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

This article has been selected as the month's *JACC: Heart Failure* CME/MOC activity, available online at http://www.acc.org/jacc-journals-cme by selecting the *JACC* Journals CME/MOC tab.

Accreditation and Designation Statement

The American College of Cardiology Foundation (ACCF) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The ACCF designates this Journal-based CME/MOC activity for a maximum of 1 *AMA PRA Category 1 Credit(s)*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Method of Participation and Receipt of CME/MOC Certificate

To obtain credit for JACC: Heart Failure CME/MOC, you must:

- 1. Be an ACC member or JACC subscriber.
- Carefully read the CME/MOC-designated article available online and in this issue of the journal.
- Answer the post-test questions. At least 2 out of the 3 questions provided must be answered correctly to obtain CME/MOC credit.
- 4. Complete a brief evaluation.
- Claim your CME/MOC credit and receive your certificate electronically by following the instructions given at the conclusion of the activity.

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.

CME/MOC Editor Disclosure: Editor-in-Chief Christopher M. O'Connor, MD, has received consultant fees/honoraria from AbbVie, Inc., Actelion Pharmaceuticals Ltd., Bayer, Bristol Myers Squibb, Cardiorentis, Merco & Co., Inc., ResMed, and Roche Diagnostics; and ownership interest in Biscardia, LLC. Executive Editor Mona Fiuzat, PharmD, has received research support from ResMed, Gilead, Critical Diagnostics, Otsuka, and Roche Diagnostics. Tariq Ahmad, MD, MPH, has received a travel scholarship from Thoratec. Abhinav Sharma, MD, has received support from Bayer-Canadian Cardiovascular Society, Alberta Innovates Health Solution, Roche Diagnostics, and Takeda. Mitchell Psotka, MD, PhD, and Kishan Parikh, MD, have no relationships relevant to the contents of this paper to disclose.

Author Disclosures: 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 Astrazeneca, Swedish Heart-Lung Foundation, and the Stockholm County Council. Dr. Singh is a consultant for Impulse Dynamics and Respicardia.

Medium of Participation: Print (article only); online (article and quiz).

CME/MOC Term of Approval

Issue date: April 2018 Expiration date: March 31, 2019

Manuscript received September 12, 2017; revised manuscript received December 18, 2017, accepted January 23, 2018.

From the ^aCardiology Department, Stavanger University Hospital, Stavanger, Norway; ^bInstitute of Internal Medicine, University of Bergen, Bergen, Norway; ^cDepartment of Cardiology, Karolinska University Hospital, and Karolinska Institutet Stockholm, Stockholm, Sweden; and the ^dDivision 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.

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.

he 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

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CRT = cardiac resynchronization therapy

CRT-D = cardiac resynchronization therapy-defibrillator

CRT-P = cardiac resynchronization therapypacemaker

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).

h 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 Decent International Guidelines on CDT Implantation Recommendations and Indications				
TABLE 1 Recent International Guidelines on CR1 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 \geq 120 ms and in those with non-LBBB, if the QRS duration is \geq 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 \geq 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 \geq 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	lla, B	lla, B	lla, B	lla, B
CCS (2017)	I, High	I, High	I, High	I, High	III, Moderate	III, Moderate
Australian Guidelines (2011)	А		А		А	
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.

TABLE 3 Comparison of Recommendations for 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	lla, B	IIb, B	IIb, B	III, A	III, A
ESC EHRA (2013)	lla, B	lla, B	IIb, B	IIb, B	IIb, B	IIb, B
ACC/AHA/HRS (2013)	lla, A	IIb, B	IIb, B	III, B	IIb, B	III, B
CCS (2017)	IIb, Low	llb, Low			III, Moderate	III, Moderate
Australian Guidelines (2011)	А		А		А	
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, MIRA-CLE, 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

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)	lla, B	I, A		
ESC EHRA (2013)	lla, B	lla, B		
ACC/AHA/HRS (2013)	lla, B	lla, C		
CCS (2017) IIb, Low IIb, Moderate				
Values are Class of Recommendation, Level of Evidence.				

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.

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 $\geq\!\!150$ 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 \leq 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 1. 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

functional class I patients if they do not have LBBB and a QRS \leq 150 ms, providing this indication with a Class III recommendation. NICE guidelines recommend implantation in patients with a QRS \geq 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 GRS. 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, 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.

REFERENCES

1. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344: 873-80.

2. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845-53.

3. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity

and mortality in heart failure. N Engl J Med 2005; 352:1539-49.

4. Linde C, Abraham WT, Gold MR, et al. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834-43.

5. Moss AJ, Hall WJ, Cannom DS, et al. Cardiacresynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361: 1329-38.

6. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-tomoderate heart failure. N Engl J Med 2010; 363:2385-95.

7. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.

Normand et al.

CRT Indications

8. Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2013;62: e6–75.

9. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2016;68:1476-88.

10. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/ AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017; 70:776–803.

11. Heart Failure Society of America, Lindenfeld J, Albert NM, et al. HFSA 2010 comprehensive heart failure practice guideline. J Cardiac Fail 2010;16: e1–194.

12. Stevenson WG, Hernandez AF, Carson PE, et al. Indications for cardiac resynchronization therapy: 2011 update from the Heart Failure Society of America Guideline Committee. J Card Fail 2012;18: 94–106.

13. Linde C, Ellenbogen K, McAlister FA. Cardiac resynchronization therapy (CRT): clinical trials, guidelines, and target populations. Heart Rhythm 2012;9:S3–13.

14. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281–329.

15. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;18:891–975.

16. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the management of heart failure. Can J Cardiol 2017;33: 1342-433.

17. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles

and summary of findings tables. J Clin Epidemiol 2011;64:383-94.

18. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. Am J Clin Nutr 1998;68: 899-917.

 Ruschitzka F, Abraham WT, Singh JP, et al. Cardiacresynchronization therapy in heart failure with a narrow QRS complex. N Engl J Med 2013;369:1395–405.

20. Krum H, Jelinek MV, Stewart S, et al. 2011 update to National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. Med J Aust 2011;194:405-9.

21. Zareba W, Klein H, Cygankiewicz I, et al. Effectiveness of cardiac resynchronization therapy by QRS morphology in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Circulation 2011;123:1061–72.

22. Gold MR, Thebault C, Linde C, et al. Effect of QRS duration and morphology on cardiac resynchronization therapy outcomes in mild heart failure: results from the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study. Circulation 2012;126:822-9.

23. Cleland JG, Abraham WT, Linde C, et al. An individual patient meta-analysis of five randomized trials assessing the effects of cardiac resynchronization therapy on morbidity and mortality in patients with symptomatic heart failure. Eur Heart J 2013;34:3547-56.

24. Leclercq C, Walker S, Linde C, et al. Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J 2002;23:1780-7.

25. Brignole M, Botto G, Mont L, et al. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. Eur Heart J 2011;32:2420–9.

26. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91: 2D-8D.

27. Gasparini M, Auricchio A, Regoli F, et al. Fouryear efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. J Am Coll Cardiol 2006;48:734-43.

28. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. N Engl J Med 2013;368: 1585-93.

29. Sharma AD, Rizo-Patron C, Hallstrom AP, et al. Percent right ventricular pacing predicts outcomes in the DAVID trial. Heart Rhythm 2005; 2:830-4.

30. Tops LF, Schalij MJ, Bax JJ. The effects of right ventricular apical pacing on ventricular function and dyssynchrony implications for therapy. J Am Coll Cardiol 2009;54:764-76.

31. Tops LF, Schalij MJ, Holman ER, van Erven L, van der Wall EE, Bax JJ. Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. J Am Coll Cardiol 2006;48: 1642-8.

32. Thibault B, Harel F, Ducharme A, et al. Cardiac resynchronization therapy in patients with heart failure and a QRS complex <120 milliseconds: the Evaluation of Resynchronization Therapy for Heart Failure (LESSER-EARTH) trial. Circulation 2013; 127:873-81.

33. Sohaib SM, Finegold JA, Nijjer SS, et al. Opportunity to increase life span in narrow QRS cardiac resynchronization therapy recipients by deactivating ventricular pacing: evidence from randomized controlled trials. J Am Coll Cardiol HF 2015;3:327-36.

34. Shah RM, Patel D, Molnar J, Ellenbogen KA, Koneru JN. Cardiac-resynchronization therapy in patients with systolic heart failure and QRS width </=130 ms: insights from a meta-analysis. Europace 2015;17:267-73.

35. Dickstein K, Normand C, Auricchio A, et al. 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? European journal of heart failure 2018 Feb 19 [E-pub ahead of print].

36. Gage RM, Burns KV, Bank AJ. Echocardiographic and clinical response to cardiac resynchronization therapy in heart failure patients with and without previous right ventricular pacing. Eur J Heart Fail 2014;16:1199-205.

37. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2013;62:1495-539.

38. National Institute for Health and Care Excellence (2014). Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure. NICE guideline (TA314). Available at: https://www.nice.org.uk/ guidance/ta314. Accessed February 12, 2018.

KEY WORDS CRT, guidelines, heart failure

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

