	472
Slovenia	Igor Zupan	119
Spain	Oscar Cano Pérez	847
Sweden	Elena Sciaraffia	255
Switzerland	Christian Sticherling	320
Turkey	Umutay Nedim Sarigül	424
UK	Chris Plummer	571
Total		**11 088**

Table 2 Hospital demographics ($n = 288$)

Inhabitants of area, median (in 100 000) (IQR)	5 (3–10)
No. of hospital beds, median (IQR)	600 (357–964)
No. of cardiology beds, median (IQR)	57 (34–80)
Type of hospital	
University hospital	59% (162/274)
Teaching hospital (non-university)	23% (64/274)
Community hospital	10% (27/274)
Private hospital	8% (21/274)
CRT implantations per year, median (IQR)	52 (30–96)
Pacemaker implantations per year, median (IQR)	250 (175–400)
ICD implantations per year, median (IQR)	80 (40–132)
Cardiac surgery on site	69% (190/274)
Angiography/PCI on site	96% (262/273)
Dedicated electrophysiological labs, median (IQR)	1 (1–2)
No. of CRT implanters, median (IQR)	
Electrophysiologists	2 (1–4)
Interventional cardiologists	0 (0–4)
Heart failure physicians	0 (1–2)
Follow-up	
Implanting centre	93% (254/272)
Heart failure clinic	68% (186/273)
Dedicated CRT clinic	59% (161/273)
Remote device monitoring service	70% (191/272)
Centre using device monitoring by telemetry	59% (169/288)
Dedicated lead extraction/management programme	45% (123/272)
Participation in a national device registry	76% (207/273)
Use of electronic medical health records	81% (221/273)
Source of reimbursement for CRT	
Public health provider	99% (270/274)
Private insurance	12% (32/274)
Private payer	7% (20/274)

In parenthesis, number of centres in each category compared to the total cohort for each data-point.
CRT, cardiac resynchronisation therapy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; PCI, percutaneous coronary intervention.

the procedure was 90 (65–120) min. The right ventricular lead was implanted first in 84% of cases and the left ventricular lead was multipolar in 57%. The left ventricular position was evaluated by biplane X-ray projection in 88% of patients. The left anterior oblique site was lateral in 84% and the right anterior oblique site was middle in 71%. The peri-procedural complication rate was 6%. The most common complications were coronary sinus dissection, bleeding and pneumothorax (*Table 5*).

Post-cardiac resynchronisation therapy implant data

The median (IQR) hospital stay was 3 (2–7) days. In 5% of patients an adverse event was reported and 0.4% died during the index hospitalisation. Follow-up was planned at the implanting centre in 86% of patients. Atrio-ventricular programming was performed prior to discharge in 58% and ventriculo-ventricular programming in 56% of patients. Device-based software was used to optimize programming in 36%. HF medications at discharge included loop diuretics (81%), beta-blockers (89%), angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) (86%) and mineralocorticoid receptor antagonists (MRAs) (63%). Overall, 47% of patients were anticoagulated, mostly (70%) with warfarin; 10% of anticoagulated patients had no history of AF (*Table 6*).

Table 3 Patient demographics ($n = 11\,088$)

Age (years), median (IQR)	70 (62–76)
Age ≥ 75 years	32% (3536/11 039)
Female gender	24% (2686/11 052)
Primary HF aetiology	
Ischaemic	45% (4875/10 953)
Non-ischaemic	55% (6078/10 953)
Past history and major co-morbidity	
Previous myocardial infarction	36% (3957/10 926)
Prior revascularisation (PCI/CABG)	39% (4245/10 924)
Hypertension	64% (6962/10 900)
Atrial fibrillation	41% (4459/10 920)
Valvular heart disease	27% (2968/10 920)
Obstructive lung disease	12% (1315/10 922)
Diabetes	31% (3428/10 921)
Anaemia	15% (1640/10 916)
Chronic kidney disease (eGFR <60 mL/min/1.73 m^2)	31% (3395/10 907)
Previous device (PPM or ICD)	28%(3059/10 992)
HF hospitalisation during past year	47% (5078/10 917)
Currently enrolled in a clinical trial	8% (918/11 028)

In parenthesis, number of patients in each category compared to the total cohort for each data-point.
CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; PCI, percutaneous coronary intervention; PPM, permanent pacemaker.

Benchmarking the top 10 recruiting countries

Data from the 10 countries that enrolled the most patients were compared. There were substantial differences amongst countries in the mean age of patients implanted (*Figure 1A*). Symptom severity varied substantially amongst countries (*Figure 1B*). The proportion of patients with AF was about 26% with a range of 16 to 29%. In all countries, most patients had LBBB but this ranged from as low as 61% to 82% (*Figure 1C*). The percentage of patients with a QRS duration <130 ms ranged from 7% to 19% but most patients had a QRS duration >150 ms (*Figure 1D*). The percentage of patients upgraded from another device was between 21% and 39% (*Figure 1E*) and those receiving a CRT-P ranged from 2% to 37% (*Figure 1F*). The median duration of hospitalisation varied markedly (*Figure 1G*), with a median of 3 days.

Discussion

This second, larger survey of CRT implantations in ESC member countries provides a valuable source of clinical information describing 'who is doing what to whom and how', permits benchmarking across Europe and provides essential feedback on guideline adherence, which supports the development of future guidelines.

The '*Who*' are implanters, and as expected, primarily electrophysiologists, although a considerable number of implanters are not (23%). The '*What*' are primarily CRT-D devices (70%) but in many countries up to 40% of implants are CRT-P devices. The '*Whom*' (patients selected for CRT implantation) are predominantly men,

Table 4 Pre-implant clinical evaluation ($n = 11\,088$)

NYHA class	
I	3% (370/10 848)
II	38% (4083/10 848)
III	55% (5909/10 848)
IV	5% (486/10 848)
BMI (kg/m^2), median (IQR)	27 (25–31)
Systolic blood pressure (mmHg), median (IQR)	122 (110–137)
Diastolic blood pressure (mmHg), median (IQR)	72 (66–80)
Laboratory measurement (most recent), median (IQR)	
BNP (ng/L)	422 (150–1115)
NT-proBNP (ng/L)	2400 (1049–5517)
Serum creatinine (μmol/L)	100 (83–129)
Haemoglobin (g/dL)	13 (12–15)
Pre-implant ECG	
Heart rate (b.p.m.), median (IQR)	70 (60–80)
Atrial rhythm	
Sinus	69% (7496/10 836)
Atrial fibrillation	26% (2778/10 836)
Atrial paced	3% (303/10 836)
Other	2% (259/10 836)
PR interval (ms), median (IQR)	180 (160–210)
AV block II/III	19% (2026/10 700)
Pacemaker dependent	14% (1511/10 752)
Intrinsic QRS morphology	
LBBB	73% (7861/10 800)
Non-LBBB	27% (2939/10 800)
Intrinsic QRS duration (ms), median (IQR)	160 (140–174)
<120	8% (711/9535)
120–129	5% (505/9535)
130–149	19% (1779/9535)
150–179	47% (4486/9535)
>180	22% (2054/9535)
Clinical indication for CRT	
HF with wide QRS	60% (6550/10 923)
HF or LV dysfunction and indication for ICD	48% (5228/10 923)
PM indication and expected RV pacing dependence	23% (2494/10 923)
Evidence of mechanical dyssynchrony	12% (1260/10 923)
Other	5% (487/10 923)
LVEF (%), median (IQR)	29 (23–34)
<25	28% (2979/10 805)
25–35	60% (6426/10 805)
>35	13% (1400/10 805)
LVEDD (mm), median (IQR)	63 (58–69)
Mitral regurgitation	
Mild	46% (4644/10 000)
Moderate	27% (2646/10 000)
Severe	7% (690/10 000)
None	20% (2020/10 000)

Note: total can be ≥100% due to rounding off. In parenthesis, number of patients in each category compared to the total cohort for each data-point.
AV, atrio-ventricular; BMI, body mass index; BNP, brain natriuretic peptide; CRT, cardiac resynchronisation therapy; ECG, electrocardiogram; HF, heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LBBB, left bundle branch block; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; RV, right ventricular.

Table 5 Cardiac resynchronisation therapy implantation procedure ($n = 11\,088$)

Elective admission	77% (8422/10 946)
Referral from another centre	25% (2770/10 938)
Admission to implantation time (days), median (IQR)	1 (1–4)
Successful implantation	97% (10 798/11 100)
Unsuccessful implantation	3% (302/11 100)
No. of attempts per patient	
One attempt per patient	99% (10 971/11 088)
Two attempts per patient	1% (106/11 088)
Three attempts per patient	<1% (11/11 088)
Type of device	
CRT-P	30% (3256/10 769)
CRT-D	70% (7513/10 769)
Operator	
Electrophysiologist	77% (8302/10 779)
HF physician	5% (541/10 779)
Invasive cardiologist	12% (1330/10 779)
Surgeon	4% (464/10 779)
Other	1% (142/10 779)
Duration of procedure (min), median (IQR)	90 (65–120)
Fluoroscopy time (min), median (IQR)	14 (8–22)
Prophylactic antibiotics	99% (10 527/10 672)
Which lead was implanted first	
RV	84% (8816/10 555)
LV	16% (1733/10 555)
RV lead placement	
Apex	61% (6280/10 253)
Septum	36% (3733/10 253)
RVOT	2% (240/10 253)
LV lead placement successful	99% (10 533/10 594)
LV lead type	
Unipolar	1% (77/10601)
Bipolar	42% (4478/10 601)
Multipolar	57% (6046/10 601)
Coronary venogram performed	92% (9636/10 529)
Venogram performed with occlusion	47% (4486/9522)
Dilatation of coronary vein performed	2% (251/10 538)
Phrenic nerve stimulation tested	90% (9556/10 568)
LV lead position evaluation	97% (9943/10 302)
Biplane X-ray projection	88% (8771/9943)
Monoplane LAO	11% (1105/9943)
Monoplane RAO	1% (67/9943)
LAO site	
Lateral	84% (8665/10 300)
Posterior	12% (1188/10 300)
Anterior	4% (447/10 300)
RAO site	
Middle	71% (7200/10 119)
Basal	15% (1505/10 119)
Apical	14% (1414/10 119)
LV position optimized	34% (3484/10 307)
Peri-procedural complications	6% (624/11 088)
Death	0.1% (8/11 088)
Bleeding	1.0% (108/11 088)
Bleeding requiring intervention	0.3% (35/11 088)
Pocket haematoma	0.8% (85/11 088)
Pneumothorax	1.0% (112/11 088)
Haemothorax	0.1% (9/11 088)
Coronary sinus dissection	1.9% (214/11 088)
Pericardial tamponade	0.3% (28/11 088)
Other	1.6% (172/11 088)

Note: total can be ≥100% due to rounding off. In parenthesis, we indicated the number of patients in each category compared to the total cohort for each data-point.
CRT, cardiac resynchronisation therapy; D, defibrillator; HF, heart failure; IQR, interquartile range; LAO, left anterior oblique; LV, left ventricular; P, pacemaker; RAO, right anterior oblique; RV, right ventricular; RVOT, right ventricular outflow tract.

<75 years, with an LVEF <35%, in sinus rhythm, with LBBB and a QRS duration ≥150 ms. The '*How*' reveals that most implantations are elective with a low peri-procedural mortality (<1%). Referrals from non-implanting centres accounted for only 25%, indicating that patients outside university or teaching hospital settings have limited access to CRT. The Swedish HF Registry, which included 12 807 patients, demonstrated that underutilisation was associated with demographic, organizational and socio-economic characteristics as well as clinical information. For example, the likelihood of being considered for CRT was much higher if the patients were managed by cardiologists rather than other specialists or primary care physicians.[18]

An excellent overview of the diverse issues that serve to explain why only about one-third of CRT candidates are actually implanted with a device has recently been published.[19] CRT Survey II also confirms that clinicians continue to extrapolate data from RCTs to patients who are not well represented in the evidence base. Clinical practice may be guided by clinical trials but differences in practice exist because clinicians have accumulated experience and try to offer the best treatment to individual patients, many of whom do not fulfil the selection criteria for the RCTs. Many devices were implanted in patients with AF or relatively narrow QRS complexes, or requiring a device upgrade. In these patient groups, guidelines either contraindicate CRT or make only weak recommendations. Compared to patients enrolled in RCTs, patients in this survey were generally older, had more co-morbidities, were less likely to have ischaemic heart disease, had higher LVEF, narrower QRS complexes and more AF but a similar proportion were women.[20]

Compared to men, the low number of women receiving CRT is of concern. Women with HF with reduced ejection fraction (HFrEF) are more likely to have LBBB and may benefit from CRT at a shorter QRS duration than men.[21,22] However, women with HF are older and less likely to have a reduced LVEF.[23] Accordingly, the low number of women receiving CRT may reflect the relatively lower number of women aged <75 years with HFrEF rather than a lower proportion of such women who are eligible for CRT.

CRT implants were upgrades from a previous PPM or ICD device in 28% of procedures. The landmark trials of CRT, with the exception of RAFT, excluded patients with a prior device. In RAFT, an upgrade from an ICD or PPM was not associated with benefit.[7]

Table 6 Post-cardiac resynchronisation therapy implantation ($n = 11\,088$)

Post-implant ECG	
Paced QRS duration (ms), median (IQR)	137 (120–151)
Device programming	
AV programming performed prior to discharge	58% (6132/10 593)
VV programming performed prior to discharge	56% (5962/10 577)
Device-based software optimisation for AV or VV	36% (3821/10 500)
Discharge status	
Alive	99.6% (10 801/10 845)
Dead	0.4% (45/10 845)
Total length of hospital stay (days), median (IQR)	3 (2–7)
Major adverse events after implantation	5% (528/11 088)
Myocardial infarction	0.1% (8/10 816)
Stroke	0.1% (6/10 816)
Infection	0.6% (60/10 816)
Worsening heart failure	0.7% (78/10 816)
Worsening renal function	1.0% (104/10 816)
Arrhythmias	1.2% (128/10 816)
Other	1.9% (208/10 816)
Planned follow-up	
Implanting centre	86% (9345/10 818)
Other hospital	8% (873/10 818)
Cardiologist in private practice	5% (569/10 818)
Primary care physician	1% (92/10 818)
CRT/pacemaker clinic	10% (1124/10 818)
Heart failure management clinic	3% (273/10 818)
Other	0% (34/10 818)
Drug therapy at discharge	
Loop diuretic	81% (8621/10 635)
ACE inhibitor/ARB	86% (9163/10 603)
MRA (aldosterone antagonist)	63% (6682/10 573)
Beta-blocker	89% (9472/10 648)
Ivabradine	6% (593/10 543)
Digoxin	10% (1100/10 544)
Calcium channel blocker	9% (946/10 531)
Amiodarone	17% (1825/10 547)
Other anti-arrhythmic agent	2% (181/10 531)
Oral anticoagulant	47% (4928/10 577)
Warfarin (coumadin)	33% (3463/10 577)
Dabigatran	3% (327/10 577)
Rivaroxaban	6% (611/10 577)
Apixaban	5% (509/10 577)
Edoxaban	<1% (18/10 577)
Anti-platelet agent	44% (4846/11 088)
Aspirin	41% (4357/10 547)
Clopidogrel	12% (1304/10 547)
Ticagrelor	1% (136/10 547)
Prasugrel	<1% (31/10 547)

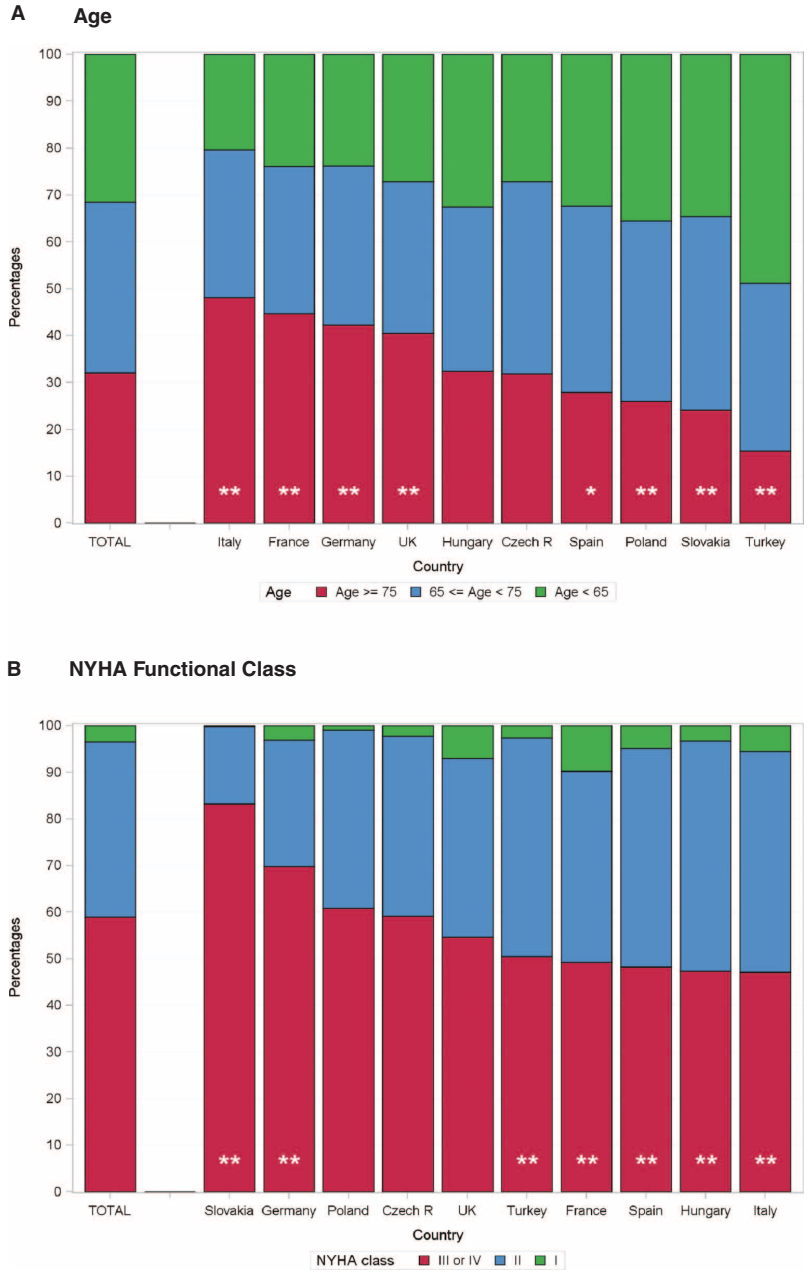
In parenthesis, number of patients in each category compared to the total cohort for each data-point.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AV, atrio-ventricular; CRT, cardiac resynchronisation therapy; ECG, electrocardiogram; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; VV, ventriculo-ventricular.

Accordingly, the 2012 ESC guidelines do not provide guidance on upgrades. Although the 2013 ESC EHRA guidelines provided a class I recommendation and level of evidence B for device upgrade for patients with persistent symptoms compatible with HF,[9] the 2016 ESC guidelines offered only a class IIb recommendation.[8] Although pacing generally prolongs QRS duration, its clinical significance with respect to CRT may differ. The importance of atrio-ventricular resynchronisation may be as or more important than bi-ventricular resynchronisation and the benefit of upgrading devices to CRT is not well established.

The rhythm at implantation was AF for 26% patients in this survey. The 2013 EHRA and 2012 and 2016 HFA guidelines provide either a IIa or IIb recommendation for patients with AF but emphasise the importance of pharmacological rate control or atrio-ventricular nodal ablation in order to adequately ensure bi-ventricular capture.[8,9,12] No substantial trial has compared CRT to a pharmacological control group for patients with AF. A subgroup of patients in the RAFT study had AF and did not appear to benefit, which was ascribed to inadequate ventricular capture.[7] Similarly, a recent report from COMPANION also suggested that patients with a prior history of AF did not benefit from CRT, although incident AF did not appear to reduce benefit in CARE-HF.[4,24] At least two trials have compared CRT to right ventricular pacing after atrio-ventricular node ablation. These suggest that CRT is superior.[25,26] However, whether this reflects a benefit from CRT or simply avoiding the harm of right ventricular pacing is unclear. For this reason, some experts think that current guidelines provide an unduly strong recommendation for CRT in patients with AF.

This survey shows that 8% of implants were in patients with a QRS <120 ms and that a further 5% had a QRS duration 120–129 ms. The 2012 HFA guidelines recommended CRT implantation only when QRS duration was >120 ms in the presence of more severe symptoms and LBBB or QRS >130 ms when symptoms were mild and LBBB was present or when QRS duration was >150 ms in the absence of LBBB.[12] In May 2016 the most recent version of the HFA guidelines, based on the results of EchoCRT and an individual-patient data meta-analysis, suggested that CRT is contraindicated when QRS duration is <130 ms.[8,27–29] This survey ran from October 2015 to December 2016. Future analyses will determine whether practice evolved over the course of the survey.[9,12] Of note, the median QRS duration was narrower (144 ms compared with 160 ms) for patients implanted only for the clinical indication 'PM indicated and expected right ventricular pacing dependence' compared to the overall cohort. A total of 10% of the survey population were implanted with only this clinical indication and 22% of this group had a QRS duration <120 ms. However, most patients in this survey had a QRS duration ≥150 ms. Individual-patient data meta-analyses of RCTs have convincingly shown that longer QRS durations predict greater long-term benefit from CRT.[28,30]

Patients in this survey were generally treated with loop diuretics (81%), ACE inhibitors/ARBs (86%), beta-blockers (89%), and MRAs (63%) at discharge from hospital. Guidelines recommend implantation of CRT only after patients have been optimally medically



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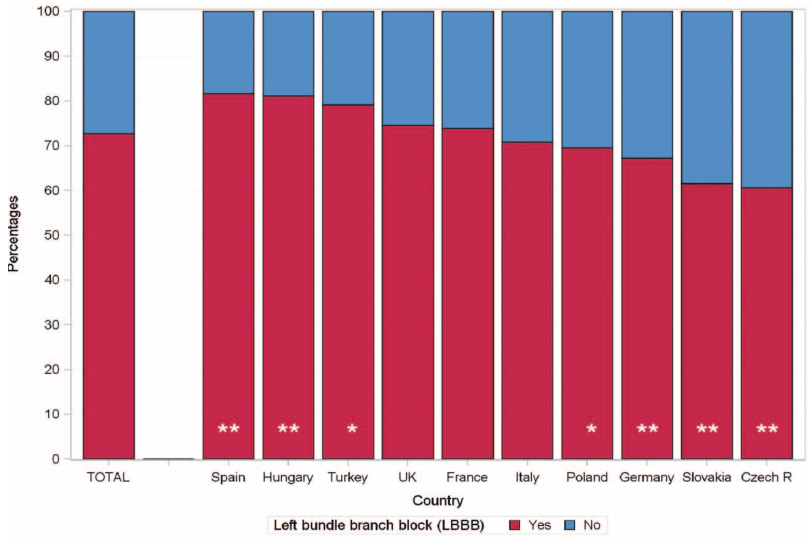
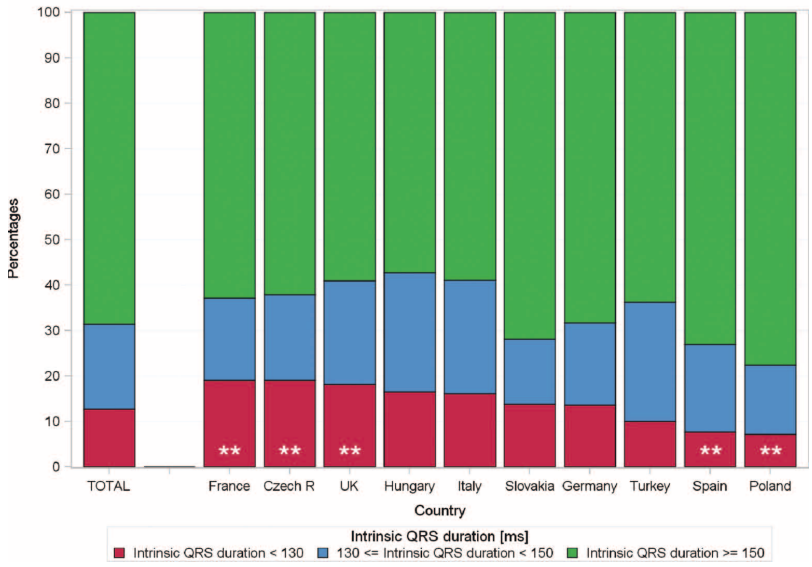
C Left Bundle Branch Block



D Intrinsic QRS



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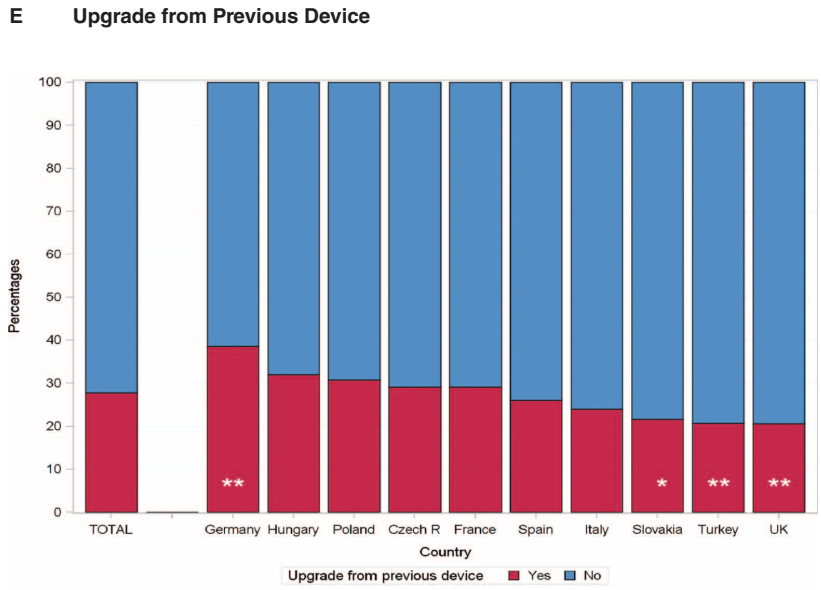

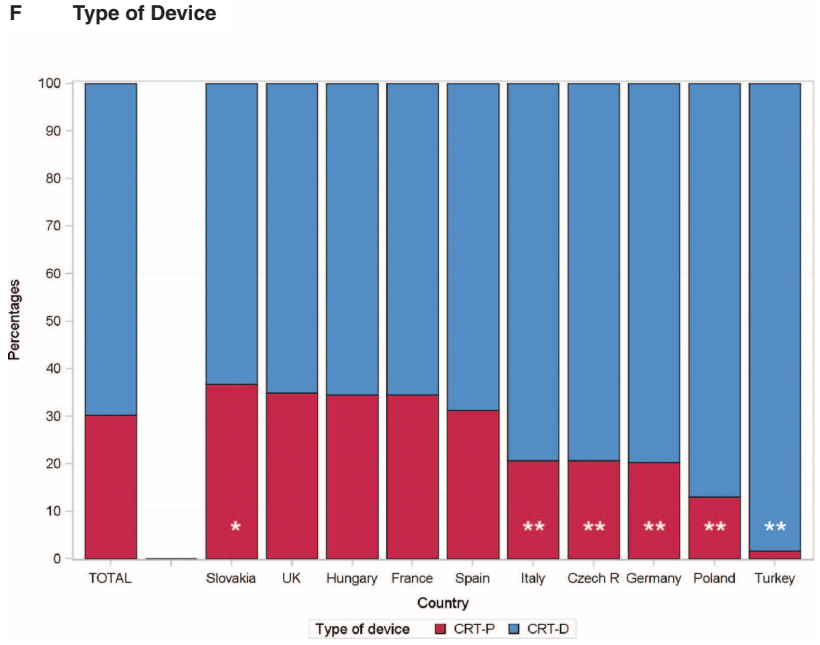

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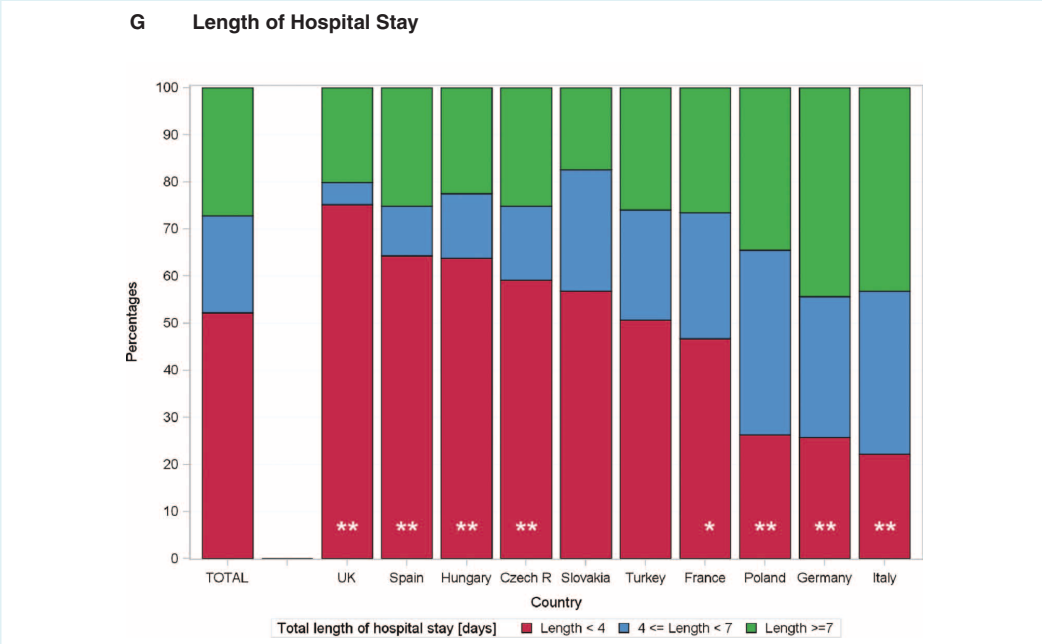

Figure 1 The figure presents a comparison of selected characteristics across the top 10 recruiting countries. (*A*) Age of patients implanted with cardiac resynchronisation therapy (CRT) devices. (*B*) New York Heart Association (NYHA) classification. (*C*) QRS morphology on pre-implant electrocardiogram. (*D*) QRS duration on pre-implant electrocardiogram. (*E*) Upgrades to CRT from previous device (permanent pacemaker or implantable cardioverter-defibrillator). (*F*) Type of device implanted (CRT-P vs. CRT-D). (*G*) Length of hospital stay. Asterisks demonstrate the level of statistical significance of the bottom red category for each country as compared to the total cohort. One asterisk denotes a *P*-value of <0.01 and two asterisks a *P*-value of <0.001.

managed. Although the proportion of patients in the survey discharged on disease-modifying medications is less than ideal and less than observed in some registries, it is still similar or greater than observed in most of the landmark clinical trials that proved the efficacy of CRT, many other registries or in clinical practice.[18,31]

The process of developing evidence-based guidelines includes both adequate evaluation by randomised clinical trials as well as feedback from surveys and registries. Survey and registries demonstrate the degree to which guidelines are adopted in practice. Therefore, the extensive observational data that we have collected highlight which guideline recommendations are or are not being adhered to as well as how physicians extrapolate existing data to clinical challenges they encounter in practice where evidence is lacking. These gaps in evidence are intentionally included in all ESC guidelines in order to identify potentially fruitful area for future research.

The one-time site questionnaire includes information such as total number of beds per hospital, type of hospital, number of CRT devices implanted annually and the number and speciality of implanters, which provides valuable information related to health care resource demands and capacity. A dedicated health care resource utilisation paper will be published.

The data selected for benchmarking are directly related to patient selection, clinical practice and health care resource utilisation in the top 10 recruiting countries. Benchmarking of these countries in the survey revealed remarkable similarities with regard to patient selection. However, there were also many highly significant differences between countries (*Figure 1*), especially the populations aged ≥75 years with QRS <130 ms, NYHA class III or IV as well as choice of device (CRT-P vs. CRT-D).

Particularly striking was the difference in index hospitalisation duration between the top 10 countries. Hospitalisation for implantation of a CRT can facilitate initiation and up-titration of optimal medical therapy, which can prolong hospital stay. Differences in the length of hospital stay depend both on the implanting centre and the collaboration with the outpatient HF services. Some of the observed differences in these countries' CRT implantation practice will be related to the country's economic strength, the proportion of their budget allocated to health care and the demographics of the population. The initial cost of CRT is substantial due to the device itself, the implantation procedure, hospitalisation and follow-up. However, the symptomatic improvement following CRT and the reduction in HF hospitalisation makes it an effective use of resources. Countries with limited financial resources may

select patients most likely to respond and also may prefer CRT-P to CRT-D due to the reduced cost. In Europe, physicians may be more willing to extrapolate beyond the existing evidence and guidelines for CRT because the risk of medical litigation is relatively low. Most procedures are funded partly or entirely by public funding and there is limited formal audit of adherence to guidelines.

Limitations

The strength and ability of a survey to address questions are related to the strength of its methodology, its representativeness and size. Although the number of patients enrolled in this survey was large, there were substantial differences amongst countries. Overall, we estimate that about 11% of patients implanted with CRT in participating countries were enrolled in the survey. We cannot assess the degree of selection bias in the choice of enrolled patients. Sites may have been less likely to report unsuccessful implants or cases with a poor outcome, accounting for low complication and mortality rates. The number of implanting sites ranged from 1 to 37. In countries with few participating centres, these centres' practice will have a great impact on the national results.

The eCRF was designed to be as user-friendly as possible in order to maximise the number of patients enrolled. Unavailable patient data could be omitted; the analyses were based on the available data, which explains the variation in the sample size for each data point. Furthermore, the interpretation of questions was up to the discretion of the investigator. Although there was no formal independent monitoring of the data collection, the IHF conducted 'front-end' data check and post database lock quality control analyses designed to prevent incorrect data being analysed. The most recent ESC HF guidelines were released during the enrolment period of the survey.[8] It requires time before new guidelines are adopted into evolving clinical practice. It is difficult to quantify the effect that this had on the selection and enrolment of patients subsequent to the release of the most recent ESC guidelines.

Conclusion

CRT Survey II provides a valuable source of information on contemporary clinical practice with respect to CRT implantation in a large sample of ESC member states. The survey demonstrates important similarities as well as substantial differences in patient selection, implantation procedure and follow-up. The data collected are sufficient to permit meaningful benchmarking between the highest recruiting countries and for assessing guideline adherence and health care resource utilisation. This should assist in educational initiatives and identifying appropriate directions for future research.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. CRT Survey II Investigators.

Acknowledgements

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Appendix

European CRT Survey II

- Electronic Case Report Form -

Institut für Herzinfarktforschung Ludwigshafen
Bremser Str. 79
67063 Ludwigshafen

Version 1.2 17.09.2015

European CRT Survey II

- Electronic Case Report Form -

Demographics				
Month/Year of CRT implantation	MM.YYYY			
Age	☐ years	Calculator		
When the user clicks on "Calculator", the EDC system will open a javascript-based calculator where the user can enter the month/year of the birth and the system will calculate the age of the patient on the user's computer. The calculation takes place only on the user's computer, only the age will be stored in the database on the server.				
Gender	○ Male	○ Female		
Elective admission	○ No	○ Yes		
Referral from another centre	○ No	○ Yes		
Is the patient currently enrolled in a clinical trial	○ No	○ Yes		
Primary HF aetiology				
Primary HF aetiology	○ Ischaemic	○ Non-ischaemic	○ Other	
Past history and major comorbidity				
Myocardial infarction	○ No	○ Yes		
Prior Revascularization (PCI/CABG)	○ No	○ Yes		
Hypertension	○ No	○ Yes		
Atrial fibrillation	○ No	○ Yes		
Type	○ Paroxysmal	○ Persistent	○ Permanent	
Valvular heart disease	○ No	○ Yes		
Obstructive lung disease	○ No	○ Yes		
Diabetes	○ No	○ Yes		
Anemia	○ No	○ Yes		
Chronic kidney disease (eGFR < 60) Estimated glomerular filtration rate	○ No	○ Yes		
Dialysis	○ No	○ Yes		
HF hospitalization during past year	○ No	○ Yes		
Previous device implantation	○ No	○ Yes		
Type of device	☐ PPM	☐ ICD	☐ CRT-P	☐ CRT-D ☐ Other
Pre-implant clinical evaluation				
NYHA class	○ I	○ II	○ III	○ IV
Body-Mass-Index	☐ kg/cm²	Calculator		

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- Electronic Case Report Form -

When the user clicks on "Calculator", the EDC system will open a javascript-based calculator where the user can enter the height and weight of the patient and the system will calculate the body-mass-index on the user's computer. The calculation takes place only on the user's computer, only the final result will be stored in the database on the server.

Blood Pressure Systolic/Diastolic	☐ / ☐ mmHg	
Laboratory measurements (most recent)		
NT-proBNP	☐ pg/ml	☐ pmol/l
BNP	☐ pg/ml	☐ pmol/l
Hb Haemoglobin	☐ g/dl	
Serum Creatinine	☐ mg/dl	☐ µmol/l
	☐ Remaining laboratory values unavailable	
Pre-implant ECG		
Heart rate	☐ bpm	
Atrial rhythm	○ Sinus	○ Atrial fibrillation ○ Atrial paced ○ Other
PR interval	☐ ms	
AV block II/III	○ No	○ Yes
Intrinsic QRS duration	☐ ms	
Pacemaker dependant	○ No	○ Yes
Paced QRS duration	☐ ms	
QRS morphology	☐ Normal ☐ Left bundle branch block (LBBB) ☐ Indeterminate ☐ Right bundle branch block (RBBB)	
AV node ablation *(if "Atrial fibrillation")*	○ No	○ Performed ○ Planned

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- Electronic Case Report Form -

Clinical indication for CRT

Clinical indication for CRT	☐ Heart failure with wide QRS ☐ Heart failure or left ventricular (LV) dysfunction and an indication for an ICD ☐ Pacemaker indication and expected right ventricular (RV) pacing dependence ☐ Evidence of mechanical dyssynchrony ☐ Other
If "Other":	

Preimplant imaging used to determine CRT indication

Echo	○ No	○ Yes
Cardiac MRI	○ No	○ Yes
CT scan	○ No	○ Yes
Scintigraphy	○ No	○ Yes
Did scar evaluation influence LV lead placement?	○ No	○ Yes
LVEF Left ventricular ejection fraction	☐ %	**(by any method)**
Method used to determine LVEF	○ LV-Angio ○ Echo ○ MRI ○ Scintigraphy	

Echo Data (if available)

LVEF	☐ %			
LVEDD LV enddiastolic dimension	☐ mm			
Mitral regurgitation	○ None	○ Mild	○ Moderate	○ Severe
Aortic stenosis	○ None	○ Mild	○ Moderate	○ Severe
Valve surgery/procedure	○ No	○ Yes		
Valve surgery/procedure	☐ Aortic valve replacement ☐ Mitral valve replacement ☐ Mitral valve repair Other			
	☐ Remaining echo data unavailable			

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- Electronic Case Report Form -

The following part of the CRF will be repeated multiple times for each implantation attempt:

CRT-Implantation Procedure

Number of days from admission to this implantation attempt	☐ days		Calculator
When the user clicks on "Calculator", the EDC system will open a javascript-based calculator where the user can enter the dates and the system will calculate the days on the user's computer. The calculation takes place only on the user's computer, only the days will be stored in the database on the server.			
Successful attempt	○ No	○ Yes	
If No: Reason	☐ LV lead placement unsuccessful ☐ Complication		
Complication	☐ Death ☐ Bleeding ☐ Pneumothorax ☐ Haemothorax ☐ Coronary sinus dissection ☐ Pericardial tamponade ☐ Other		
If "bleeding"	☐ Requiring intervention	☐ Pocket haematoma	

Only for the successful attempt, the following information has to be provided:

Successful attempt

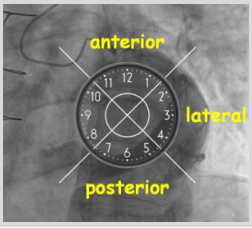
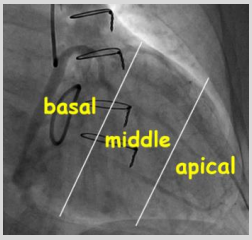
Type of device:	○ CRT-P	○ CRT-D	
Operator	○ Electrophysiologist ○ HF physician ○ Invasive Cardiologist ○ Surgeon ○ Other		
Location of procedure	○ Cathlab ○ Dedicated electrophysiology lab ○ Device implantation lab ○ Operating theatre ○ Other		
Duration	☐ min		
Fluroscopy time	☐ min		
Prophylactic antibiotics	○ No	○ Yes	
Test shock	○ No	○ Yes	
Which lead was implanted first	○ RV	○ LV	
RV lead placement	○ Apex	○ Septum	○ RVOT
LV lead placement successful	○ No	○ Yes	

If LV lead placement is unsuccessful what was main reason?	○ Coronary sinus not identified ○ Extracardiac stimulation ○ No suitable coronary vein ○ Complication ○ Other		
If LV lead placement is unsuccessful, was the patient referred to another center?	○ No	○ Yes	
LV lead type	○ unipolar	○ bipolar	○ multipolar
Was a coronary venogram performed	○ No	○ Yes	
Was the venogram performed with occlusion	○ No	○ Yes	
Was dilatation of coronary vein performed	○ No	○ Yes	
Was phrenic nerve stimulation tested	○ No	○ Yes	

LV Lead Position Evaluation

LV lead position evaluation	○ No	○ Yes, biplane x-ray projection ○ Yes, monoplane (LAO) ○ Yes, monoplane (RAO)

Please indicate the approximate position of the electrode(s) actually used for LV pacing (e.g. in multipolar leads) using the schematic views provided.

LAO site evaluation (clock-face evaluation)	○ Anterior (h 11-01) ○ Lateral (h 02-04) ○ Posterior (h 05-06)	
RAO site evaluation	○ Basal ○ Middle ○ Apical	
Was LV position optimized?	○ No	○ Yes
by electrical delay such as QLV?	○ No	○ Yes
by paced QRS	○ No	○ Yes

duration?		
by other means?	○ No	○ Yes

European CRT Survey II

- Electronic Case Report Form -

Peri-procedural complications

Peri-procedural complications	☐ None	☐ Death ☐ Bleeding ☐ Pneumothorax ☐ Haemothorax ☐ Coronary sinus dissection ☐ Pericardial tamponade ☐ Other
If "bleeding"	☐ Requiring intervention	☐ Pocket haematoma

Post-implant ECG

Paced QRS duration	☐ ms

Device programming

Was AV programming performed prior to discharge	○ No	○ Yes
Was VV programming performed prior to discharge	○ No	○ Yes
Was Device-based software for AV or VV optimization used	○ No	○ Yes
If "Yes", was it	○ Automatic	○ Manual

Discharge status and major adverse events

Discharge status	○ Alive	○ Dead
Cardiovascular death	○ No	○ Yes
Progressive heart failure	○ No	○ Yes
Total length of hospital stay Number of days from admission to discharge or death	☐ days	Calculator

When the user clicks on "Calculator", the EDC system will open a javascript-based calculator where the user can enter the dates and the system will calculate the days on the user's computer. The calculation takes place only on the user's computer, only the days will be stored in the database on the server.

Adverse clinical events during index hospitalisation following implantation	☐ None	☐ MI ☐ Stroke ☐ Infection ☐ Worsening HF ☐ Worsening renal function ☐ Arrhythmias ☐ Other
Was there a complication that necessitated an intervention	☐ None	☐ Phrenic nerve stimulation ☐ Lead dislocation or displacement ☐ Lead malfunction ☐ Infection

		☐ Other
Drug therapy at discharge		
(For deceased patients please enter last known drug therapy.)		
Loop diuretic	○ No	○ Yes
ACE inhibitor/ARB	○ No	○ Yes
MRA (aldosterone antagonist)	○ No	○ Yes
Betablocker	○ No	○ Yes
Ivabradine	○ No	○ Yes
Digoxin	○ No	○ Yes
Calcium channel blocker	○ No	○ Yes
Amiodarone	○ No	○ Yes
Other anti-arrhythmic agent	○ No	○ Yes
Oral anticoagulant	○ No	○ Warfarin (Coumadin) ○ Dabigatran ○ Rivaroxaban ○ Apixaban ○ Edoxaban
Anti-platelet agent	☐ No	☐ Aspirin ☐ Clopidogrel ☐ Ticagrelor ☐ Prasugrel
	☐ Remaining drug therapy information unavailable	
Follow-Up		
Where is follow-up planned	☐ Implanting centre ☐ Other hospital ☐ Cardiologist in private practice ☐ Primary care physician ☐ CRT/pacemaker clinic ☐ Heart failure management clinic ☐ Other	
Device remote monitoring		
Will the device be monitored by telemetry?	○ No	○ Yes

European CRT Survey II

- Site Questionnaire -

Institut für Herzinfarktforschung Ludwigshafen
Bremser Str. 79
67063 Ludwigshafen

Version 1.2, 16.09.2015

European CRT Survey II

- Site Questionnaire Draft -

Hospital information (Description of site and facilities)	
Hospital name	
Head of cardiology department	
Address	
City	
Country	
First contact person for this survey:	
Name	
E-Mail	
Telephone	
Second contact person for this survey:	
Name	
E-Mail	
Telephone	
Hospital facilities	
Total number of hospital beds	☐ of beds
Number of cardiology department beds	☐ of beds
Type of hospital	○ University hospital ○ Teaching hospital (non-university) ○ Community hospital ○ Private hospital
Number of inhabitants of catchment area	☐ ☐ Unknown
Cardiac surgery on site	○ No ○ Yes
Angiography/PCI on site	○ No ○ Yes
Total number of:	
Catheterization laboratories	☐
Dedicated electrophysiological labs	☐
Other sites where devices are implanted	☐ None ☐ Hybrid ☐ Surgical ☐ Radiology

European CRT Survey II

- Site Questionnaire Draft -

Cardiology activity profile annually			
Coronary angiograms	☐ / year		
PCI procedures	☐ / year		
CRT-P implantations	☐ / year		
CRT-D implantations	☐ / year		
ICD implantations	☐ / year		
Pacemaker implantations	☐ / year		
Arrhythmia ablations	☐ / year		
Number of CRTs implanters			
Electrophysiologists	☐		
Interventional cardiologists	☐		
Heart failure physicians	☐		
Cardiac surgeons	☐		
General cardiologists	☐		
Others	☐		
Follow-up, do you have a			
Heart failure clinic for patient follow-up?	○ No	○ Yes	
Dedicated CRT clinic for follow-up?	○ No	○ Yes	
A remote device monitoring follow-up service?	○ No	○ Yes	
Are most patients followed-up at implanting centre?	○ No	○ Yes	
A dedicated lead extraction/management program?	○ No	○ Yes	
Does your centre:			
Participate in a national device registry?	○ No	○ Yes	
Use electronic medical health records?	○ No	○ Yes	
Reimbursement			
What is the source of reimbursement for CRT devices?	☐ Public health provider	☐ Private insurance	☐ Private payer

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