Cardiac Resynchronization Therapy: An Overview on Guidelines

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KEYWORDS

• Atrial fibrillation • Bundle branch block • Cardiac resynchronization therapy • Guidelines • Heart failure • QRS interval

KEY POINTS

- Cardiac resynchronization therapy (CRT) is included in international consensus guidelines as a treatment with proven efficacy in well-selected patients on top of optimal medical therapy. Although all the guidelines strongly recommend CRT for LBBB with QRS duration greater than 150 milliseconds, lower strength of recommendation is reported for QRS duration of 120 to 150 milliseconds, especially if not associated with LBBB. CRT is not recommended for a QRS of less than 120 milliseconds.
- The process of translating consensus guidelines into "real-world" practice is incomplete. Efforts should be dedicated to "synchronize" the competence and expertise of many physicians in order to deliver this treatment to the right patient, at the right time, and in the appropriate setting.

INTRODUCTION

Clinical guidelines are systematically developed statements and recommendations regarding clinical decision making to help practitioners and patients to make the most appropriate decisions about management and treatment of specific clinical conditions and diseases. Clinical guidelines are produced on the basis of a systematic revision process of the medical literature and opinion of experts and should provide extensive, critical, and well-balanced information on the benefits and limitations of a series of therapeutic and diagnostic choices to assist in taking decisions in individual cases. Application of guidelines to the management of individual patients always requires rational judgment and informed considerations, even when guidelines recommendations are properly linked to evidence.

Since the mid 1980s, national and international guidelines focused on different diseases have been developed. The reasonable expectation included an improvement in the process of health care provision by making it more effective and efficient. Despite the great efforts dedicated to development and implementation of evidence-based guidelines, contradictory results emerge by analysis of guidelines implementation and medical decisions in the "real world." A series of surveys indicate that around 30% to 40% of patients do not receive treatments based on scientific evidence, and around 20% to 25% receive treatments that may be unnecessary and sometimes even harmful.[1]

With regard to pacemaker and implantable electrical devices, the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society (formerly the North American

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Society of Cardiac Pacing and Electrophysiology) published the first guidelines for the implantation of cardiac pacemakers and antiarrhythmia devices in 1984.[2] Since that time, major advancements in technology and clinical evidence of benefit occurred with regard to device therapy and these developments have led to periodic updating of the guidelines in 1991, 1998, 2002, 2008, and 2012.[3] The European Society of Cardiology released the first document including recommendations on use of implantable cardioverter defibrillators in 1992[4] and then released guidelines on pacing and cardiac resynchronization therapy (CRT) in 2006 and 2013.[5,6]

CARDIAC RESYNCHRONIZATION THERAPY AS AN EFFECTIVE TREATMENT IN HEART FAILURE

CRT was proposed as the result of pioneering experiences performed in France around 20 years ago.[7–9] CRT is an electrical treatment based on biventricular or left ventricular-only pacing that was initially applied as a last resort therapeutic solution for patients with severe heart failure (HF) associated with left bundle branch block (LBBB). Despite the novelty of the approach and the technical limitations of implantable leads in the first phases of clinical use, the evaluation of CRT moved rapidly from isolated case reports and small case series or uncontrolled studies to randomized controlled trials (**Table 1**). Multisite Stimulation in Cardiomyopathy (MUSTIC) was the first randomized study on CRT[21] and was followed by a randomized controlled trial with blinded assessment of the effects, namely, the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study.[10,11] The MIRACLE trial included implant of a CRT device followed by randomization to biventricular pacing "on" or "off" for 6 months with blinded assessment of the presence/absence of improvement in symptoms, HF status, and quality of life.[10] A paradigm shift in obtaining solid evidence in favor of CRT use in patients with moderate to severe HF were the Cardiac Resynchronization—Heart Failure (CARE HF) and the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trials[13,14] that randomized patients to optimal medical therapy versus CRT (with a pacemaker in CARE HF, with or without a defibrillator in COMPANION), using "hard endpoints"[13,14] as primary endpoints of efficacy (all-cause mortality or hospitalization).

As a result of the randomized controlled trials performed in the last 15 years (see **Table 1**), CRT has been proposed by all the international consensus guidelines as a treatment with proven efficacy in improving symptoms, reducing hospitalizations, inducing reverse remodeling, and reducing mortality in well-selected patients with wide QRS (and LBBB), left ventricular dysfunction, and moderate to severe (New York Heart Association [NYHA] class III-IV) or mild (NYHA class II) HF, on top of optimal medical therapy.[6] More recently, patients with conventional indications for pacing, a left ventricular ejection fraction of 50% or less and NYHA class I to III resulted to benefit from biventricular pacing in a relatively long follow-up,[19] although with a number needed to treat, much higher than that of others CRT trials.[22]

GUIDELINES ON CARDIAC RESYNCHRONIZATION THERAPY

In the present review, we analyze the recommendations for CRT implant included in the guidelines on pacing and CRT delivered by the European Society of Cardiology and in the guidelines by the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society, as well as the recommendations for CRT included guidelines on HF delivered by the same societies. Moreover, we analyze the guidelines on CRT delivered by the Canadian Cardiovascular Society and by National Institute for Health and Care Excellence (NICE; **Table 2**). These guidelines have some differences with regard to the grading of recommendations (see **Table 2**), which is very explicit and associated with a predefined wording of recommendations in both European and American guidelines. Conversely, NICE does not report in the guidance specific explanations focused on grading of recommendations, implying that the reader can find some information in another NICE publication.[27] The recent NICE guidelines on implantable cardioverter defibrillators (ICDs) and CRT are in some way unique, because they are based on individual patient data network meta-analyses, based on 12,638 patients from 13 clinical trials, taking into account not only evidence but also cost-effectiveness estimates.[28] The approach of NICE of considering cost effectiveness is quite original because, even if economic evaluations are an important aspect of health technology assessment,[29–32] economic estimates were deliberately excluded from clinical recommendations in guidelines delivered by the European Society of Cardiology[33] and has never been considered in guidelines from North America.

We analyze the recommendations delivered from these guidelines with regard to class of recommendation and level of evidence, if available, taking into account different categories of patients, on the basis of clinical aspects (severity

Table 1
Randomized clinical trials on cardiac resynchronization therapy enrolling more than 100 patients: patient population and main findings

Trial	No. of Patients	Trial Design (Follow-up Duration)	NYHA Class	LVEF (%)	QRS Duration (ms)	Primary Endpoints	Secondary Endpoints	Main Findings
MIRACLE[10]	453	Double-blind, randomized trial CRT vs OMT (6 mo)	III–IV	≤35	≥130	NYHA class, exercise capacity, QoL	Peak Vo_2, LVEDD, LVEF, clinical composite response	CRT-P improved NYHA class, QoL, exercise capacity and LVEDD, and increased LVEF
MIRACLE-ICD[11]	369	Double-blind, randomized trial CRT-D vs ICD (6 mo)	III–IV	<35	≥130	NYHA class, exercise capacity, QoL	Peak Vo_2, LVEDD, LVEF, clinical composite response	CRT-D improved NYHA class, QoL, peak Vo_2
CONTAK CD[12]	490	Double-blind, randomized trial CRT-D vs ICD (6 mo)	II–III–IV	≤35	≥120	NYHA class, exercise capacity, QoL	LV volume, LVEF composite of mortality, VT/VF, hospitalizations	CRT-D improved exercise capacity, NYHA class, QoL, reduced LV volumes and increased LVEF

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Table 1
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Trial	No. of Patients	Trial Design (Follow-up Duration)	NYHA Class	LVEF (%)	QRS Duration (ms)	Primary Endpoints	Secondary Endpoints	Main Findings
CARE-HF[13]	813	Double-blind, randomized trial OMT vs CRT-P (29.4 mo)	III–IV	≤35	≥120	All-cause mortality or hospitalization	All-cause mortality, NYHA class, QoL	CRT-P decreased all-cause mortality and hospitalizations and improved NYHA class and QoL
COMPANION[14]	1520	Double-blind, randomized trial OMT vs CRT-P/or vs CRT-D (15 mo)	III–IV	≤35	≥120	All-cause mortality or hospitalization	All-cause mortality, cardiac mortality	CRT-P and CRT-D decreased all-cause mortality or hospitalizations
MIRACLE-ICD II[15]	186	Double-blind, randomized trial CRT-D vs ICD (6 mo)	II	≤35	≥130	Peak Vo_2	VE/VCO_2, NYHA, QoL, functional capacity, LV volumes and LVEF, composite clinical endpoint	CRT-D improved NYHA, VE/CO_2 and LV volumes and improved LVEF
REVERSE[16]	610	Double-blind, randomized trial CRT on vs CRT off (12 mo)	I–II	≤40	≥120	Worsening of clinical composite endpoint	LVESV index, HF hospitalizations and all-cause mortality	CRT-P/CRT-D did not improve the primary endpoint and did not reduce all-cause mortality but decreased LVESV index and HF hospitalizations

MADIT-CRT[17]	1820	Single-blind, randomized trial CRT-D vs ICD (12 mo)	I–II	≤30	≥130	All-cause mortality or HF hospitalization	All-cause mortality or LVESV	CRT-D decreased the endpoint of HF hospitalizations or all-cause mortality; LVESV was reduced; CRT-D did not reduce all-cause mortality
RAFT[18]	1798	Double-blind, randomized trial CRT-D vs ICD (40 mo)	II–III	≤30	≥120	All-cause mortality or HF hospitalizations	All-cause mortality and cardiovascular death	CRT-D decreased the endpoint all-cause mortality or HF hospitalizations; in NYHA III, CRT-D only decreased all-cause mortality
BLOCK HF[19]	918	Double-blind, randomized trial RV vs BIV pacing (37 mo)	I–II–III	≤50	123–125 (mean value)	All-cause mortality, acute HF, increase in LVESV >15%	Composite endpoint of death from any cause, acute HF, death from any causes, hospitalizations	BIV pacing was superior to RV pacing in patients with atrioventricular block, mild-to-moderate HF and abnormal LV systolic function
ECHO CRT[20]	1680	Multicenter, randomized trial, CRT in patients with echo dyssynchrony (19, 4 mo)	I–II–III–IV	≤35	<130	Composite endpoint (death from any hospitalization for worsening HF)	Death from any cause and hospitalization for HF	CRT did not decrease hospitalizations for HF or death from any cause; CRT increased mortality in patients with LVEF ≤35% and narrow QRS

Abbreviations: BIV, biventricular; BLOCK HF, Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block; CARE-HF, Cardiac Resynchronization—Heart Failure; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with a defibrillator; CRT-P, cardiac resynchronization therapy with a pacemaker; ECHO CRT, Echocardiography Guided Cardiac Resynchronization Therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MADIT-CRT, Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD, The Multicenter InSync ICD Randomized Clinical Evaluation; NYHA, New York Heart Association; OMT, optimal medical therapy; QoL, quality of life; RAFT, Resynchronization–Defibrillation for Ambulatory Heart Failure Trial; REVERSE, Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; RV, right ventricular.

Data from Refs.[10–20]

Table 2
Comparison of grading of recommendations

Recommendations	ESC Guidelines on Cardiac Pacing and CRT 2013[6]	ACCF/AHA/HRS Guidelines for Device-based Therapy 2012[3]	ESC Guidelines HF 2012[23]	ACCF/AHA/ HRS Guidelines HF 2013[24]	Canadian Cardiovascular Society Guidelines on the Use of CRT 2013[25]	NICE 2014[26]
Class of recommendations						
Evidence and/or general agreement that given treatment or procedure is beneficial, useful, effective.	Class I	Class I	Class I	Class I	Strong recommendations	Based on evidence plus cost-effectiveness estimates
Conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy of the given treatment or procedure. Weight of evidence/ opinion is in favor of usefulness/efficacy.	Class IIa	Class IIa	Class IIa	Class IIa	Weak recommendations	—
Conflicting evidence and/or a divergence of opinion about the usefulness/ efficacy of the given treatment or procedure. Usefulness/efficacy is less well-established by evidence/efficacy.	Class IIb	Class IIb	Class IIb	Class IIb	Weak recommendations	—

Evidence or general agreement that the given treatment or procedure is not useful/effective.	Class III	Class III no benefit	Class III	Class III no benefit	No recommendations	—
Evidence or general agreement that the given treatment or procedure in some cases may be harmful.	Class III	Class III harmful	Class III	Class III harmful	No recommendations	—
Levels of evidence						
Data derived from multiple randomized clinical trials or metaanalyses.	Level of evidence A	Level of evidence A	Level of evidence A	Level of evidence A	High quality of evidence	—
Data derived from a single randomized clinical trial or large nonrandomized studies.	Level of evidence B	Level of evidence B	Level of evidence B	Level of evidence B	Low quality of evidence	—
Consensus of opinion of the experts and/or small studies, retrospective studies, registries.	Level of evidence C	Level of evidence C	Level of evidence C	Level of evidence C	No evidence	—

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; HF, heart failure; HRS, Heart Rhythm Society; NICE, National Institute for Health and Care Excellence.

Data from Refs.[3,6,23–26]

of HF, sinus rhythm or atrial fibrillation, electrocardiographic aspects, etc). We also consider potential indications to apply CRT with a pacemaker or a defibrillator.

RECOMMENDATIONS FOR CARDIAC RESYNCHRONIZATION THERAPY WITH REGARD TO PATIENTS IN SINUS RHYTHM WITH MODERATE TO SEVERE HEART FAILURE

Table 3 shows, in parallel, the recommendation for implanting a CRT device in patients in sinus rhythm with moderate to severe HF (NYHA functional class III-IV). Although all the guidelines strongly recommend CRT in case of LBBB with a QRS duration of greater than 150 milliseconds, lower strength of recommendations, with some heterogeneity, appears when QRS duration is 120 to 150 milliseconds, especially if not associated with LBBB. Of note, for all the guidelines CRT is not recommended or not considered in case of a QRS duration of less than 120 milliseconds and, specifically, no indication emerges for guiding the implant on the basis of echocardiographic evaluation of dyssynchrony.

RECOMMENDATIONS FOR CARDIAC RESYNCHRONIZATION THERAPY WITH REGARD TO PATIENTS IN SINUS RHYTHM WITH MILD HEART FAILURE

Table 4 shows, in parallel, the recommendation for implanting a CRT device in patients in sinus rhythm with mild HF (NYHA functional class II). Although all the guidelines strongly recommend CRT in case of LBBB with a QRS duration of greater than 150 milliseconds, lower strength of recommendations, with some heterogeneity, appears when there is not a LBBB and the QRS is 120 to 150 milliseconds.

RECOMMENDATIONS FOR CARDIAC RESYNCHRONIZATION THERAPY WITH REGARD TO PATIENTS WITH PERMANENT ATRIAL FIBRILLATION AND LEFT VENTRICULAR DYSFUNCTION/HEART FAILURE

Table 5 shows, in parallel, the recommendation for implanting a CRT device in patients with permanent atrial fibrillation and left ventricular dysfunction or HF. The use of CRT in this setting has never been object of a dedicated, randomized clinical trial targeted on hard endpoints. Therefore, no class I recommendation were delivered by the specific guidelines on CRT (see Table 5).

PATIENTS ALREADY IMPLANTED WITH A CONVENTIONAL PACEMAKER OR IMPLANTABLE CARDIOVERTER DEFIBRILLATOR: INDICATIONS FOR UPGRADE TO A CARDIAC RESYNCHRONIZATION THERAPY DEVICE

Use of CRT in these cases is related to patients presenting with HF, but also to patients with atrial fibrillation with uncontrolled heart rate who are candidates for AV junction ablation. As shown in Table 6, no major differences can be found in guidelines recommendations. A corrigendum was delivered on HF guidelines delivered by the European Society of Cardiology on this topic.[34]

PATIENTS WITH CONVENTIONAL PACEMAKER INDICATIONS AND LEFT VENTRICULAR DYSFUNCTION/HEART FAILURE: INDICATIONS FOR IMPLANT OF A CARDIAC RESYNCHRONIZATION THERAPY DEVICE

Use of CRT in these cases is covered by the guidelines according to the recommendations shown in Table 7. This indication has been object of a controlled trial, Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF),[19] published in April 2013, so a key factor in interpreting the variable level of evidence coupled with delivered recommendations is the date of guidelines drafting and delivery. In general, a class IIa recommendation is delivered by most guidelines for this type of indication.

INDICATIONS TO IMPLANT A CARDIAC RESYNCHRONIZATION THERAPY PACEMAKER VERSUS A CARDIAC RESYNCHRONIZATION THERAPY DEFIBRILLATOR DEVICE IN CANDIDATES TO CARDIAC RESYNCHRONIZATION THERAPY IN THE SETTING OF PRIMARY PREVENTION OF SUDDEN DEATH

This issue has been object of several controversies and debates and has relevance in view of the financial impact of choosing a pacemaker versus a defibrillator,[35,36] also with implications on reimbursement.[37] Table 8 reports in parallel the different approaches proposed by the guidelines we analyzed.

Patient profile, costs, expected patient longevity, and risk of complications are all variables to be considered in clinical decision making.[38–40] In this regard, both the European Society of Cardiology Guidelines on cardiac pacing and CRT 2013[6] and the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society guidelines on HF

Table 3
Patients in sinus rhythm with moderate to severe HF (NYHA III-IV): indications for implant of a CRT device

Indication	ESC Guidelines on Cardiac Pacing and CRT 2013[6]	ACCF/AHA/HRS Guidelines for Device-based Therapy 2012[3]	ESC Guidelines HF 2012[23]	ACCF/AHA/HRS Guidelines HF 2013[24]	Canadian Cardiovascular Society Guidelines on the Use of CRT 2013[25]	NICE 2014[26]
LBBB with QRS duration >150 ms	CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment Class I Level of evidence A	CRT is indicated for patients who have LVEF ≤35% NYHA class III, or ambulatory IV symptoms on guideline-directed medical therapy Class I Level of evidence A	CRT is recommended in patients with LVEF ≤35% in NYHA functional class III and ambulatory IV despite adequate medical treatment, who are expected to survive with good functional status for >1 y Class I Level of evidence A	CRT is recommended in patients with LVEF ≤35% in NYHA functional class III and ambulatory IV despite adequate medical treatment Class I Level of evidence A	CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment Strong recommendation High quality evidence	CRT is recommended

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Table 3
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Indication	ESC Guidelines on Cardiac Pacing and CRT 2013[6]	ACCF/AHA/HRS Guidelines for Device-based Therapy 2012[3]	ESC Guidelines HF 2012[23]	ACCF/AHA/HRS Guidelines HF 2013[24]	Canadian Cardiovascular Society Guidelines on the Use of CRT 2013[25]	NICE 2014[26]
LBBB with QRS duration 120–150 ms	CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment Class I Level of evidence B	CRT is indicated for patients who have LVEF ≤35% NYHA class III, or ambulatory IV symptoms on guideline-directed medical therapy Class IIa Level of evidence B	CRT is recommended in patients with LVEF ≤35% in NYHA functional class III and ambulatory IV despite adequate medical treatment, who are expected to survive with good functional status for >1 y Class I Level of evidence A	CRT is recommended in patients with LVEF ≤35% in NYHA functional class III and ambulatory IV despite adequate medical treatment Class IIa Level of evidence B	CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment Strong recommendation High quality evidence	CRT is recommended
Non–LBBB with QRS duration >150 ms	CRT should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment Class IIa Level of evidence B	CRT is indicated for patients who have LVEF ≤35% NYHA class III, or ambulatory IV symptoms on guideline-directed medical therapy Class IIa Level of evidence A	CRT should be considered in patients with LVEF ≤35% in NYHA functional class III and ambulatory IV despite adequate medical treatment, who are expected to survive with good functional status for >1 y Class IIa Level of evidence A	CRT is recommended in patients with LVEF ≤35% in NYHA functional class III and ambulatory IV despite adequate medical treatment Class IIa Level of evidence A	CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment Weak recommendation Low quality evidence	CRT is recommended

Non–LBBB with QRS duration 120–150 ms	CRT may be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class III and ambulatory IV despite adequate medical treatment Class IIb Level of evidence B	CRT is indicated for patients who have LVEF ≤35% NYHA class III, or ambulatory IV symptoms on guideline-directed medical therapy Class IIb Level of evidence B	CRT is not considered	CRT is recommended in patients with LVEF ≤35% in NYHA functional class III and ambulatory IV despite adequate medical treatment Class IIb Level of evidence B	There is no clear evidence of benefit with CRT among patients with QRS duration <150 ms because of non–LBBB conduction No recommendation Low-quality evidence	CRT is not considered
QRS duration <120 ms	CRT in chronic HF patients and LVEF ≤35% is not recommended Class III Level of evidence B	CRT is not considered	CRT is not considered	CRT in chronic HF patients and LVEF ≤35% is not recommended Class III Level of evidence B	There is no clear evidence of benefit with CRT among patients with QRS duration <150 ms because of non–LBBB conduction No recommendation Low-quality evidence	CRT is not considered

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; HF, heart failure; HRS, Heart Rhythm Society; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association.

Data from Refs.[3,6,23–26]

Table 4
Patients in sinus rhythm with mild HF (NYHA II): indications for implant of a CRT device

Indication	ESC Guidelines on Cardiac Pacing and CRT 2013[6]	ACCF/AHA/HRS Guidelines for Device-based Therapy 2012[3]	ESC Guidelines HF 2012[23]	ACCF/AHA/HRS Guidelines HF 2013[24]	Canadian Cardiovascular Society Guidelines on the Use of CRT 2013[25]	NICE 2014[26]
LBBB with QRS duration > 150 ms	CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II Class I Level of evidence A	CRT is indicated for patients who have LVEF ≤35% NYHA class II Class I Level of evidence B	CRT is recommended in patients with LVEF ≤35% in NYHA functional class II who are expected to survive with good functional status for >1 y Class I Level of evidence A	CRT is recommended in patients with LVEF ≤35% in NYHA functional class II Class I Level of evidence B	CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II Strong recommendation High-quality evidence	CRT is recommended
LBBB with QRS duration 120–150 ms	CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II Class I Level of evidence B	CRT is indicated for patients who have LVEF ≤35% NYHA class II Class IIa Level of evidence B	CRT is recommended in patients with LVEF ≤35% in NYHA functional class II, who are expected to survive with good functional status for >1 y Class I Level of evidence A	CRT is recommended in patients with LVEF ≤35% in NYHA functional class II Class IIa Level of evidence B	CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II Strong recommendation High-quality evidence	CRT is recommended
Non–LBBB with QRS duration >150 ms	CRT should be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II Class IIa Level of evidence B	CRT is indicated for patients who have LVEF ≤35% NYHA class II Class IIb Level of evidence B	CRT should be considered in patients with LVEF ≤35% in NYHA functional class II, who are expected to survive with good functional status for >1 y Class IIa Level of evidence A	CRT is recommended in patients with LVEF ≤35% in NYHA functional class II Class IIb Level of evidence B	CRT is recommended in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II. Weak recommendation Low-quality evidence	CRT is recommended

Non–LBBB with QRS duration 120–150 ms	CRT may be considered in chronic HF patients and LVEF ≤35% who remain in NYHA functional class II Class IIb Level of evidence B	CRT is indicated for patients who have LVEF ≤35% NYHA class II Class III Level of evidence B	CRT is not considered	CRT is not recommended in patients with LVEF ≤35% in NYHA functional class II Class III Level of evidence B	There is no clear evidence of benefit with CRT among patients with QRS duration <150 ms because of non–LBBB conduction No recommendation Low-quality evidence	CRT is not considered
QRS duration <120 ms	CRT in chronic HF patients and LVEF ≤35% is not recommended Class III Level of evidence B	CRT is not considered	CRT is not considered	CRT in chronic HF patients and LVEF ≤35% is not recommended Class III Level of evidence B	There is no clear evidence of benefit with CRT among patients with QRS duration <150 ms because of non–LBBB conduction No recommendation Low-quality evidence	CRT is not considered

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; HF, heart failure; HRS, Heart Rhythm Society; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association.

Data from Refs.[3,6,23–26]

Table 5
Patients with permanent atrial fibrillation and LV dysfunction/HF: indications for implant of a CRT device

Indication	ESC Guidelines on Cardiac Pacing and CRT 2013[6]	ACCF/AHA/HRS Guidelines for Device-based Therapy 2012[3]	ESC Guidelines HF 2012[23]	ACCF/AHA/HRS Guidelines HF 2013[24]	Canadian Cardiovascular Society Guidelines on the Use of CRT 2013[25]	NICE 2014[26]
Patients with HF, wide QRS, and reduced LVEF	CRT should be considered in chronic HF patients, intrinsic QRS ≥120 ms, and LVEF ≤35% who remain in NYHA class III and ambulatory IV despite adequate medical treatment, provided that a BIV pacing as close to 100% as possible can be achieved Class IIa Level of evidence B	CRT can be useful in patients with atrial fibrillation and LVEF ≤35% despite adequate medical treatment if the patients requires ventricular pacing or otherwise meets CRT criteria Class IIa Level of evidence B	CRT-P/CRT-D should be considered in patients in NYHA functional class III or ambulatory class IV with a QRS duration ≥120 ms and an EF ≤35%, who are expected to survive with good functional status for >1 y, to decrease the risk of HF worsening if the patient is pacemaker dependent as a result of AV nodal ablation Class IIa Level of evidence B CRT-P/CRT-D may be considered in patients in NYHA functional class III or ambulatory class IV with a QRS duration ≥120 ms and an EF ≤35%, who are expected to survive with good functional status for >1 y, to reduce the risk of HF worsening if the patient requires pacing because of an intrinsically slow ventricular rate or the patient's ventricular rate is ≤60 bpm at rest and ≤90 bpm during exercise Class IIb Level of evidence C	CRT can be useful in patients with atrial fibrillation and LVEF ≤35% despite adequate medical treatment if the patients requires ventricular pacing or otherwise meets CRT criteria Class IIa Level of evidence B	CRT may be considered for patients in permanent AF who are otherwise suitable for this therapy Weak recommendation Low-quality Evidence	CRT is recommended

Patients with uncontrolled heart rate who are candidates for AV junction ablation	CRT should be considered in patients with reduced LVEF who are candidates for AV junction ablation for rate control Class IIa Level of evidence B	CRT can be useful in patients with atrial fibrillation and LVEF $\leq$35% despite adequate medical treatment if AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT Class IIa Level of evidence B	CRT may be considered in patients in NYHA class III or ambulatory IV, with a QRS $\geq$120 ms and LVEF $\leq$35% who are expected to survive with good functional status for >1 y, to reduce the risk of HF worsening if the patients will be pacemaker dependent as a result of AV nodal ablation Class IIa Level of evidence B	CRT can be useful in patients with atrial fibrillation and LVEF $\leq$35% despite adequate medical treatment if AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT Class IIa Level of evidence B	Not considered	Not considered

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; AV, atrioventricular; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with a defibrillator; CRT-P, cardiac resynchronization therapy with a pacemaker; ESC, European Society of Cardiology; HF, heart failure; HRS, Heart Rhythm Society; IV, intravenous; LVEF, left ventricular ejection fraction; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association.

Data from Refs.[3,6,23–26]

Table 6
Patients already implanted with a conventional pacemaker or ICD: indications for upgrade to a CRT device

Indication	ESC Guidelines on Cardiac Pacing and CRT 2013[6]	ACCF/AHA/HRS Guidelines for Device-based Therapy 2012[3]	ESC Guidelines HF 2012[23]	ACCF/AHA/HRS Guidelines HF 2013[24]	Canadian Cardiovascular Society Guidelines on the Use of CRT 2013[25]	NICE 2014[26]
Previous pacemaker or ICD implant	CRT is indicated in HF patients with LVEF <35% and high percentage of ventricular pacing who remain in NYHA class III and ambulatory IV despite adequate medical treatment Class I Level of evidence B	Patients with LV dysfunction in the setting of chronic RV pacing, and possibly as a result of RV pacing AF patients who experience HF after AV junction ablation and RV pacing Class IIa Level of evidence B	Not considered	CRT can be useful for patients on GDMT who have LVEF $\leq$35% and are undergoing replacement device implantation with ventricular pacing (>40%). Class IIa Level of evidence C	CRT may be considered for patients with chronic RV pacing or who are likely to be chronically paced, have signs and/or symptoms of HF, and an LVEF value $\leq$35% Weak recommendation, low-quality evidence	Not considered

Abbreviations: ACCF, American College of Cardiology Foundation; AF, atrial fibrillation; AHA, American Heart Association; CRT, cardiac resynchronization therapy; ESC, European Society of Cardiology; GDMT, guideline determined medical therapy; HF, heart failure; HRS, Heart Rhythm Society; ICD, implantable cardioverter defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; RV, right ventricular.
Data from Refs.[3,6,23–26]

Table 7
Patients with conventional pacemaker indications and LV dysfunction/HF: indications for implant of a CRT device

Indication	ESC Guidelines on Cardiac Pacing and CRT 2013[6]	ACCF/AHA/HRS Guidelines for Device-based Therapy 2012[3]	ESC Guidelines HF 2012[23]	ACCF/AHA/HRS Guidelines HF 2013[24]	Canadian Cardiovascular Society Guidelines on the Use of CRT 2013[25]	NICE 2014[26]
Candidate to permanent pacing	CRT should be considered in HF patients, reduced EF and expected high percentage of ventricular pacing to decrease the risk of worsening HF Class IIa Level of evidence B	Regardless of the duration of the native QRS complex, patients with LV dysfunction who have a conventional indication for pacing and in whom ventricular pacing is expected to predominate may benefit from biventricular pacing Class IIa Level of evidence B	In patients with an indication for conventional pacing and no other indication for CRT who are expected to survive with good functional status for >1 y: CRT should be considered in those in NYHA functional class III or IV with an EF $\leq$35%, irrespective of QRS duration, to decrease the risk of worsening of HF Class IIa Level of evidence C CRT may be considered in those in NYHA functional class II with an EF $\leq$35%, irrespective of QRS duration, to reduce the risk of worsening of HF Class IIb Level of evidence C	CRT can be useful for patients on GDMT who have LVEF $\leq$35% and are undergoing new device implantation with anticipated ventricular pacing percent of >40. Class IIa Level of evidence C CRT can be useful in patients with AF and LVEF $\leq$35% on GDMT if (1) the patient requires ventricular pacing and (2) AV nodal ablation or rate control allows near 100% ventricular pacing with CRT Class IIa Level of evidence B	Not considered	Not considered

Abbreviations: ACCF, American College of Cardiology Foundation; AF, atrial fibrillation; AHA, American Heart Association; AV, atrioventricular; CRT, cardiac resynchronization therapy; EF, ejection fraction; ESC, European Society of Cardiology; GDMT, guideline directed medical therapy; HF, heart failure; HRS, Heart Rhythm Society; LVEF, left ventricular ejection fraction; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association.
Data from Refs.[3,6,23–26]

Table 8
Indications to implant CRT-P versus CRT-D device in candidates to CRT in the setting of primary prevention of sudden death

Indication	ESC Guidelines on Cardiac Pacing and CRT 2013[6]	ACCF/AHA/HRS Guidelines for Device-based Therapy 2012[3]	ESC Guidelines HF 2012[23]	ACCF/AHA/HRS Guidelines HF 2013[24]	Canadian Cardiovascular Society Guidelines on the Use of CRT 2013[25]	NICE 2014[26]
Factors favoring CRT-D	Life expectancy >1 y, stable HF, NYHA II, ischemic heart disease (low and intermediate MADIT risk score) Lack of comorbidities Class IIa Level of evidence B	All patients without factors favoring CRT-P	Not considered	HF ≥40 d post-myocardial infarction with LVEF <35%, NYHA class II/III symptoms on chronic medical therapy, expected to live >1 y Class I Level of evidence A High risk of nonsudden death, such as frequent hospitalizations, frailty, or severe comorbidities Class IIb Level of evidence B	Patients who are suitable for resynchronization therapy and for an ICD Strong recommendation, high-quality evidence	Patients in NYHA II with: • 120–149 ms with LBBB • ≥150 ms with or without LBBB Patients in NYHA I with: • ≥150 milliseconds with or without LBBB
Factors favoring CRT-P	Advanced HF Severe renal insufficiency or dialysis Other major comorbidities Frailty Cachexia Class IIa Level of evidence B	Elderly patients with important comorbidities	Not considered	Not considered	Patients who are suitable for resynchronization therapy, but not for an ICD Strong recommendation, moderate-quality evidence	Patients in NYHA IV with: • 120–149 ms without LBBB • 120–149 ms with LBBB • ≥150 ms with or without LBBB

Abbreviations: ACCF, American College of Cardiology Foundation; AHA, American Heart Association; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with a defibrillator; CRT-P, cardiac resynchronization therapy with a pacemaker; ESC, European Society of Cardiology; HF, heart failure; HRS, Heart Rhythm Society; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association.

Data from Refs.[3,6,23–26]

2013[24] offer a clinically oriented approach that takes into account comorbidities and patients' profiles before implantation.

BEYOND GUIDELINES: DEFINITION OF APPROPRIATE USE CRITERIA FOR CARDIAC RESYNCHRONIZATION THERAPY

The process of delivering guidelines recommendations is usually responsibility of a committee of well-respected leaders who rigorously review available data from the literature, adding clinical experience and consensus among experts in the field when evidence is lacking (this is the case of level of evidence C recommendations). Because there are many clinical decisions that need to be taken in the absence of trial data, the American College of Cardiology in collaboration with the Heart Rhythm Society recently proposed a different approach: the definition of appropriate use criteria for CRT for prespecified clinical scenarios.[41,42] In detail, a review of common clinical scenarios where ICDs and CRT devices are considered was performed, resulting in coverage of several aspects related to secondary prevention, primary prevention, comorbidities, device replacements, CRT, and other. As a result, 369 clinical scenarios related to use and management of ICDs and CRT devices were developed by a multidisciplinary writing group and scored by an independent technical panel of experts, involved in a modified Delphi exercise, with delivery of scenario-specific scores on a scale of 1 to 9 to designate care that is appropriate (median, 7–9), may be appropriate (median, 4–6), and is rarely appropriate (median, 1–3). The results of this process in terms of final ratings delivered by 17 technical panel members were that 45% of the indications were rated as appropriate, 33% were rated as may be appropriate, and 22% were rated as rarely appropriate. In general, the judgment appropriate was assigned to scenarios for which clinical trial evidence and/or clinical experience was available and supported device implantation.[41]

It is premature to evaluate how much the approach of appropriate use criteria can substantially help physician decision making, also improving the complex process of health care delivery, coverage, and reimbursement. This approach has yet to be proposed in Europe.

FROM GUIDELINES TO "THE REAL WORLD": HETEROGENEITY IN USE OF CARDIAC RESYNCHRONIZATION THERAPY

CRT is an effective treatment, if appropriately targeted, but the process of translating consensus guidelines into "real-world" practice is incomplete. Many data indicate that CRT is underused and there is great heterogeneity in its implementation, both in North America and Europe, with marked variability in implant rates either when cross-country or within country analysis are performed.[43–47]

SUMMARY

Renewed and improved efforts should be dedicated to "synchronize" the competence and expertise of many physicians including cardiologists, electrophysiologists, HF specialists, physicians of cardiac imaging departments, physicians involved in the practice of internal medicine and general practitioners to deliver this effective treatment at the right patient, at the right time and in the appropriate setting.[48] Consensus guidelines are the first step in the complex process of health care delivery, which involves many stakeholders and important policy decisions; only joint efforts can improve appropriate access to effective treatments such as CRT.[29]

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