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POSITION PAPER

Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care

A joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology

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Cardiac resynchronization therapy (CRT) is one of the most effective therapies for heart failure with reduced ejection fraction and leads to improved quality of life, reductions in heart failure hospitalization rates and all-cause mortality. Nevertheless, up to two-thirds of eligible patients are not referred for CRT. Furthermore, post-implantation follow-up is often fragmented and suboptimal, hampering the potential maximal treatment effect. This joint position statement from three European Society of Cardiology Associations, Heart Failure Association (HFA), European Heart Rhythm Association (EHRA) and European Association of Cardiovascular Imaging (EACVI),

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focuses on optimized implementation of CRT. We offer theoretical and practical strategies to achieve more comprehensive CRT referral and post-procedural care by focusing on four actionable domains: (i) overcoming CRT underutilization, (ii) better understanding of pre-implant characteristics, (iii) abandoning the term 'non-response' and replacing this by the concept of disease modification, and (iv) implementing a dedicated post-implant CRT care pathway.

Keywords Cardiac resynchronization therapy • Response • Heart failure • Implementation • Utilization • Care pathways • Disease modification • Disease management • Outcome

Introduction

Cardiac resynchronization therapy (CRT) is one of the most effective therapies for heart failure with reduced ejection fraction (HFrEF) resulting in improved quality of life, beneficial reverse remodelling and reductions in heart failure hospitalization rates and all-cause mortality.[1–7] Despite its well established clinical benefits and cost-effectiveness, it remains a widely underutilized treatment option; recent European data suggest only one in three eligible patients actually receives a CRT device.[8] In contrast, the topic of 'non-response' to CRT ('failure to improve') has received disproportionally large research attention, with rates of non-response reported in 30% of implanted patients.[9] A binary definition of 'response' classified by arbitrary magnitudes of improvements in a variety of variables of questionable clinical significance underestimates the true benefits of CRT reported in the randomized clinical trials. This is in contrast with the message from all randomized controlled CRT trials in HFrEF patients with a QRS >130 ms, which consistently show a spectrum of stabilization or improvement of disease progression to even recovery of the disease.[10,11] Moreover, in addition to this 'failure to refer', optimization of both the device and the care of the patient following implant is hampered by a lack of integration of cardiological and non-specialist care, leading to suboptimal and variable post-implant management.[12,13] As a result, many heart failure patients are not exposed to the full potential benefit of CRT. This position paper aims to improve the implementation of CRT and follow-up of patients with CRT, by addressing the following topics: (i) underutilization of CRT, (ii) redefining response as disease modification of heart failure, (iii) better understanding of pre-implant patient characteristics, and (iv) integration and optimization of post-implant CRT care.

Action plan for referral and optimization of cardiac resynchronization therapy-related care

Action I: Overcome the underutilization of cardiac resynchronization therapy

Eligibility vs. actual implantation

Observational data indicate that 35% to 40% of patients with HFrEF have a prolonged QRS width (classically defined as QRS >120 ms) and 20–30% of HFrEF patients have left bundle branch block (LBBB).[14,15] Since a considerable proportion of HFrEF patients do not tolerate or improve after other heart failure therapies have been introduced, ultimately 5–10% of all heart failure patients remain eligible for CRT. As such, estimates using eligibility criteria as stated in professional practice guidelines (QRS >130 ms) suggest that up to 400 patients per million inhabitants of European countries might be candidates for CRT implantation annually.[16,17] Between 2005 and 2013, European and US guideline indications have expanded to also include patients with less severe symptoms [New York Heart Association ((NYHA) class II], and in 2016 the guidelines tightened the proportion of patients eligible to CRT by prolonging the QRS duration and altering the morphology criteria.[18] Data from the European Heart Rhythm Association (EHRA) White Book indicate that within the European Union between 2010 and 2013 the average implantation rate varied between 106–123 per million inhabitants,[8] and more recent data from device registries reported a rate of 56 CRT pacemaker (CRT-P) and 119 CRT defibrillator (CRT-D) implants per million inhabitants in 2018 in Europe, with a slight increase of mainly CRT-P over recent years (*Figure 1*). Although significant geographical differences are clearly present, these data suggest that up to two thirds of those eligible for CRT on current guidelines are not implanted. Registry data provide some insights into factors associated with the non-referral of CRT, indicating that older age (>75 years), lack of CRT implant centres, shorter duration of heart failure, absence of a heart failure nurse and non-cardiology follow-up are factors that are independently associated with non-delivery of CRT.[19] One key issue is that many patients with heart failure including those eligible for CRT are managed in primary or non-specialist care where there is possibly less familiarity with the indications and benefits of CRT.[17] This lack of awareness is also illustrated in the recent European Society of Cardiology (ESC) CRT Survey II, which highlighted that most of those implanted had been identified within the cardiology department. Only a minority had been referred from other departments, including primary care.[20] Moreover, despite the well-established benefit of CRT in women, CRT remains underused in female patients. This gender gap has remained unchanged in Europe over the past 10 years with female CRT patients representing only 27% and 24% of all implants in the ESC CRT Survey I and II, respectively.

Guidelines vs. registries

Professional practice guidelines have formulated recommendations for CRT in HFrEF patients based upon morbidity and mortality

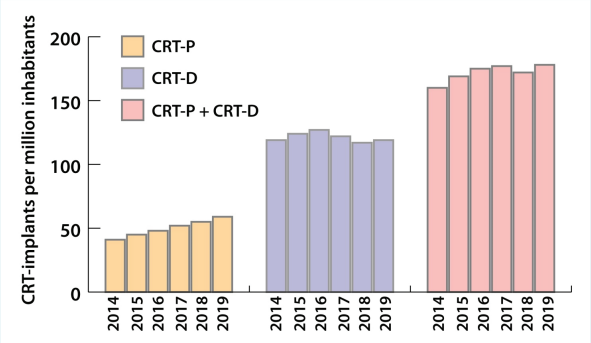

Figure 1 Cardiac resynchronization therapy pacemaker (CRT-P) and cardiac resynchronization therapy defibrillator (CRT-D) implants in Europe between 2014 and 2019. Source: https://www.medtecheurope.org/.

reductions.[12,21–24] Guidelines offer a strong level of recommendation for patients in sinus rhythm, a wide QRS duration or LBBB. Data from the EuroCRT Survey II indicates that 67% of implanted patients had a class I indication, with 26% having a class IIa indication, 5% a class IIb indication and 2% a class III indication. It would appear that while CRT is globally underused, in clinical practice CRT is frequently offered to patients in whom the level of evidence is either less robust than a class I indication or non-existent.[25]

Health economic considerations

Implantable devices such as CRT are often approached with scrutiny by health care regulating agencies and payers, due to their significant up-front cost and the fact that they are implanted in a patient population (if left untreated) with a relatively limited life expectancy. The cost of any intervention needs to balance the willingness to pay, which is typically reflected in the incremental cost-effectiveness ratio (ICER). This is expressed as the amount of money which has to be spent to gain a quality-adjusted life-year (QALY). A Markov model with Monte-Carlo simulation from the CARE-HF and COMPANION trials indicates an ICER of €7538 for CRT-P and €18 017 for CRT-D, which is below the generally accepted thresholds for cost-effectiveness (€30 000–40 000 or gross domestic product (GDP) per capita) in high income countries.[26] In the REVERSE trial focusing on NYHA class II patients, CRT was linked to 0.94 life years or 0.80 QALYs at an additional cost of €11 455, yielding an ICER of €14 278 per QALY gained.[27] Despite the additional up-front cost of a CRT-D device in comparison to a CRT-P device, it is still within the accepted cost-effectiveness boundaries for the USA and Europe.[27,28] Data from the EHRA White Book indicate lower utilization of CRT in European countries with a lower GDP per capita,[8] suggesting that supportive guidelines aiding appropriate selection between CRT-P vs. CRT-D in lower GDP countries might help to increase CRT implant rates in these areas.

Strategies to overcome the underutilization of cardiac resynchronization therapy

Since one of the barriers to implantation is referral, improved strategies to identify potential eligible CRT candidates by cardiologists and non-cardiologists are urgently needed.[20] Importantly, electrocardiogram surveillance in heart failure patients is warranted as abnormalities (which often change over time) not only provide information on aetiology, but they also help to identify appropriate therapy. Furthermore, thorough and repeated education within primary and secondary care (including cardiologists less familiar with devices) about CRT, and openly addressing deeply-rooted myths that contribute to non-referral may improve CRT implementation (*Table 1*). Finally, deeper engagement with patient associations or support groups could improve the dissemination of information about therapeutic options. Screening through automated alerts in electronic health records based on information from QRS duration, left ventricular (LV) function and heart failure status might trigger more actionable referrals. Given the expansion of electronic health records, screening for patients eligible for optimization of heart failure therapy including CRT might be effective as it has been for other treatments for heart failure.[18,29]

Action II: Replace 'response to cardiac resynchronization therapy' by 'disease modification by cardiac resynchronization therapy'

Due to the up-front cost, life-long presence of the device, and potential device- and procedure-related complications, decisions for device-based interventions are often delayed until all other non-device-based therapies have 'failed'.[30] This situation is exacerbated by the unique and widespread concept of 'non-response' where, based upon arbitrary cut-offs of remodelling (most often LV end-systolic volume reduction of >15%) or symptomatic 'improvement', it has been suggested that one in three patients do not 'respond' to CRT. As a result of these factors, CRT has been approached with an unprecedented scrutiny despite its firmly established benefits on morbidity and mortality in patients with heart failure and a wide QRS (>130 ms).[31,32] This situation is especially worrisome since no consensus exists on how or when to measure response to CRT and what magnitude of change constitutes response.[33] Adding to the confusion is a long list of potential 'predictors of response' of which many are based upon results of observational studies, which, due to a lack of control data, cannot conclusively determine the relation between the predictor and the clinical outcome benefit (risk reduction) from CRT.

Response parameters, agreement and timing

Numerous variables including functional, event-based, imaging or composite outcomes have been used to describe response to CRT.[12] The importance of certain metrics might also differ according to the stakeholders, such as patients, their carers, doctors, payers, or industry. The placebo effect of an implant on functional outcomes is also often underestimated as noted after implantation

Table 1 Myths and strategies for better implementation

Common myths of CRT	Explanation
Myths related to the pre-implant phase of CRT	
30% of patients do not respond to CRT	CRT response has been classified by arbitrary definitions: its effect in any one individual should be seen as continuous disease modification and whilst they may not feel 'better', they are highly likely to be 'better than without the device'.
Patients with an ischaemic aetiology of heart failure benefit less from CRT	On average, patients with an ischaemic aetiology of heart failure manifest less reverse remodelling but have an equal relative risk reduction after CRT for heart failure admission and death as the non-ischaemic group.
If the QRS is narrow, patients will never have an indication for CRT	In patients with HFrEF, remodelling of the left ventricle is accompanied by electrical remodelling such that QRS duration lengthens. Follow-up ECG is necessary. Consideration should be given to those with poor LVEF and a pacing indication that will lead to high proportion of RV pacing.
CRT is an expensive therapy	CRT is a cost-effective heart failure therapy.
Consideration of CRT should only occur after repeated (failed) attempts to achieve guideline-recommended doses of RAASi and beta-blockers	Only a minority of patients included in CRT trials were on optimal doses of RAASi and beta-blockers, and the effects of these drugs on LVEF improvement are far less pronounced in LBBB than in narrow QRS. CRT can help achieve guideline-recommended doses.
Patients with multiple comorbidities derive no benefit of CRT	Patients with comorbidities derive significant benefit from CRT, especially when the comorbidities are addressed. The need for CRT-D should be dealt with openly in this population.
All patients should receive CRT-D	The benefit of the ICD is determined by the risk of sudden cardiac death over the risk of non-sudden cardiac death. Those at highest risk of heart failure death derive no benefit from an ICD.
Physicians know when to refer patients for CRT	Most patients are only referred within cardiology. The non-cardiology medical and allied health community and patients need education to improve referral.
Echocardiography should be used as a technique to select patients that will not respond to CRT	Echocardiography is poor at determining 'need' or 'response' to CRT. Patients should not be denied CRT based upon echocardiography.
Access to CRT is not an issue as CRT implantation can be done by everyone who can implant a DDD pacemaker	CRT implant does have a higher risk, and does require more training than conventional DDD pacemakers. Efforts should be made to increase access.
Myths related to the post-implant phase of CRT	
Optimization of CRT is only needed in non-responders	Ideally, all CRT patients should receive regular review of their heart failure therapy, which should include a review of medical treatment (including drug doses) and device programming. Not only is heart failure a progressive disease, such that adjustments can be of benefit, but recent and future developments in medical therapy should be applied to this group as rapidly as possible.
Patients on CRT are on optimal medical therapy	Only a minority are on optimal dosages of GDMT at the moment of implant, more than 60% can be further up-titrated after CRT
Out of the box device programming suffices in most CRT patients	All CRT patients should receive regular (at least annual) device checks and might need optimization of device settings (brady/tachy) by physicians specifically trained in cardiac device programming and troubleshooting.
Remote monitoring is not useful	Comprehensive remote monitoring including device/lead integrity, % of biventricular pacing and arrhythmias in CRT patients has been demonstrated to improve clinical outcome in at least one randomized trial with tightly controlled review and action systems in place. Regular device checks (at least once per year) remain important in patients undergoing remote monitoring.

CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; ECG, electrocardiogram; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; RAASi, renin–angiotensin–aldosterone system inhibitor; RV, right ventricular.

during the run-in phase before LV only pacing was switched on in the GREATER-EARTH study.[34] Moreover, the agreement between outcomes is remarkably poor. It is well recognized that resting LV function is poorly related to exercise capacity or symptoms,[35] so it is not surprising that LV reverse remodelling poorly relates to the degree of functional improvement in many studies.[36–38] Indeed, the size and shape of the ventricle is irrelevant for patients complaining of exercise intolerance. Yet, LV reverse remodelling remains a commonly used endpoint, largely based upon the close relationship between changes in LV structure and outcomes.[39] However, these data have been over interpreted to imply that patients without significant LV reverse remodelling (e.g. LV end-systolic volume reduction >15%), derive no benefit from CRT whereas up to 30% of patients lacking remodelling benefits *will* experience an improvement in symptoms. Importantly, even patients who fail to demonstrate reverse remodelling and require a heart failure admission, still derive haemodynamic benefit from their device, as they often deteriorate when biventricular pacing is temporarily stopped.[40] Finally, the REVERSE trial showed a continuous reduction of both LV systolic and diastolic volumes for at least up to 2 years after CRT, which questions the appropriateness of any point-in-time assessment of therapy efficacy.[41]

Baseline variables suggested to predict outcome following cardiac resynchronization therapy

In addition to the difficulty of timing, magnitude, congruity and outcome in assessing 'response', there is a plethora of pre-implantation features that are associated with certain response parameters and often wrongly drive decisions on implantation. Commonly quoted features predicting less LV reverse remodelling in observational studies include male sex, ischaemic aetiology, high LV volumes, low glomerular filtration rate, and absence of mechanical dyssynchrony.[42–46] In contrast, post-hoc analyses of the major CRT trials powered for mortality and morbidity (CARE-HF, RAFT, COMPANION and MADIT-CRT) revealed no heterogeneity between these aforementioned baseline characteristics and benefits on mortality or heart failure admission. Therefore, these subgroups gain similar relative risk reduction with CRT despite lesser degrees of LV reverse remodelling, and should not be used to de-select patients from receiving CRT.[3,4,6,47] More importantly, these patients often have a high risk for heart failure admission and mortality (baseline event rate) and might actually therefore have a higher absolute risk reduction after CRT. None of the studies have shown an adverse effect of CRT in patients with a QRS width >130 ms, especially in the LBBB population.[48,49] Finally, in the recent ADVANCE-CRT registry, patients labelled as responders, were less likely to have their therapy optimized following CRT implant,[13] suggesting that there are risks from suboptimal care delivery if someone is actually labelled a responder.

Removing the term 'response'

Apart from rare isolated situations, heart failure is incurable. CRT is therefore not a curative therapy but rather should be seen as a treatment to ameliorate the contribution of electromechanical dyssynchrony to the heart failure syndrome in the hope that this will ultimately reduce heart failure-related morbidity and mortality. A slowing of a progressive disease is a positive outcome (*Figure 2*). Despite frequently quoted parallels between heart failure and cancer, the important concepts of 'remission' and 'non-progression' seem not to have permeated to cardiology. Therefore, this position statement calls to stop the current binary approach of CRT response, but rather we suggest that CRT should be classified as a treatment for 'disease modification'. One step towards such an approach is the Packer hierarchical scoring system which takes into account (lack of) mortality, (lack of) hospital admission for heart failure and stable functional status (without additional diuretic therapy), where lack of deterioration and therefore 'stability' is seen as a positive outcome (online supplementary *Figure S1*).[50] Furthermore, it needs to be underscored that if CRT is being implanted in HFrEF patients with a QRS width >130 ms (especially in the presence of LBBB), there is no proven patient population that experiences a negative response to CRT.[10]

Action III: Better clinical interpretation of pre-implant characteristics

Patient selection

European and American guidelines give a class I recommendation for CRT in symptomatic HFrEF patients in sinus rhythm with wide QRS (online supplementary *Table S1*).[23,24,51] The EchoCRT and RethinQ trials showed that the benefit of CRT does not extend to patients with a narrow QRS, even in the presence of some echocardiographic characteristics indicative of LV mechanical dyssynchrony.[48,49] The 2016 Heart Failure Association (HFA) guidelines reflect these data and do not recommend CRT in patients with a narrow QRS, defined as QRS <130 ms (class of recommendation III, level of evidence A).[48,49] The observation that QRS duration is dependent on body/heart size has resulted in ongoing research to determine if QRS duration should be individualized.[52–54]

Guidelines recommend the presence of LV ejection fraction (LVEF) <35%, as this was a major inclusion criterion in most CRT trials.[23,24,51] However, there is reason to believe that CRT may be effective in the higher range of reduced LVEF from both the MADIT-CRT and REVERSE trial.[55] For example, a core lab assessment of baseline LVEF from the MADIT-CRT trial indicated that 38% of patients actually had a LVEF above the entry criteria cut-off, with LVEFs up to 45%.[56] These patients had similar benefit in terms of death and heart failure hospitalization, and might also have a greater degree of reverse remodelling. This, together with the standard error of the measurement of LVEF by echocardiography, should be taken into account when determining eligibility based upon LVEF.

It is well acknowledged that visible pre-implant mechanical dyssynchrony (apical rocking, septal flash) is associated with an acute haemodynamic improvement following CRT.[57,58] However, using mechanical dyssynchrony for the selection of CRT does not select patients more likely to gain benefit.[48,49,59] As such, the absence of pre-implant mechanical dyssynchrony should not defer the implantation of a CRT device in patients with a guideline indication. Other imaging techniques or echocardiographic parameters

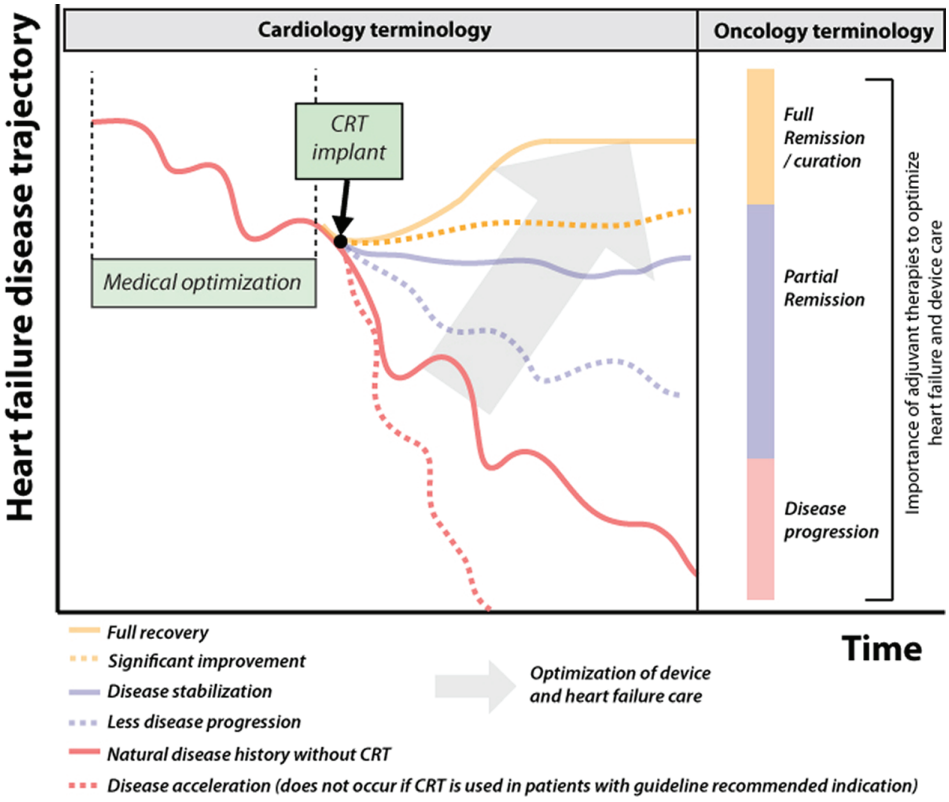

Figure 2 Role of cardiac resynchronization therapy (CRT) in disease modification of the heart failure disease trajectory. The grey arrow indicates the role of auxiliary heart failure optimization following CRT implant.

have not been used to guide treatment in the randomized controlled trials, and should therefore not be used for the *de-selection* of patients otherwise eligible. That is not to say, however, that pre-implant imaging is not required. For instance, pre-implant magnetic resonance imaging is useful in the assessment of the risk for sudden cardiac death (SCD) (e.g. mid-wall fibrosis), and might therefore be helpful in determining the choice between CRT-P vs. CRT-D.[60,61] Additionally, echocardiography remains an indispensable tool to detect disease progression following CRT, and the mechanism(s) related to ongoing disease following implant, which might be amenable for auxiliary therapies (e.g. residual functional mitral regurgitation amenable for mitral edge-to-edge repair).[62,63]

Guidelines state a IIa indication for CRT in patients with atrial fibrillation (AF), despite the fact that only 262 patients with AF were randomized in the original CRT trials, which indicates that there is virtually no randomized trial data on CRT in AF patients. The RAFT trial randomized patients to an ICD vs. CRT-D stratified by the presence of permanent AF. In AF patients, there was only a trend towards fewer heart failure hospitalization in CRT-treated patients, and the primary outcome of death or heart failure hospitalization between those assigned to ICD vs. CRT-D was similar.[64] Despite this limited trial evidence, up to 26% of patients enrolled into the EuroCRT Survey II had AF.[20] Furthermore guidelines state that a pre-requisite for CRT to work in AF is a strategy to ensure biventricular capture is in place.[23,24,51] Observational data indicate that AF with rapid conduction is the leading reason for loss of biventricular pacing.[65,66] Furthermore, observational studies relate a low percentage of biventricular pacing to poor outcome. Although this is often interpreted that a strategy that ensures 100% of biventricular pacing results in better prognosis, it needs to pointed out that the phenotype of patients that suffer from low percentages of biventricular pacing might be sicker. This could partially explain the observed relation between biventricular pacing percentages and outcome. Indeed to date, no randomized trial study has proven that a higher number of biventricular pacing is better than a lower percentage of biventricular pacing.

Device-based features have been designed to attain higher percentages of biventricular pacing through fusion pacing [right ventricular (RV) sense will result in LV pacing], but should not be an alternative to optimal medical therapy, pulmonary vein isolation or atrio-ventricular (AV) junction ablation to ensure effective CRT in AF. Gasparini *et al.*[67] demonstrated in a small prospective study that CRT patients in permanent AF, only had improvement in LV function and functional capacity if AV junction ablation was performed. Furthermore, AV junction ablation has been associated with a reduced incidence of inappropriate ICD interventions.[68] The use of AV junction ablation in clinical practice is variable, but should be considered if pharmacologic therapies fail to result in

adequate percentage (target of >90–95%) of biventricular pacing. The current position paper recognizes the scarce data of CRT in AF. Nevertheless, despite the lack of large randomized clinical trials, guidelines as well as this position statement still recommend the use of CRT in permanent AF patients with similar indications as for patients in sinus rhythm, provided that AV junction ablation (or pulmonary vein isolation if indicated) is added in those with incomplete (<90–95%) biventricular pacing.[66,69,70] In addition, other causes for incomplete biventricular pacing such as premature ventricular beats might need to be treated as well. RAFT-PermAF (NCT01994252), which investigates whether CRT reduces heart size in CRT patients with permanent AF, is currently ongoing.

Next to selected patients in sinus rhythm and AF, guidelines recommend CRT in HFrEF patients with a classic pacing indication who are expected to receive a high burden of RV pacing (IA recommendation) or patients with a classic pacemaker or ICD who develop heart failure (IIa recommendation for upgrade).[23,24,51] In the EuroCRT II Survey, 23% of the entire CRT population were upgrades.[20] The American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines underscore that a high burden (e.g. >40%) of RV pacing is a prerequisite for benefit of an upgrade.[21] Few data are available from clinical trials. CRT was superior to conventional RV pacing in patients in sinus rhythm with AV block and LV systolic dysfunction in the BLOCK-HF trial.[71] Additionally, reduced clinical manifestations of heart failure were noted with CRT pacing compared to RV pacing in heart failure patients with symptomatic permanent AF who underwent AV junction ablation in the APAF trial.[72] Given the incremental risk of device upgrade or risk of pacemaker dependency after AV junction ablation, the benefits and risks should be assessed individually given the rather low level of evidence. The ongoing BUDAPEST-CRT trial (NCT02270840) will determine the effects of upgrade from an ICD to a CRT-D in symptomatic HFrEF patients with RV pacing (>20%).[73]

Guideline-directed medical therapy

The evidence for CRT lies with HFrEF patients with residual symptoms and a persistently reduced LVEF despite optimal background treatment with neurohormonal blockers. However, only a minority of patients implanted with CRT are on maximal guideline-recommended doses of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (30%) and beta-blockers (20%) before CRT.[74] Although this might be the result of inertia in care, patients might not be able to tolerate higher doses due bradycardia and hypotension. While patients with HFrEF and narrow QRS often exhibit significant reverse remodelling to medical therapy, patients with HFrEF and LBBB seem to reverse remodel less following initiation of neurohormonal blockers.[75] For example, in one study, patients with LBBB experienced an improvement in LVEF of 2% whereas those with a narrow QRS had an increase of 8% after 6 months of medical therapy, which might be the result of differential expression of contractile genes in those with electromechanical dyssynchrony.[75,76] Therefore, this position statement from HFA, EHRA and European Association of Cardiovascular Imaging (EACVI) encourages clinicians not to postpone CRT implant too long, particularly in patients with LBBB and a QRS duration >150 ms.

Role of comorbidities

Comorbidities are frequent in heart failure and affect the delivery and effect of heart failure therapy, functional status, and clinical outcomes.[77–80] Due to this competing risk patients with comorbidities derive less benefit from an ICD (see next section). However, an elegant analysis from the MADIT-CRT trial demonstrated that this was not the case for CRT, where the relative reduction in morbidity and mortality was consistent.[81] Hence, patients with comorbidities should not be denied CRT, although appropriate assessment of potential benefit of the combination of CRT with ICD therapy is particularly important in this population.[82]

Certain comorbidities are of particular interest in CRT candidates as they might influence the success of the implantation procedure, choice between CRT-P vs. CRT-D, symptomatic improvement, and reverse remodelling response after implant.[12] Although a history of valve replacement might make LV lead placement more challenging, it is not associated with less benefit from CRT.[83,84] Furthermore, while renal disease was an exclusion criteria in the major CRT trials and early observational data suggested less reverse remodelling in patients with chronic kidney disease stage IV and V,[1,3–6,47] more recent data indicate that patients with chronic kidney disease derive similar mortality benefit from lesser reverse remodelling.[31,45] Iron deficiency, which is common in CRT recipients (around 55%), might be associated with less functional improvement and less reverse remodelling following CRT,[85] possibly due to the role of iron as an essential co-factor for protein synthesis and normal cell functioning.[86]

In conclusion, CRT selection and optimization must occur in the context of other heart failure interventions and other comorbidities. With a growing heart failure treatment armamentarium, this is becoming increasingly challenging for the cardiologist, highlighting the need for early referral to a heart failure management team.[18,29]

Cardiac resynchronization therapy pacemaker vs. cardiac resynchronization therapy defibrillator: individualizing choice

In order to derive maximal benefit from an ICD, patients need to have a high risk of dying from SCD mediated by ventricular arrhythmias, and a low risk of dying from other causes (non-SCD-mediated death).[87–89] This balance should be taken into account prior to device implantation (*Figure 3*). For example, large areas of scar and an ischaemic aetiology of heart failure or a high burden of non-sustained ventricular tachyarrhythmias (NSVTs) on Holter monitoring are associated with a higher risk of SCD.[60,90–94] Monitored SCD in patients with a CRT-P device is often pre-dated by an increasing burden of NSVTs, suggesting a role for remote monitoring to detect patients who might benefit from upgrade to a CRT-D.[95] On the other hand, women have a lower risk of SCD,[96] and data from the DANISH trial illustrate that a strategy for routine primary prevention ICD for patients with a non-ischaemic aetiology does not improve overall long-term survival.[97] This is in

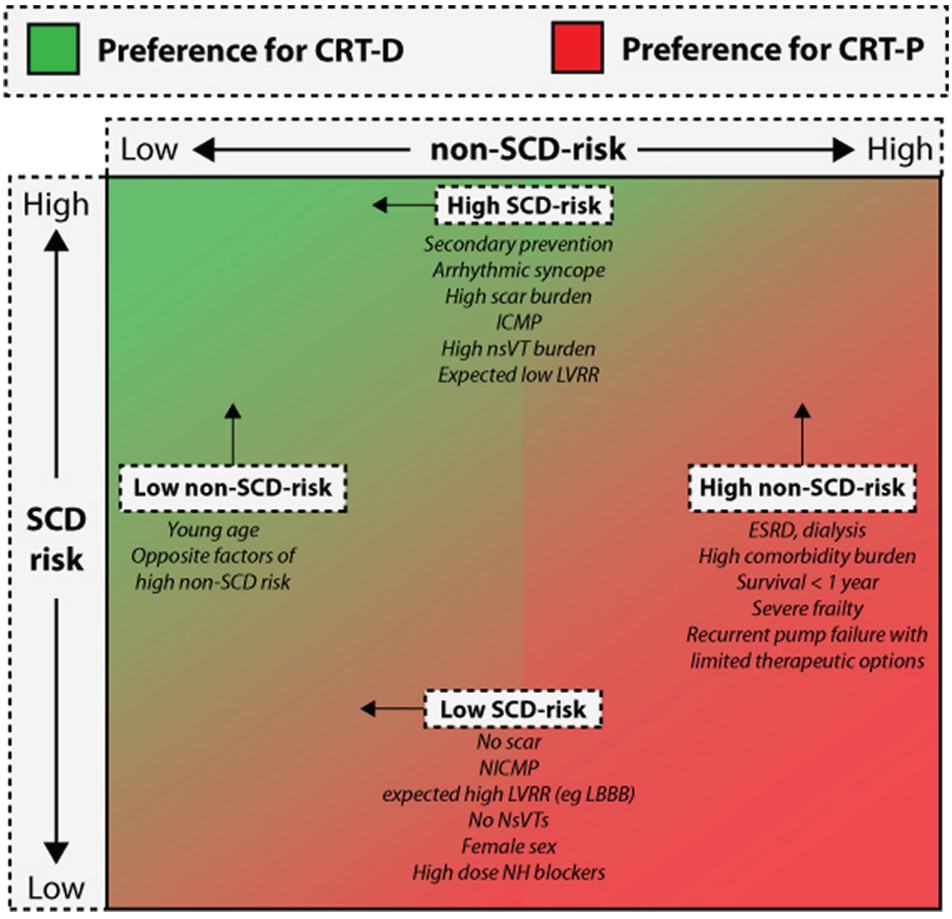

Figure 3 Conceptual framework for individualizing of prescription of cardiac resynchronization therapy pacemaker (CRT-P) vs. cardiac resynchronization therapy defibrillator (CRT-D). Framework for individualizing CRT-P vs. CRT-D to help patients who have not opted to avoid an implantable cardioverter-defibrillator. Red indicates preference for CRT-P and green indicates preference for CRT-D. Balancing of choice is made by evaluating risk for sudden cardiac death (SCD) (yellow factors, with dark yellow indicating high SCD risk and light yellow indicating SCD risk) and the risk for non-SCD depicted in blue (dark blue indicates high risk for non-SCD and light blue indicates low risk for non-SCD). ESRD, end-stage renal disease; ICMP, ischaemic cardiomyopathy; LBBB, left bundle branch block; LVRR, left ventricular reverse remodelling; NH, neurohormonal; NICMP, non-ischaemic cardiomyopathy; nsVT, non-sustained ventricular tachycardia

line with other studies indicating that the risk for SCD is intrinsically lower in patients with a non-ischaemic aetiology of heart failure.[98] Notably, there was an age-by-therapy interaction in DANISH suggesting that younger patients (possibly those younger than 70 years) have a greater chance of benefiting from ICD implantation than older patients probably because of lower competing risk from comorbidities and the higher duration of exposure to the risk of SCD, which is reflected in the lower rate of SCD and all-cause mortality.[99–101] Finally, accurate estimation of the risk of life-threatening ventricular tachyarrhythmias by risk calculators in patients with underlying genetic mutations (i.e. LMNA mutations) helps to select candidates for ICD implantation.[102] CRT-D comes at higher cost and carries the risk of inappropriate therapy[103] and all post-hoc analyses including a Bayesian network analysis suggest equivalence between the two approaches but the randomized controlled trials also point at a favourable effect of CRT alone on the risk of sudden death. For example, the CARE-HF and REVERSE trials indicate that resynchronization therapy, and its potential to increase beta-blocking agents, diminishes ventricular tachycardia/fibrillation (VT/VF), especially in patients with extensive LV reverse remodelling,[104] possibly due to diminished electrical dispersion, early after depolarization and other cellular substrates for VT/VF.[105–107] Therefore, although factors associated with greater reverse remodelling following CRT, such as LBBB morphology, long QRS duration, female sex and non-ischaemic aetiology should not be used to select candidates for CRT, they could be considered in the decision to offer CRT-P over CRT-D (*Figure 3*). Advanced cardiac imaging technologies including assessment of conduction channels by cardiac resonance imaging and possibly radiomics may further help in individualizing risk of VT/VF in the future. Additional clinical factors favouring the use of CRT-P could include advanced age, more severe symptoms (NYHA class III/IV), and life-shortening

comorbidity (e.g. severe lung disease or Stage IV chronic kidney disease). Nevertheless, the difficult and currently unanswered paradox remains that whilst CRT reduces the need for ICD, it improves survival and reduces the rate of death due to heart failure, thereby exposing patients to an increased duration of life in which SCD can occur.

As such, individualized decision making based on patient characteristics, national/local resources, and patient preference for either CRT-P or CRT-D remains important given the lack of head-to-head trials. Supportive guidelines aiding appropriate selection between CRT-P vs. CRT-D in countries with lower GDP might help to increase CRT implant rates in these areas. The RESET-CRT (NCT03494933) trial will further provide information regarding this topic.

Action IV: Organize a dedicated post-implant optimized cardiac resynchronization therpay care pathway

Follow-up of CRT patients is often divided over several cardiology subspecialties and large differences exist between hospitals and health care systems.[108] Although a comprehensive post-CRT implant follow-up programme has not been tested in randomized controlled trials, there are several easily-modifiable factors applicable directly following implant, before discharge, at early and longer follow-up that could improve short and longer-term outcomes following implantation (*Figure 4* and *Table 2*).[109,110] Furthermore, although such a comprehensive dedicated CRT follow-up programme is endorsed by several cardiac societies (EHRA, HRS, Heart Failure Society of America, American Society of Echocardiography, AHA, EACVI and HFA), and results in improvement of workflow of a typical multi-morbid complex patient population, an ongoing barrier is the need for focused training of medical and allied health care professionals in the holistic care of patients with heart failure and device-based interventions.[111] Such training has been endorsed by the European HFA and forms part of the certification by the EHRA.[112,113] Interestingly, just as referral for CRT is inadequate, referral for further interventions in patients who already have CRT is also inadequate, underscoring the importance of broad knowledge of the CRT team/CRT expert. For example, it has been shown that the need for heart transplantation and LV assist device was grossly underestimated among patients followed in CRT/ICD clinics.[18,29] The remainder of this section discusses major topics in the optimization of care following CRT implant.

Improvement of heart failure management

Higher doses of both beta-blockers and renin–angiotensin system blockers are associated with lower event rates,[114,115] and the benefits of dose titration is especially important in patients at highest risk.[116] Although CRT is often considered only after implementation of optimal medical heart failure therapy, it needs to be emphasized that in clinical practice only a minority of patients are able to tolerate maximal doses of neurohormonal blockers before CRT implant.[74] On the other hand, the acute and chronic haemodynamic effects of CRT might significantly change tolerability and acceptance of medical therapy. For example, in the CARE-HF and COMPANION trials, CRT was associated with a 6–7 mmHg increase in systolic blood pressure.[3,4] Furthermore, CRT protects patients against slowing of AV conduction, bradycardia and sinoatrial nodal pauses allowing safe up-titration of beta-blockers. Two randomized controlled trials have tested higher vs. lower doses of neurohormonal blockers in heart failure, indicating a lower event rate with higher doses.[114,115] Attaining guideline-directed doses of evidence-based neurohormonal blockers is a cornerstone of the treatment of heart failure including patients with CRT devices which is insufficiently emphasized in current guidelines. Real-world data indicate that 45% of patients on submaximal dose of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers are able to tolerate up-titration following CRT implant, and up to 57% of patients on submaximal dose of beta-blockers are able to tolerate higher doses after CRT implant.[117] Although biased by the observational nature, up-titration was associated with a lower risk for heart failure hospitalization and mortality.[117,118] Furthermore, although between 73–97% of patients were taking loop diuretics at the time of implant in the major CRT trials,[1,3,4,6,47] loop diuretic down-titration is often feasible following CRT implant, with possible benefits on long-term renal function.[119]

Although initiation of sacubitril/valsartan improved outcome in the PARADIGM-HF trial, remarkably few were treated with CRT.[120] Sacubitril/valsartan use in CRT and ICD patients results in incremental reverse remodelling, and a significant reduction in the burden of VT/VF, appropriate ICD therapies, and premature ventricular complexes (PVCs), which can have additional benefits on CRT delivery.[121–123]

Although often underappreciated by patients and primary care physicians, physical exercise following CRT or ICD implant has proven to be safe in the HF-ACTION trial.[124] Furthermore, observational and randomized data suggested that cardiac rehabilitation following CRT implant is associated with a larger degree of functional improvement, LV reverse remodelling and reduction in heart failure hospitalization and mortality.[125–128]

Optimal device programming

Individual programming of devices following implant and at each follow-up should be the aim. At each clinic visit an electrocardiogram and device analysis may help with assessment of patient status (*Table 3*). The key target of programming has been to deliver 100% of biventricular capture in order to achieve the optimal outcomes.[12,23] Although no randomized controlled trials exist comparing a lower vs. a higher degree of biventricular pacing, observational data link a low degree of biventricular pacing to poorer outcome. Although this might be to some extent a reflection of a different patient population, guidelines emphasize to try to attain a maximal percentage of biventricular pacing (class IIa recommendation).[23] There are a range of other programmable options including pacing mode, pacing rate, upper tracking rate, rate-adaptive pacing, capture output, AV and interventricular (VV) intervals and tachy-programming which should be reviewed at each clinic visit.

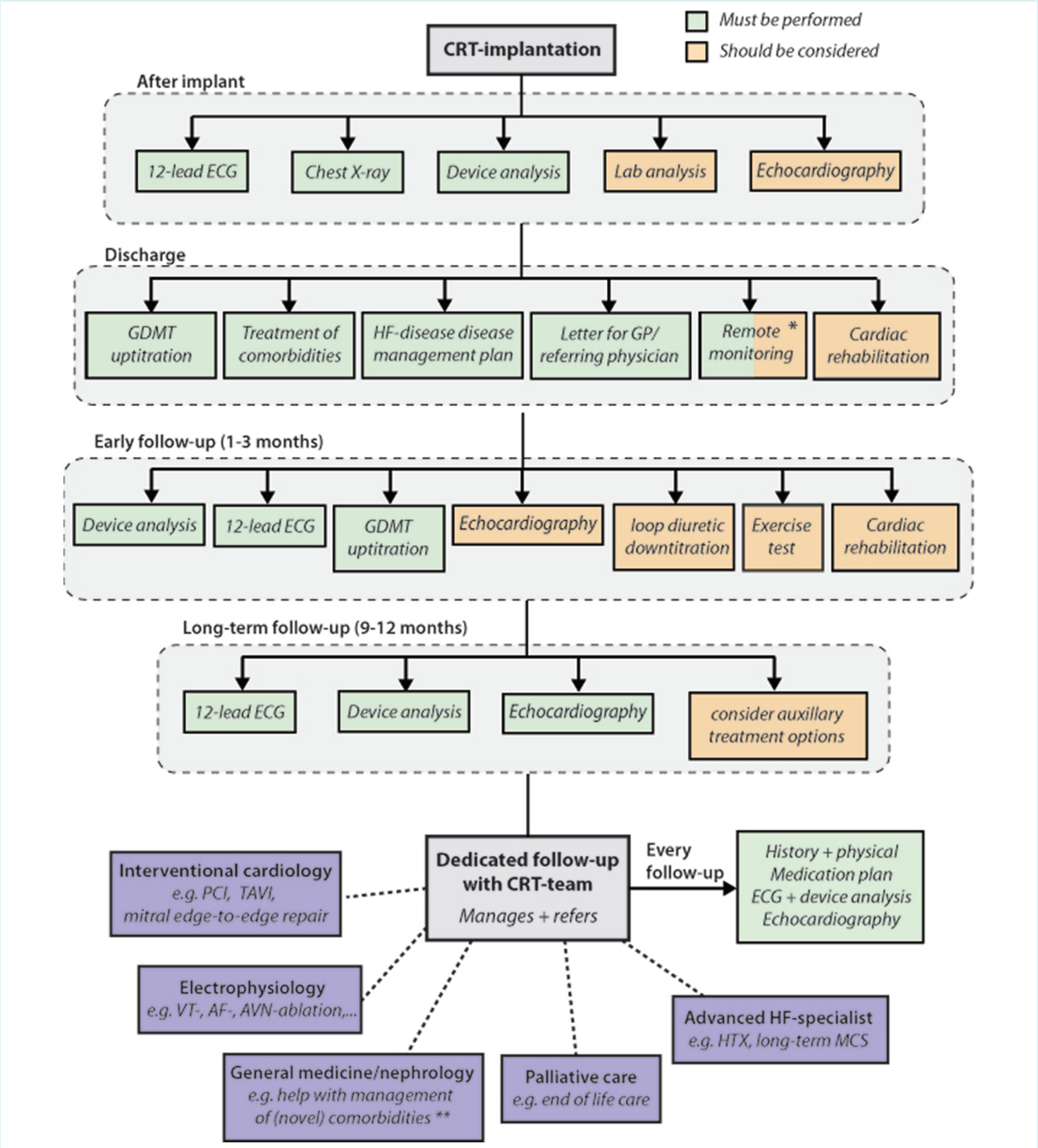

Figure 4 Structured post-implant cardiac resynchronization therapy (CRT) care. Flowchart of essential elements of post-CRT care. AF, atrial fibrillation; AVN, atrio-ventricular node; ECG, electrocardiogram; GDMT, guideline-directed medical therapy; GP, general practitioner; HF, heart failure; HTX, heart transplant; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; VT, ventricular tachycardia. *The evidence for remote monitoring for device-related technical issues is stronger as for remote monitoring of HF parameters to detect worsening of HF, hence the different colours. **Comorbidities often change during follow-up and also novel comorbidities need to be persistently addressed. The type of exercise test can be according to local expertise, but the aim is to see if there is persistent biventricular pacing during exercise or presence of chronotropic incompetence. The extent of application of this flowchart depends on the physical status (e.g. ability to perform an exercise test), but also the eligibility towards more advanced therapies such as a left ventricular assist device or HTX.

Table 2 Role and utility of interventions in cardiac resynchronization therapy follow-up

Intervention	Potential relevance
12-lead ECG	• Ensure and determine BiV-paced complex (QRS width, degree of QRS reduction, capture, morphology and LV latency), ECG after implant is the template for future troubleshooting • Consider performing at least once ECG with BiV off and LV and RV only pacing (large QRS difference between LV and RV only pacing might indicate need for VV optimization) • Positive R-wave V1? If not, rule out LV lead displacement and loss of LV capture, and if other causes are negative if lead was placed in middle or anterior cardiac vein • Always repeat ECG following significant device changes
Chest X-ray (PA and lateral)	• Detect complication or comorbid condition such a pneumothorax, COPD, pleural effusion • Determine position of LV lead after implant, and use as template for future troubleshooting
Laboratory assessment	• Determine creatinine and potassium in patients with CKD as they received i.v. contrast, and neurohormonal blocker up-titration will follow • Consider determining Hb, ferritin and TSAT and treating iron deficiency accordingly
Device analysis, consists of: (1) Diagnostics (2) Measurements (3) Programming	• Essential testing; battery status, lead impedance, sensing, pacing thresholds • Analyse device counters; BiV pacing should be 100% (dedicated counters differ from company, quid percentage true BiV pacing, e.g. LV pace on ventricular sensed complexed), V-sensing should be 0%, assess PVC burden (might be reason for low % BiV pacing). High PVC burden can also indicate atrial undersensing or ventricular oversensing • Optimize brady and tachy-programming (see text) • Consider optimizing AV and VV interval • Assess presence of phrenic nerve stimulation at maximal LV output • Assess atrial pacing vs. atrial sensing %, aim to lower basic pacing rate to reduce unnecessary and deleterious atrial pacing. • Assess rate histograms; sufficient heart rate increase? Consider programming R-mode • Determine AT/AF burden; high AT/AF burden could be reason for low % BiV pacing. Determine appropriateness of mode switches (might be due to atrial oversensing, with DDI/VDI pacing as a result and potentially pacemaker syndrome) • Evaluate presence of VT/VF episode triggers (appropriate vs. non-appropriate) • Assess NSVT burden; high burden might be reason for low % of BiV pacing, but could also reflect atrial undersensing or ventricular oversensing
Transthoracic echocardiography	• Detect potential new pericardial effusions • Consider evaluating the mitral inflow pattern, consider AV optimization in selected cases • Consider assessing the effects of CRT pacing: acute vs. chronic
Exercise test	• Ensure persistent BiV pacing at high heart rate (solution: rate adaptive AV optimization) • Presence of chronotropic incompetence, best assessed once beta-blocker up-titration is performed (need for R modus)
Holter evaluation	• Detection of QRS-fused beats if suspicion of intrinsic conduction fused beats (not detected by device counters) • Determine morphology of PVCs if frequent PVCs lead to low % of BiV pacing • Detect arrhythmias not detected by device, detect device malfunction

Diagnostic procedures should be individualized to the patients' need and physical status and not be considered 'routine' (e.g. repeat treadmill tests in older adults, or those with frailty or comorbidity, may not be helpful or useful).

AF, atrial fibrillation; AT, atrial tachycardia; AV, atrio-ventricular; BiV, biventricular; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; Hb, haemoglobin; i.v., intravenous; LV, left ventricular; NSVT, non-sustained ventricular tachycardia; PA, posterior–anterior; PVC, premature ventricular complex; RV, right ventricular; TSAT, transferrin saturation; VV, interventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.

The pacing mode depends on the underlying atrial rhythm. In patients in sinus rhythm, a DDD pacing mode is preferred but the base rate should allow sensing of intrinsic sinus rhythm as much as possible to avoid unnecessary atrial pacing. Landmark CRT trials often used a lower rate of 35–40/min with hysteresis off.[129,130] Atrial support pacing (base rate of 70/min in DDDR mode) did not show benefit in the PEGASUS-CRT trial,[131] possibly because right atrial pacing is associated with left atrial dyssynchrony and progressive left atrial remodelling, which also are independent predictors for the development of AF.[132–134] Therefore, lower rates are generally programmed low (40–50/min) in patients in sinus rhythm, although in patients in whom AF leads to mode switch, attention should be given to program a high enough base rate when this occurs (DDIR or VDIR mode). In patients in permanent AF, an inhibited mode is preferred, which can be DDIR or VVIR depending on the presence of an atrial lead. The DDDR mode

Table 3 Template for cardiac resynchronization therapy device analysis

Diagnostics

1. Battery longevity
2. %ASVP/%APVP/%BiV vs. LV only/% BiV vs. RV sense response/% effective
3. Heart failure log: HR variability, activity, lung impedance, sleep …
4. Arrhythmias (AF, ectopy, VT, V-sense response …)
5. Impedance trends

Measurements

1. Impedance
2. Sensitivity
3. Thresholds

Programming

1. Lower/upper frequency (+ mode switch)
2. R-response (accelerometer/CLS/minute ventilation)
3. BiV vs. RV vs. LV only
4. AV/VV times (manual: fixed vs. dynamic/device-based)
5. Output leads
6. Sensitivity
7. BiV sense response
8. Tachy-settings

AF, atrial fibrillation; APVP, atrial pace ventricular pace; ASVP, atrial sense ventricular pace; AV, atrio-ventricular; BiV, biventricular; CLS, closed loop stimulation; HR, heart rate; LV, left ventricular; RV, right ventricular; VT, ventricular tachycardia; VV, interventricular.

should be reserved for patients with paroxysmal AF.[12,23] In patients with AF who receive adequate rate control, a slightly higher base rate of 60 bpm together with rate-adaptive pacing might improve the proportion of biventricular capture.[12,23] However, in those with sinus rhythm, rate-adaptive pacing should be programmed off until the presence of significant iatrogenic or intrinsic chronotropic incompetence affecting exercise intolerance is proven, bearing in mind that simple age-related rate-adaptive pacing does not improve exercise capacity and may be disadvantageous in some.[116,135,136]

Whether rate-adaptive pacing is activated or not, the upper tracking rate should be programmed sufficiently high (e.g. 80% of maximal age-predicted heart rate), to ensure persistent biventricular pacing during periods of faster intrinsic sinus rhythm (e.g. exercise). Device diagnostics can be used to check this, although an exercise test is also useful.

Left ventricular output should be programmed with sufficient margin to ensure biventricular capture. Modern devices are equipped with auto-capture features that might improve battery longevity in some,[137] although nocturnal threshold testing can be unpleasant if there is diaphragmatic capture at higher outputs. Quadripolar LV leads and their multiple vectors offer the opportunity of avoiding phrenic nerve stimulation, and output optimization to extend battery longevity,[138] whereas the use of multiple vectors simultaneously (multi-point pacing) has not shown clinical benefit whilst reducing battery life.[139]

The most commonly assessed programming options include the AV and VV intervals. Poor attention to detail around especially AV delays is a contributor to reduced efficacy of CRT.[109] However, routine echocardiographic AV interval optimization is not superior in comparison to empiric programming of a 100–120 ms sensed AV interval.[140] Most new devices from different vendors have automated algorithms that individualize AV/VV intervals, creating fusion between spontaneous conduction and LV stimulation to avoid RV pacing, or optimizing AV/VV intervals using a haemodynamic sensor.[141,142] None of these algorithms have proven to be superior to echocardiographic optimization, although a superiority study with LV fusion pacing is ongoing.[143] In the light of the neutral clinical results of a routine approach of optimizing AV and VV intervals, one can consider this for specific patients (e.g. long interatrial delay). Nevertheless post-implant echocardiography with assessment of the mitral inflow pattern allows for a quick evaluation of the appropriateness of the AV interval programming. Indeed, if the A-wave is truncated or there is a lot of wasted mechanical time (fusion of E and A wave with A-wave ending before beginning of electrical systole), this should prompt the attention that the AV interval is not programmed correctly.

The programming of therapies for tachycardia should be individualized based on the indication for the ICD (primary vs. secondary prevention) and has been reviewed in more detail recently.[144] Adequate brady- and tachy-programming requires specialist device knowledge and expertise which aims at preventing morbidity, rather than to react to it (e.g. preventing ICD interventions, ensuring high biventricular-pacing, etc.). Therefore, these patients should be followed at specialized centres having multidisciplinary collaboration (i.e. heart failure and arrhythmology) and by physicians having undergone extensive device training and certification.

Inclusion in remote monitoring

In remote monitoring of CRT devices, a distinction should be made between device-related remote monitoring and monitoring of heart failure status through measurement of physiological variables. Patients with CRT have heart failure, and are therefore at an increased risk of clinical events such as ventricular or supraventricular arrhythmias which can interrupt CRT or worsen heart failure status.[145] Additionally, technical problems related to battery and leads can have an impact on patient status and prognosis, and might warrant detection and appropriate action as early as possible. These variables can be monitored by the device and remotely transmitted to the treating team.[146] Early detection of clinical or technical issues improved clinical outcomes in the IN-TIME trial,[147] although several larger trials failed to show benefit of remote monitoring.[148–151] Large registries have shown benefits of remote monitoring in CRT patients especially when devices are capable of collecting multiple key physiological parameters such as heart rate, respiration frequency, heart sounds and physical activity, in addition to technical checks on the device.[23,152] This approach requires an organizational change including funding of virtual visits and training of personnel who should react appropriately to transmitted information.[153] With the recent EU General Data Protection Regulation, hospitals and physicians must be aware of certain rules

that need to be complied with and agreements with manufacturers that need to be in place to implement remote monitoring. Finally, patients preference should be taken into account, as observational data indicates that around 20–35% of patients prefer in-clinic visits instead of remote monitoring.[154]

Managing arrhythmias in cardiac resynchronization therapy

Arrhythmias are common in heart failure patients, and often have an impact on morbidity, mortality and functioning of the CRT device. Atrial tachyarrhythmias and frequent PVCs are responsible for 50% and 10%, respectively, of the cases of a low percentage of biventricular pacing, thereby further compromising LV systolic dysfunction and contributing to decompensation.[66,155]

Whether suppression of atrial tachyarrhythmia, mainly AF, in the presence of HFrEF is of benefit and which strategy might be appropriate is unknown.[156,157] Despite concerns around long-term safety and overall neutral clinical outcomes,[153,158] guidelines recommend amiodarone (IA recommendation) if a rhythm control strategy is chosen. AF ablation has gained a lot of interest (IIA recommendation),[24,157] due to possible improvements in LVEF, functional capacity and quality of life in comparison to rate control in heart failure patients.[159–163] For example, long-term follow-up of the highly-selected CASTLE-AF patients suggests that AF ablation is associated with a lower risk of heart failure admission and all-cause mortality.[160] Importantly, the benefit was demonstrated not by elimination of AF but rather by reducing overall AF burden.[160] In patients with HFrEF and AF who have a CRT device, AF ablation could be considered for those with a high likelihood of attaining sinus rhythm and thus subsequently 100% of biventricular pacing. AV nodal ablation should be considered as a treatment strategy for patients who fail to achieve sufficient biventricular pacing despite AV blocking medical therapy or efforts to maintain sinus rhythm (e.g. amiodarone or AF ablation in selected patients).

Frequent PVCs can also result in a low percentage of biventricular pacing and further worsen LV systolic function.[66] If despite heart failure therapy optimization, PVCs continue to cause low proportions of biventricular pacing, amiodarone or PVC ablation can be considered.[157] A study in which patients with poor improvement after CRT and more than >10 000 PVCs per 24 h were subjected to PVC ablation showed improvements in symptoms and incremental reverse remodelling.[164]

Ventricular arrhythmias are a key concern in HFrEF patients especially in those with reduced LVEF and ischaemic heart disease.[82] The prevalence of ventricular arrhythmias is associated with the disease severity of HFrEF.[165–167] The event rates for mortality and heart failure admission are markedly higher following appropriate ICD therapy, but not after inappropriate therapy,[168,169] which indicates that a ventricular arrhythmic event in HFrEF is a marker of disease progression. Hence, heart failure therapy optimization is mandatory not only to treat, but also to prevent ventricular arrhythmias in HFrEF.[170] Additionally, triggers such as volume overload, ion disturbances, loss of biventricular pacing and others should be actively assessed and treated. Furthermore, guidelines recommend consideration of amiodarone and VT ablation in CRT-D patients after a first sustained episode.[170] Any arrhythmic event should also prompt a review of the device programming.[144]

Disease progression and remission

As indicated in *Figure 2*, CRT can stabilize the disease trajectory but some patients have persistent symptoms and will eventually deteriorate. Some of these patients might be indicated for advanced heart failure therapies. Therefore, the CRT specialist team should not only be experienced in the management of technical aspects of the CRT devices, and medical therapy for heart failure, but should also be competent to detect and understand the mechanisms underlying disease progression (*Figure 4*). Imaging plays an essential role[171] in identifying persistence of secondary mitral regurgitation, and progressive atrial, LV and RV remodelling, all of which indicate progression of the heart failure syndrome, and warrant consideration of appropriate interventions,[172–174] including additional device therapies such as mitral edge-to-edge repair,[175,176] or newer medical therapies.[120,177] Cardiopulmonary exercise test with determination of peak oxygen consumption and other variables might[29,178] provide information on prognosis and appropriate timing of more advanced interventions in selected patients.[179,180] The CRT specialist team should be able to determine if palliative care is more suitable than onward referral for more invasive therapies.[181]

Cardiac resynchronization therapy teams are also the best at determining whether and when the possibility for ICD interventions should be withdrawn. For example, at time of battery depletion and box change, patient and physician perspective might warrant consideration of withdrawal of ICD therapy by replacement of a CRT-D device with a CRT-P device.[182–184] Unfortunately, this is increasingly difficult in the absence of a DF-4 to IS-1 connector necessitating an additional RV pace-sense lead implantation. Additional liability issues might occur if patients, following downgrading from CRT-D to CRT-P, die suddenly or subsequently show a deterioration in cardiac function, and therefore this should be comprehensively discussed with the expert team and with the patient and/or his family and in the light of therapeutic aims and relevant comorbidity, such as dementia or malignancy.

A very small subgroup of CRT patients demonstrate overwhelming benefit from CRT that every aspect of their heart failure disease seems to dissipate (normalization of echocardiogram and N-terminal pro B-type natriuretic peptide, and resolution of symptoms). These patients can be considered to be in 'full remission'. A small prospective randomized pilot trial suggested that closely supervised neurohumoral blocker withdrawal ('CRT only strategy') is feasible and safe in patients with myocardial recovery after CRT.[185] These results differ from TRED-HF in that those in TRED-HF did not have LBBB with improved LV function following CRT.[186] In contrast, data from MUSTIC and MADIT-CRT indicated that turning off biventricular pacing ('medical strategy only') led to a re-occurrence of the heart failure syndrome.[7]

Patient engagement and education

Cardiac resynchronization therapy recipients are often older adults with multiple comorbidities. Adequate information on the purpose

Table 4 Element of patient-centred cardiac resynchronization therapy education

Pre-implantation	Early post-implantation	Living with CRT
• Discuss the position in the heart failure trajectory • Include patient and caregiver in decision making • Provide information and understanding of the device indication (ask-tell-ask) • Provide information on the procedure • Discuss expectations • Provide information of consequences (long and short term) • Include family caregivers • Discussion of potential complications (lead displacement, shocks, infection) with the patients and caregivers	• Discuss questions related to discomfort, pain, placement • Discuss effect and expectations • Discuss the role of CRT in heart failure treatment and consequence for treatment (lifestyle and medication changes) • Discuss how to adjust medications after implant • Inform on when to contact a health care provider • Include family caregivers	• Provide tailored follow-up • Discuss the role of CRT in the heart failure trajectory • Discuss consequences for survival, treatment, lifestyle, exercise • Be open for coping issues (feeling dependent on technology, anxiety for failure) • Inform the patients about relevant issues: insurance, travel • If relevant, discuss deactivation of the ICD • Include family caregivers • End of life care

CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

of CRT, the implant procedure including risk and post-implant care is essential for them and their family. A recent survey indicated that almost half of patients felt insufficiently informed about technical aspects or had worries about aspects of their implantable devices.[187] A considerable number of heart failure patients suffer from depressive symptoms, which are associated with worse outcomes.[188] Psychosocial concerns and worries should be addressed in a multidisciplinary approach. Furthermore, end of life decisions such as ICD withdrawal are rarely discussed.[187] Information through health care providers (e.g. CRT specialist, heart failure nurse) and paper and web-based education (e.g. www.heartfailurematters.org) might improve patients' understanding and engagement. *Table 4* summarizes important patient-centred aspects regarding the education of patients and families with regard to use of CRT.

Future perspectives

Alternative resynchronization strategies have been developed that might also effectively treat the electromechanical dyssynchrony in HFrEF patients. Such strategies include His bundle and LBBB area pacing, endocardial LV lead pacing, wireless LV stimulation, or even deep interventricular septal LV pacing.[189–191] In patients with a classical CRT indication, pacing strategies such as His bundle pacing are often propagated as an alternative because of the equipoise induced by the 30% non-response rate to CRT.[192] However, it is clear from this manuscript that this concept of non-response to CRT is intrinsically flawed. Although acute haemodynamic and short-term reverse remodelling studies with these novel pacing strategies illustrate a similar haemodynamic, functional and remodelling improvement as CRT,[190,193–198] they will have to show at least equal benefit in terms of morbidity and mortality endpoints in HFrEF and be as safe in order to be implemented in clinical practice as an alternative to CRT.[197] Additionally, His bundle is also being tested in HFrEF for other indications such as PR prolongation.[199] Whether CRT might be of benefit in patients with heart failure with preserved ejection fraction is also under investigation.[200]

Conclusion

Cardiac resynchronization therapy is an underutilized lifesaving therapy, strongly recommended in guidelines for a common subgroup of HFrEF patients. This HFA, EHRA and EACVI endorsed document offers theoretical and practical strategies to achieve more comprehensive CRT referral and post-procedural care by focusing on several actionable domains.

Supplementary Information

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

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References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J; MIRACLE (Multicenter InSync Randomized Clinical Evaluation) Study Group. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**:1845–1853.
2. Abraham WT, Young JB, Leon AR, Adler S, Bank AJ, Hall SA, Lieberman R, Liem LB, O'Connell JB, Schroeder JS, Wheelan KR; Multicenter InSync ICD II Study Group. Effects of cardiac resynchronization on disease progression in patients with left ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 2004;**110**:2864–2868.
3. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**:2140–2150.
4. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539–1549.
5. Linde C, Abraham WT, Gold MR, St John SM, Ghio S, Daubert C; REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. 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**:1834–1843.
6. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010;**363**:2385–2395.
7. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, Garrigue S, Kappenberger L, Haywood GA, Santini M, Bailleul C, Daubert JC; Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;**344**:873–880.
8. Raatikainen MJ, Arnar DO, Zeppenfeld K, Merino JL, Levya F, Hindriks G, Kuck KH. Statistics on the use of cardiac electronic devices and electrophysiological procedures in the European Society of Cardiology countries: 2014 report from the European Heart Rhythm Association. *Europace* 2015;**17** (Suppl 1):i1–75.
9. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. *Eur Heart J* 2017;**38**:1463–1472.
10. Cleland JG, Abraham WT, Linde C, Gold MR, Young JB, Claude DJ, Sherfesee L, Wells GA, Tang AS. 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**:3547–3556.
11. Woods B, Hawkins N, Mealing S, Sutton A, Abraham WT, Beshai JF, Klein H, Sculpher M, Plummer CJ, Cowie MR. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart* 2015;**101**:1800–1806.
12. Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF, Breithard O, Brignole M, Cleland J, Delurgio DB, Dickstein K, Exner DV, Gold M, Grimm RA, Hayes DL, Israel C, Leclercq C, Linde C, Lindenfeld J, Merkely B, Mont L, Murgatroyd F, Prinzen F, Saba SF, Shinbane JS, Singh J, Tang AS, Vardas PE, Wilkoff BL, Zamorano JL, Anand I, Blomstrom-Lundqvist C, Boehmer JP, Calkins H, Cazeau S, Delgado V, Estes NA, Haines D, Kusumoto F, Leyva P, Ruschitzka F, Stevenson LW, Torp-Pedersen CT. 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. *Europace* 2012;**14**:1236–1286.
13. Varma N, Boehmer J, Bhargava K, Yoo D, Leonelli F, Costanzo M, Saxena A, Sun L, Gold MR, Singh J, Gill J, Auricchio A. Evaluation, management, and

outcomes of patients poorly responsive to cardiac resynchronization device therapy. *J Am Coll Cardiol* 2019;**74**:2588–2603.
14. Lund LH, Benson L, Stahlberg M, Braunschweig F, Edner M, Dahlstrom U, Linde C. Age, prognostic impact of QRS prolongation and left bundle branch block, and utilization of cardiac resynchronization therapy: findings from 14,713 patients in the Swedish Heart Failure Registry. *Eur J Heart Fail* 2014;**16**:1073–1081.
15. Lund LH, Jurga J, Edner M, Benson L, Dahlstrom U, Linde C, Alehagen U. Prevalence, correlates, and prognostic significance of QRS prolongation in heart failure with reduced and preserved ejection fraction. *Eur Heart J* 2013;**34**:529–539.
16. Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M, Campana C, Perini G, Deorsola A, Masotti G, Tavazzi L, Maggioni AP; Italian Network on Congestive Heart Failure Investigators. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J* 2002;**143**:398–405.
17. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L; EuroHeart Survey Investigators; Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725–2736.
18. Lund LH, Svennblad B, Dahlstrom U, Stahlberg M. Effect of expanding evidence and evolving clinical guidelines on the prevalence of indication for cardiac resynchronization therapy in patients with heart failure. *Eur J Heart Fail* 2018;**20**:769–777.
19. Lund LH, Braunschweig F, Benson L, Stahlberg M, Dahlstrom U, Linde C. Association between demographic, organizational, clinical, and socio-economic characteristics and underutilization of cardiac resynchronization therapy: results from the Swedish Heart Failure Registry. *Eur J Heart Fail* 2017;**19**:1270–1279.
20. Dickstein K, Normand C, Auricchio A, Bogale N, Cleland JG, Gitt AK, Stellbrink C, Anker SD, Filippatos G, Gasparini M, Hindricks G, Blomstrom LC, Ponikowski P, Ruschitzka F, Botto GL, Bulava A, Duray G, Israel C, Leclercq C, Margitfalvi 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;**20**:1039–1051.
21. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA 3rd, Ferguson TB Jr, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD. 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;**61**:e6–75.
22. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**128**:e240–e327.
23. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 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**:2281–2329.
24. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 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 J Heart Fail* 2016;**18**:891–975.
25. Fein AS, Wang Y, Curtis JP, Masoudi FA, Varosy PD, Reynolds MR. Prevalence and predictors of off-label use of cardiac resynchronization therapy in patients enrolled in the National Cardiovascular Data Registry Implantable Cardiac-Defibrillator Registry. *J Am Coll Cardiol* 2010;**56**:766–773.
26. Yao G, Freemantle N, Calvert MJ, Bryan S, Daubert JC, Cleland JG. The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. *Eur Heart J* 2007;**28**:42–51.
27. Linde C, Mealing S, Hawkins N, Eaton J, Brown B, Daubert JC; REVERSE Study Group. Cost-effectiveness of cardiac resynchronization therapy in patients with asymptomatic to mild heart failure: insights from the European cohort of the REVERSE (Resynchronization Reverses remodeling in Systolic Left Ventricular Dysfunction). *Eur Heart J* 2011;**32**:1631–1639.
28. Noyes K, Veazie P, Hall WJ, Zhao H, Buttaccio A, Thevenet-Morrison K, Moss AJ. Cost-effectiveness of cardiac resynchronization therapy in the MADIT-CRT trial. *J Cardiovasc Electrophysiol* 2013;**24**:66–74.
29. Thorvaldsen T, Lund LH. Focusing on referral rather than selection for advanced heart failure therapies. *Card Fail Rev* 2019;**5**:24–26.
30. Han JJ, Brown CR. The heart team: a powerful paradigm for the future training of cardiovascular surgeons. *J Am Coll Cardiol* 2018;**71**:2702–2705.
31. Bax JJ, Marwick TH, Molhoek SG, Bleeker GB, van Erven L, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. *Am J Cardiol* 2003;**92**:1238–1240.
32. Butter C, Auricchio A, Stellbrink C, Fleck E, Ding J, Yu Y, Huvelle E, Spinelli J. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. *Circulation* 2001;**104**:3026–3029.
33. Steffel J, Ruschitzka F. Superresponse to cardiac resynchronization therapy. *Circulation* 2014;**130**:87–90.
34. Thibault B, Ducharme A, Harel F, White M, O'Meara E, Guertin MC, Lavoie J, Frasure-Smith N, Dubuc M, Guerra P, Macle L, Rivard L, Roy D, Talajic M, Khairy P; Resynchronization Therapy for Heart Failure (GREATER-EARTH) Investigators. Left ventricular versus simultaneous biventricular pacing in patients with heart failure and a QRS complex ≥120 milliseconds. *Circulation* 2011;**124**:2874–2881.
35. Witte KK, Nikitin NP, de Silva R, Cleland JG, Clark AL. Exercise capacity and cardiac function assessed by tissue Doppler imaging in chronic heart failure. *Heart* 2004;**90**:1144–1150.
36. Ypenburg C, van Bommel RJ, Borleffs CJ, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol* 2009;**53**:483–490.
37. Lafitte S, Reant P, Zaroui A, Donal E, Mignot A, Bougted H, Belghiti H, Bordachar P, Deplagne A, Chabaneix J, Franceschi F, Deharo JC, Dos SP, Clementy J, Roudaut R, Leclercq C, Habib G. Validation of an echocardiographic multiparametric strategy to increase responders patients after cardiac resynchronization: a multicentre study. *Eur Heart J* 2009;**30**:2880–2887.
38. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE, Chan YS, Kong SL, Bax JJ. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation* 2005;**112**:1580–1586.
39. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *J Am Coll Cardiol* 2010;**56**:392–406.
40. Mullens W, Verga T, Grimm RA, Starling RC, Wilkoff BL, Tang WH. Persistent hemodynamic benefits of cardiac resynchronization therapy with disease progression in advanced heart failure. *J Am Coll Cardiol* 2009;**53**:600–607.
41. Linde C, Gold MR, Abraham WT, St John SM, Ghio S, Cerkvenik J, Daubert C; REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction Study Group. Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. *Eur Heart J* 2013;**34**:2592–2599.
42. Ypenburg C, Roes SD, Bleeker GB, Kaandorp TA, de Roos A, Schalij MJ, van der Wall EE, Bax JJ. Effect of total scar burden on contrast-enhanced magnetic resonance imaging on response to cardiac resynchronization therapy. *Am J Cardiol* 2007;**99**:657–660.
43. Dupont M, Rickard J, Baranowski B, Varma N, Dresing T, Gabi A, Finucan M, Mullens W, Wilkoff BL, Tang WH. Differential response to cardiac resynchronization therapy and clinical outcomes according to QRS morphology and QRS duration. *J Am Coll Cardiol* 2012;**60**:592–598.

44. Ypenburg C, Schalij MJ, Bleeker GB, Steendijk P, Boersma E, Dibbets-Schneider P, Stokkel MP, van der Wall EE, Bax JJ. Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. *Eur Heart J* 2007;**28**:33–41.
45. Ter Maaten JM, Martens P, L'hoyes W, Maass AH, Damman K, Dupont M, Mullens W. Response to cardiac resynchronization therapy across chronic kidney disease stages. *J Card Fail* 2019;**25**:803–811.
46. Molhoek SG, Bax JJ, van Erven L, Bootsma M, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Comparison of benefits from cardiac resynchronization therapy in patients with ischemic cardiomyopathy versus idiopathic dilated cardiomyopathy. *Am J Cardiol* 2004;**93**:860–863.
47. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;**361**:1329–1338.
48. Beshai JF, Grimm RA, Nagueh SF, Baker JH, Beau SL, Greenberg SM, Pires LA, Tchou PJ; RethinQ Study Investigators. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;**357**:2461–2471.
49. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J 3rd, Gras D, Krum H, Sogaard P, Holzmeister J; EchoCRT Study Group. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**:1395–1405.
50. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001;**7**:176–182.
51. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 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**:1476–1488.
52. Varma N, Sogaard P, Bax JJ, Abraham WT, Borer JS, Dickstein K, Singh JP, Gras D, Holzmeister J, Brugada J, Ruschitzka F. Interaction of left ventricular size and sex on outcome of cardiac resynchronization therapy among patients with a narrow QRS duration in the EchoCRT trial. *J Am Heart Assoc* 2018;**7**:e009592.
53. Varma N, Lappe J, He J, Niebauer M, Manne M, Tchou P. Sex-specific response to cardiac resynchronization therapy: effect of left ventricular size and QRS duration in left bundle branch block. *JACC Clin Electrophysiol* 2017;**3**:844–853.
54. Linde C, Cleland JG, Gold MR, Claude DJ, Tang AS, Young JB, Sherfesee L, Abraham WT. The interaction of sex, height, and QRS duration on the effects of cardiac resynchronization therapy on morbidity and mortality: an individual-patient data meta-analysis. *Eur J Heart Fail* 2018;**20**:780–791.
55. Linde C, Daubert C, Abraham WT, St John SM, Ghio S, Hassager C, Herre JM, Bergemann TL, Gold MR. Impact of ejection fraction on the clinical response to cardiac resynchronization therapy in mild heart failure. *Circ Heart Fail* 2013;**6**:1180–1189.
56. Kutyifa V, Kloppe A, Zareba W, Solomon SD, McNitt S, Polonsky S, Barsheshet A, Merkely B, Lemke B, Nagy VK, Moss AJ, Goldenberg I. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy). *J Am Coll Cardiol* 2013;**61**:936–944.
57. Breithardt OA, Stellbrink C, Kramer AP, Sinha AM, Franke A, Salo R, Schiffgens B, Huvelle E, Auricchio A. Echocardiographic quantification of left ventricular asynchrony predicts an acute hemodynamic benefit of cardiac resynchronization therapy. *J Am Coll Cardiol* 2002;**40**:536–545.
58. Verbeek XA, Auricchio A, Yu Y, Ding J, Pochet T, Vernooy K, Kramer A, Spinelli J, Prinzen FW. Tailoring cardiac resynchronization therapy using interventricular asynchrony. Validation of a simple model. *Am J Physiol Heart Circ Physiol* 2006;**290**:H968–H977.
59. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J 3rd, St John Sutton M, De Sutter J, Murillo J. Results of the predictors of response to CRT (PROSPECT) trial. *Circulation* 2008;**117**:2608–2616.
60. Gutman SJ, Costello BT, Papapostolou S, Voskoboinik A, Iles L, Ja J, Hare JL, Ellims A, Kistler PM, Marwick TH, Taylor AJ. Reduction in mortality from implantable cardioverter-defibrillators in non-ischaemic cardiomyopathy patients is dependent on the presence of left ventricular scar. *Eur Heart J* 2019;**40**:542–550.
61. Leyva F, Foley PW, Chalil S, Ratib K, Smith RE, Prinzen F, Auricchio A. Cardiac resynchronization therapy guided by late gadolinium-enhancement cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2011;**13**:29.
62. Mullens W, Martens P. Sacubitril/valsartan to reduce secondary mitral regurgitation. *Circulation* 2019;**139**:1366–1370.
63. Martens P, Verbrugge FH, Bertrand PB, Verhaert D, Vandervoort P, Dupont M, Tang WHW, Janssens S, Mullens W. Effect of cardiac resynchronization therapy on exercise-induced pulmonary hypertension and right ventricular-arterial coupling. *Circ Cardiovasc Imaging* 2018;**11**:e007813.
64. Healey JS, Hohnloser SH, Exner DV, Birnie DH, Parkash R, Connolly SJ, Krahn AD, Simpson CS, Thibault B, Basta M, Philippon F, Dorian P, Nair GM, Sivakumaran S, Yetisir E, Wells GA, Tang AS; RAFT Investigators. Cardiac resynchronization therapy in patients with permanent atrial fibrillation: results from the Resynchronization for Ambulatory Heart Failure Trial (RAFT). *Circ Heart Fail* 2012;**5**:566–570.
65. Ruwald MH, Mittal S, Ruwald AC, Aktas MK, Daubert JP, McNitt S, Al-Ahmad A, Jons C, Kutyifa V, Steinberg JS, Wang P, Moss AJ, Zareba W. Association between frequency of atrial and ventricular ectopic beats and biventricular pacing percentage and outcomes in patients with cardiac resynchronization therapy. *J Am Coll Cardiol* 2014;**64**:971–981.
66. Cheng A, Landman SR, Stadler RW. Reasons for loss of cardiac resynchronization therapy pacing: insights from 32 844 patients. *Circ Arrhythm Electrophysiol* 2012;**5**:884–888.
67. Gasparini M, Auricchio A, Regoli F, Fantoni C, Kawabata M, Galimberti P, Pini D, Ceriotti C, Gronda E, Klersy C, Fratini S, Klein HH. Four-year 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**:734–743.
68. Gasparini M, Kloppe A, Lunati M, Anselme F, Landolina M, Martinez-Ferrer JB, Proclemer A, Morani G, Biffi M, Ricci R, Rordorf R, Mangoni L, Manotta L, Grammatico A, Leyva F, Boriani G. Atrioventricular junction ablation in patients with atrial fibrillation treated with cardiac resynchronization therapy: positive impact on ventricular arrhythmias, implantable cardioverter-defibrillator therapies and hospitalizations. *Eur J Heart Fail* 2018;**20**:1472–1481.
69. Koplan BA, Kaplan AJ, Weiner S, Jones PW, Seth M, Christman SA. Heart failure decompensation and all-cause mortality in relation to percent biventricular pacing in patients with heart failure: is a goal of 100% biventricular pacing necessary? *J Am Coll Cardiol* 2009;**53**:355–360.
70. Hayes DL, Boehmer JP, Day JD, Gilliam FR 3rd, Heidenreich PA, Seth M, Jones PW, Saxon LA. Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. *Heart Rhythm* 2011;**8**:1469–1475.
71. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T, Sutton MS; Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block (BLOCK HF) Trial Investigators. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med* 2013;**368**:1585–1593.
72. Brignole M, Botto G, Mont L, Iacopino S, De Marchi G, Oddone D, Luzi M, Tolosana JM, Navazio A, Menozzi C. Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial. *Eur Heart J* 2011;**32**:2420–2429.
73. Merkely B, Kosztin A, Roka A, Geller L, Zima E, Kovacs A, Boros AM, Klein H, Wranicz JK, Hindricks G, Clemens M, Duray GZ, Moss AJ, Goldenberg I, Kutyifa V. Rationale and design of the BUDAPEST-CRT Upgrade Study: a prospective, randomized, multicentre clinical trial. *Europace* 2017;**19**:1549–1555.
74. Heywood JT, Fonarow GC, Yancy CW, Albert NM, Curtis AB, Gheorghiade M, Inge PJ, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN. Comparison of medical therapy dosing in outpatients cared for in cardiology practices with heart failure and reduced ejection fraction with and without device therapy: report from IMPROVE HF. *Circ Heart Fail* 2010;**3**:596–605.
75. Sze E, Samad Z, Dunning A, Campbell KB, Loring Z, Atwater BD, Chiswell K, Kisslo JA, Velazquez EJ, Daubert JP. Impaired recovery of left ventricular function in patients with cardiomyopathy and left bundle branch block. *J Am Coll Cardiol* 2018;**71**:306–317.
76. St John SM, Linde C, Gold MR, Abraham WT, Ghio S, Cerkvenik J, Daubert JC; REVERSE Study Group. Left ventricular architecture, long-term reverse remodeling, and clinical outcome in mild heart failure with cardiac resynchronization: results from the REVERSE trial. *JACC Heart Fail* 2017;**5**:169–178.
77. Lee CS, Chien CV, Bidwell JT, Gelow JM, Denfeld QE, Masterson CR, Buck HG, Mudd JO. Comorbidity profiles and inpatient outcomes during hospitalization for heart failure: an analysis of the U.S. Nationwide inpatient sample. *BMC Cardiovasc Disord* 2014;**14**:73.
78. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M, Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. *Acta Cardiol* 2018;**73**:115–123.
79. Verbrugge FH, Dupont M, Rivero-Ayerza M, de Vusser P, Van Herendael H, Vercammen J, Jacobs L, Verhaert D, Vandervoort P, Tang WH, Mullens W. Comorbidity significantly affects clinical outcome after cardiac resynchronization therapy regardless of ventricular remodeling. *J Card Fail* 2012;**18**:845–853.

80. Leyva F, Zegard A, Okafor O, de Bono J, McNulty D, Ahmed A, Marshall H, Ray D, Qiu T. Survival after cardiac resynchronization therapy: results from 50 084 implantations. *Europace* 2019;**21**:754–762.
81. Zeitler EP, Friedman DJ, Daubert JP, Al-Khatib SM, Solomon SD, Biton Y, McNitt S, Zareba W, Moss AJ, Kutyifa V. Multiple comorbidities and response to cardiac resynchronization therapy: MADIT-CRT long-term follow-up. *J Am Coll Cardiol* 2017;**69**:2369–2379.
82. Martens P, Verbrugge FH, Nijst P, Dupont M, Nuyens D, Herendael HV, Rivero-Ayerza M, Tang WH, Mullens W. Incremental benefit of cardiac resynchronisation therapy with versus without a defibrillator. *Heart* 2017;**103**:1977–1984.
83. Bose A, Upadhyay GA, Kandala J, Heist EK, Mela T, Parks KA, Singh JP. Does prior valve surgery change outcome in patients treated with cardiac resynchronization therapy? *J Cardiovasc Electrophysiol* 2014;**25**:1206–1213.
84. Boriani G, Gasparini M, Landolina M, Lunati M, Biffi M, Santini M, Padeletti L, Molon G, Botto G, De Santo T, Valsecchi S; InSync/InSync ICD Italian Registry Investigators. Effectiveness of cardiac resynchronization therapy in heart failure patients with valvular heart disease: comparison with patients affected by ischaemic heart disease or dilated cardiomyopathy. The InSync/InSync ICD Italian Registry. *Eur Heart J* 2009;**30**:2275–2283.
85. Martens P, Verbrugge F, Nijst P, Dupont M, Tang WH, Mullens W. Impact of iron deficiency on response to and remodeling after cardiac resynchronization therapy. *Am J Cardiol* 2017;**119**:65–70.
86. Martens P, Dupont M, Dauw J, Somers F, Herbots L, Timmermans P, Verwerft J, Mullens W. Rationale and design of the IRON-CRT trial: effect of intravenous ferric carboxymaltose on reverse remodelling following cardiac resynchronization therapy. *ESC Heart Fail* 2019;**6**:1208–1215.
87. Daubert JC, Leclercq C, Mabo P. There is plenty of room for cardiac resynchronization therapy devices without back-up defibrillators in the electrical treatment of heart failure. *J Am Coll Cardiol* 2005;**46**:2204–2207.
88. Levy WC. Should nonischemic CRT candidates receive CRT-P or CRT-D? *J Am Coll Cardiol* 2017;**69**:1679–1682.
89. McMurray JJ. The ICD in heart failure - time for a rethink? *N Engl J Med* 2016;**375**:1283–1284.
90. Gupta A, Harrington M, Albert CM, Bajaj NS, Hainer J, Morgan V, Bibbo CF, Bravo PE, Osborne MT, Dorbala S, Blankstein R, Taqueti VR, Bhatt DL, Stevenson WG, Di Carli MF. Myocardial scar but not ischemia is associated with defibrillator shocks and sudden cardiac death in stable patients with reduced left ventricular ejection fraction. *JACC Clin Electrophysiol* 2018;**4**:1200–1210.
91. Acosta J, Fernandez-Armenta J, Borras R, Anguera I, Bisbal F, Marti-Almor J, Tolosana JM, Penela D, Andreu D, Soto-Iglesias D, Evertz R, Matiello M, Alonso C, Villuendas R, de Caralt TM, Perea RJ, Ortiz JT, Bosch X, Serra L, Planes X, Greiser A, Ekinci O, Lasalvia L, Mont L, Berruezo A. Scar characterization to predict life-threatening arrhythmic events and sudden cardiac death in patients with cardiac resynchronization therapy: the GAUDI-CRT study. *JACC Cardiovasc Imaging* 2018;**11**:561–572.
92. Di Marco A, Anguera I, Schmitt M, Klem I, Neilan TG, White JA, Sramko M, Masci PG, Barison A, Mckenna P, Mordi I, Haugaa KH, Leyva F, Rodriguez CJ, Satoh H, Nabeta T, Dallaglio PD, Campbell NG, Sabate X, Cequier A. Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. *JACC Heart Fail* 2017;**5**:28–38.
93. Mittal S, Aktas MK, Moss AJ, McNitt S, Kutyifa V, Steinberg JS, Zareba W. The impact of nonsustained ventricular tachycardia on reverse remodeling, heart failure, and treated ventricular tachyarrhythmias in MADIT-CRT. *J Cardiovasc Electrophysiol* 2014;**25**:1082–1087.
94. Marijon E, Leclercq C, Narayanan K, Boveda S, Klug D, Lacaze-Gadonneix J, Defaye P, Jacob S, Piot O, Deharo JC, Perier MC, Mulak G, Hermida JS, Milliez P, Gras D, Cesari O, Hidden-Lucet F, Anselme F, Chevalier P, Maury P, Sadoul N, Bordachar P, Cazeau S, Chauvin M, Empana JP, Jouven X, Daubert JC, Le Heuzey JY; CeRtiTuDe Investigators. Causes-of-death analysis of patients with cardiac resynchronization therapy: an analysis of the CeRtiTuDe cohort study. *Eur Heart J* 2015;**36**:2767–2776.
95. Boveda S, Marijon E, Jacob S, Defaye P, Winter JB, Bulava A, Gras D, Albenque JP, Combes N, Pavin D, Delarche N, Teubl A, Lambiez M, Chevalier P; Mona Lisa Study Group. Incidence and prognostic significance of sustained ventricular tachycardias in heart failure patients implanted with biventricular pacemakers without a back-up defibrillator: results from the prospective, multicentre, Mona Lisa cohort study. *Eur Heart J* 2009;**30**:1237–1244.
96. Rho RW, Patton KK, Poole JE, Cleland JG, Shadman R, Anand I, Maggioni AP, Carson PE, Swedberg K, Levy WC. Important differences in mode of death between men and women with heart failure who would qualify for a primary prevention implantable cardioverter-defibrillator. *Circulation* 2012;**126**:2402–2407.
97. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–1230.
98. Barra S, Boveda S, Providencia R, Sadoul N, Duehmke R, Reitan C, Borgquist R, Narayanan K, Hidden-Lucet F, Klug D, Defaye P, Gras D, Anselme F, Leclercq C, Hermida JS, Deharo JC, Looi KL, Chow AW, Virdee M, Fynn S, Le Heuzey JY, Marijon E, Agarwal S. Adding defibrillation therapy to cardiac resynchronization on the basis of the myocardial substrate. *J Am Coll Cardiol* 2017;**69**:1669–1678.
99. Sharma A, Al-Khatib SM, Ezekowitz JA, Cooper LB, Fordyce CB, Michael FG, Bardy GH, Poole JE, Thomas BJ, Buxton AE, Moss AJ, Friedman DJ, Lee KL, Steinman R, Dorian P, Cappato R, Kadish AH, Kudenchuk PJ, Mark DB, Peterson ED, Inoue LY, Sanders GD. Implantable cardioverter-defibrillators in heart failure patients with reduced ejection fraction and diabetes. *Eur J Heart Fail* 2018;**20**:1031–1038.
100. Bansal N, Szpiro A, Reynolds K, Smith DH, Magid DJ, Gurwitz JH, Masoudi F, Greenlee RT, Tabada GH, Sung SH, Dighe A, Go AS. Long-term outcomes associated with implantable cardioverter defibrillator in adults with chronic kidney disease. *JAMA Intern Med* 2018;**178**:390–398.
101. Elming MB, Nielsen JC, Haarbo J, Videbaek L, Korup E, Signorovitch J, Olesen LL, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjaer H, Brandes A, Thogersen AM, Gustafsson F, Egstrup K, Videbaek R, Hassager C, Svendsen JH, Hofsten DE, Torp-Pedersen C, Pehrson S, Kober L, Thune JJ. Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. *Circulation* 2017;**136**:1772–1780.
102. Wahbi K, Ben YR, Gandjbakhch E, Anselme F, Gossios T, Lakdawala NK, Stalens C, Sacher F, Babuty D, Trochu JN, Moubarak G, Savvatis K, Porcher R, Laforet P, Fayssoil A, Marijon E, Stojkovic T, Behin A, Leonard-Louis S, Sole G, Labombarda F, Richard P, Metay C, Quijano-Roy S, Dabaj I, Klug D, Vantyghem MC, Chevalier P, Ambrosi P, Salort E, Sadoul N, Waintraub X, Chikhaoui K, Mabo P, Combes N, Maury P, Sellal JM, Tedrow UB, Kalman JM, Vohra J, Androulakis AF, Zeppenfeld K, Thompson T, Barnerias C, Becane HM, Bieth E, Boccara F, Bonnet D, Bouhour F, Boule S, Brehin AC, Chapon F, Cintas P, Cuisset JM, Davy JM, De Sandre-Giovannoli A, Demurger F, Desguerre I, Dieterich K, Durigneux J, Echaniz-Laguna A, Eschalier R, Ferreiro A, Ferrer X, Francannet C, Fradin M, Gaborit B, Gay A, Hagege A, Isapof A, Jeru I, Juntas MR, Lagrue E, Lamblin N, Lascols O, Laugel V, Lazarus A, Leturcq F, Levy N, Magot A, Manel V, Martins R, Mayer M, Mercier S, Meune C, Michaud M, Minot-Myhie MC, Muchir A, Nadaj-Pakleza A, Pereon Y, Petiot P, Petit F, Praline J, Rollin A, Sabouraud P, Sarret C, Schaeffer S, Taithe F, Tard C, Tiffreau V, Toutain A, Vatier C, Walther-Louvier U, Eymard B, Charron P, Vigouroux C, Bonne G, Kumar S, Elliott P, Duboc D. Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. *Circulation* 2019;**140**:293–302.
103. Shen L, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JG, Dargie HJ, Granger CB, Kjekshus J, Kober L, Latini R, Maggioni AP, Packer M, Pitt B, Solomon SD, Swedberg K, Tavazzi L, Wikstrand J, Zannad F, Zile MR, McMurray JJ. Declining risk of sudden death in heart failure. *N Engl J Med* 2017;**377**:41–51.
104. Gold MR, Linde C, Abraham WT, Gardiwal A, Daubert JC. The impact of cardiac resynchronization therapy on the incidence of ventricular arrhythmias in mild heart failure. *Heart Rhythm* 2011;**8**:679–684.
105. Aiba T, Hesketh GG, Barth AS, Liu T, Daya S, Chakir K, Dimaano VL, Abraham TP, O'Rourke B, Akar FG, Kass DA, Tomaselli GF. Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. *Circulation* 2009;**119**:1220–1230.
106. Aiba T, Barth AS, Hesketh GG, Hashambhoy YL, Chakir K, Tunin RS, Greenstein JL, Winslow RL, Kass DA, Tomaselli GF. Cardiac resynchronization therapy improves altered Na channel gating in canine model of dyssynchronous heart failure. *Circ Arrhythm Electrophysiol* 2013;**6**:546–554.
107. Aiba T, Tomaselli G. Electrical remodeling in dyssynchrony and resynchronization. *J Cardiovasc Transl Res* 2012;**5**:170–179.
108. Gorodeski EZ, Magnelli-Reyes C, Moennich LA, Grimaldi A, Rickard J. Cardiac resynchronization therapy-heart failure (CRT-HF) clinic: a novel model of care. *PLoS One* 2019;**14**:e0222610.
109. Mullens W, Grimm RA, Verga T, Dresing T, Starling RC, Wilkoff BL, Tang WH. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. *J Am Coll Cardiol* 2009;**53**:765–773.
110. Mullens W, Kepa J, De Vusser P, Vercammen J, Rivero-Ayerza M, Wagner P, Dens J, Vrolix M, Vandervoort P, Tang WH. Importance of adjunctive heart failure optimization immediately after implantation to improve long-term outcomes with cardiac resynchronization therapy. *Am J Cardiol* 2011;**108**:409–415.
111. Adamson PB, Abraham WT, Love C, Reynolds D. The evolving challenge of chronic heart failure management: a call for a new curriculum for training heart failure specialists. *J Am Coll Cardiol* 2004;**44**:1354–1357.

112. McDonagh TA, Gardner RS, Lainscak M, Nielsen OW, Parissis J, Filippatos G, Anker SD. Heart Failure Association of the European Society of Cardiology specialist heart failure curriculum. *Eur J Heart Fail* 2014;**16**:151–162.
113. Riley JP, Astin F, Crespo-Leiro MG, Deaton CM, Kienhorst J, Lambrinou E, McDonagh TA, Rushton CA, Stromberg A, Filippatos G, Anker SD. Heart Failure Association of the European Society of Cardiology heart failure nurse curriculum. *Eur J Heart Fail* 2016;**18**:736–743.
114. Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, Riegger GA, Malbecq W, Smith RD, Guptha S, Poole-Wilson PA. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009;**374**:1840–1848.
115. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF; ATLAS Study Group. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. *Circulation* 1999;**100**:2312–2318.
116. Witte KK, Drozd M, Walker AM, Patel PA, Kearney JC, Chapman S, Sapsford RJ, Gierula J, Paton MF, Lowry J, Kearney MT, Cubbon RM. Mortality reduction associated with beta-adrenoceptor inhibition in chronic heart failure is greater in patients with diabetes. *Diabetes Care* 2018;**41**:136–142.
117. Martens P, Verbrugge FH, Nijst P, Bertrand PB, Dupont M, Tang WH, Mullens W. Feasibility and association of neurohumoral blocker up-titration after cardiac resynchronization therapy. *J Card Fail* 2017;**23**:597–605.
118. Schmidt S, Hurlimann D, Starck CT, Hindricks G, Luscher TF, Ruschitzka F, Steffel J. Treatment with higher dosages of heart failure medication is associated with improved outcome following cardiac resynchronization therapy. *Eur Heart J* 2014;**35**:1051–1060.
119. Martens P, Verbrugge FH, Nijst P, Dupont M, Mullens W. Changes in loop diuretic dose and outcome after cardiac resynchronization therapy in patients with heart failure and reduced left ventricular ejection fractions. *Am J Cardiol* 2017;**120**:267–273.
120. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
121. de Diego C, Gonzalez-Torres L, Nunez JM, Centurion IR, Martin-Langerwerf DA, Sangio AD, Chochowski P, Casasnovas P, Blazquez JC, Almendral J. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. *Heart Rhythm* 2018;**15**:395–402.
122. Martens P, Belien H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. *Cardiovasc Ther* 2018;**36**:e12435.
123. Martens P, Nuyens D, Rivero-Ayerza M, Van Herendael H, Vercammen J, Ceyssens W, Luwel E, Dupont M, Mullens W. Sacubitril/valsartan reduces ventricular arrhythmias in parallel with left ventricular reverse remodeling in heart failure with reduced ejection fraction. *Clin Res Cardiol* 2019;**108**:1074–1082.
124. Zeitler EP, Piccini JP, Hellkamp AS, Whellan DJ, Jackson KP, Ellis SJ, Kraus WE, Keteyian SJ, Kitzman DW, Ewald GA, Fleg JL, Pina IL, O'Connor CM; HF-ACTION Investigators. Exercise training and pacing status in patients with heart failure: results from HF-ACTION. *J Card Fail* 2015;**21**:60–67.
125. Conraads VM, Beckers P, Bosmans J, De Clerck LS, Stevens WJ, Vrints CJ, Brutsaert DL. Combined endurance/resistance training reduces plasma TNF-alpha receptor levels in patients with chronic heart failure and coronary artery disease. *Eur Heart J* 2002;**23**:1854–1860.
126. Conraads VM, Vanderheyden M, Paelinck B, Verstreken S, Blankoff I, Miljoen H, De Sutter J, Beckers P. The effect of endurance training on exercise capacity following cardiac resynchronization therapy in chronic heart failure patients: a pilot trial. *Eur J Cardiovasc Prev Rehabil* 2007;**14**:99–106.
127. Martens P, Jacobs G, Dupont M, Mullens W. Effect of multidisciplinary cardiac rehabilitation on the response to cardiac resynchronization therapy. *Cardiovasc Ther* 2018;**36**:e12467.
128. Patwala AY, Woods PR, Sharp L, Goldspink DF, Tan LB, Wright DJ. Maximizing patient benefit from cardiac resynchronization therapy with the addition of structured exercise training: a randomized controlled study. *J Am Coll Cardiol* 2009;**53**:2332–2339.
129. Moss AJ, Brown MW, Cannom DS, Daubert JP, Estes M, Foster E, Greenberg HM, Hall WJ, Higgins SL, Klein H, Pfeffer M, Wilber D, Zareba W. Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT): design and clinical protocol. *Ann Noninvasive Electrocardiol* 2005;**10**(4 Suppl):34–43.
130. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Klein W, Tavazzi L; CARE-HF study Steering Committee and Investigators. The CARE-HF study (CArdiac REsynchronisation in Heart Failure study): rationale, design and end-points. *Eur J Heart Fail* 2001;**3**:481–489.
131. Martin DO, Day JD, Lai PY, Murphy AL, Nayak HM, Villareal RP, Weiner S, Kraus SM, Stolen KQ, Gold MR. Atrial support pacing in heart failure: results from the multicenter PEGASUS CRT trial. *J Cardiovasc Electrophysiol* 2012;**23**:1317–1325.
132. Martens P, Deferm S, Bertrand PB, Verbrugge FH, Ramaekers J, Verhaert D, Dupont M, Vandervoort PM, Mullens W. The detrimental effect of RA pacing on LA function and clinical outcome in cardiac resynchronization therapy. *JACC Cardiovasc Imaging* 2020;**13**:895–906.
133. Adelstein E, Saba S. Right atrial pacing and the risk of postimplant atrial fibrillation in cardiac resynchronization therapy recipients. *Am Heart J* 2008;**155**:94–99.
134. Sade LE, Atar I, Ozin B, Yuce D, Muderrisoglu H. Determinants of new-onset atrial fibrillation in patients receiving CRT: mechanistic insights from speckle tracking imaging. *JACC Cardiovasc Imaging* 2016;**9**:99–111.
135. Jamil HA, Gierula J, Paton MF, Byrom R, Lowry JE, Cubbon RM, Cairns DA, Kearney MT, Witte KK. Chronotropic incompetence does not limit exercise capacity in chronic heart failure. *J Am Coll Cardiol* 2016;**67**:1885–1896.
136. Thackray SD, Ghosh JM, Wright GA, Witte KK, Nikitin NP, Kaye GC, Clark AL, Tweddel A, Cleland JG. The effect of altering heart rate on ventricular function in patients with heart failure treated with beta-blockers. *Am Heart J* 2006;**152**:713.e9–13.
137. Boriani G, Rusconi L, Biffi M, Pavia L, Sassara M, Malfitano D, Bongiorni MG, Padeletti L, Filice I, Sanfelici D, Maffei P, Vicentini A, Branzi A. Role of ventricular Autocapture function in increasing longevity of DDDR pacemakers: a prospective study. *Europace* 2006;**8**:216–220.
138. Erath JW, Benz AP, Hohnloser SH, Vamos M. Clinical outcomes after implantation of quadripolar compared to bipolar left ventricular leads in patients undergoing cardiac resynchronization therapy: a systematic review and meta-analysis. *Europace* 2019;**21**:1543–1549.
139. Leclercq C, Burri H, Curnis A, Delnoy PP, Rinaldi CA, Sperzel J, Lee K, Calo L, Vicentini A, Concha JF, Thibault B. Cardiac resynchronization therapy non-responder to responder conversion rate in the more response to cardiac resynchronization therapy with MultiPoint Pacing (MORE-CRT MPP) study: results from Phase I. *Eur Heart J* 2019;**40**:2979–2987.
140. Ellenbogen KA, Gold MR, Meyer TE, Fernndez L, Mittal S, Waggoner AD, Lemke B, Singh JP, Spinale FG, Van Eyk JE, Whitehill J, Weiner S, Bedi M, Rapkin J, Stein KM. Primary results from the SmartDelay determined AV optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy (SMART-AV) trial: a randomized trial comparing empirical, echocardiography-guided, and algorithmic atrioventricular delay programming in cardiac resynchronization therapy. *Circulation* 2010;**122**:2660–2668.
141. Martin DO, Lemke B, Birnie D, Krum H, Lee KL, Aonuma K, Gasparini M, Starling RC, Milasinovic G, Rogers T, Sambelashvili A, Gorcsan J 3rd, Houmsse M. Investigation of a novel algorithm for synchronized left-ventricular pacing and ambulatory optimization of cardiac resynchronization therapy: results of the adaptive CRT trial. *Heart Rhythm* 2012;**9**:1807–1814.
142. Bordachar P, Garrigue S, Ritter P, Ploux S, Labrousse L, Casset C, Haissaguerre M, Dos SP. Contributions of a hemodynamic sensor embedded in an atrial lead in a porcine model. *J Cardiovasc Electrophysiol* 2011;**22**:579–583.
143. Filippatos G, Birnie D, Gold MR, Gerritse B, Hersi A, Jacobs S, Kusano K, Leclercq C, Mullens W, Wilkoff BL. Rationale and design of the AdaptResponse trial: a prospective randomized study of cardiac resynchronization therapy with preferential adaptive left ventricular-only pacing. *Eur J Heart Fail* 2017;**19**:950–957.
144. Wilkoff BL, Fauchier L, Stiles MK, Morillo CA, Al-Khatib SM, Almendral J, Aguinaga L, Berger RD, Cuesta A, Daubert JP, Dubner S, Ellenbogen KA, Estes NA 3rd, Fenelon G, Garcia FC, Gasparini M, Haines DE, Healey JS, Hurtwitz JL, Keegan R, Kolb C, Kuck KH, Marinskis G, Martinelli M, Mcguire M, Molina LG, Okumura K, Proclemer A, Russo AM, Singh JP, Swerdlow CD, Teo WS, Uribe W, Viskin S, Wang CC, Zhang S. 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. *Europace* 2016;**18**:159–183.
145. Ousdigian KT, Borek PP, Koehler JL, Heywood JT, Ziegler PD, Wilkoff BL. The epidemic of inadequate biventricular pacing in patients with persistent or permanent atrial fibrillation and its association with mortality. *Circ Arrhythm Electrophysiol* 2014;**7**:370–376.
146. Whellan DJ, Ousdigian KT, Al-Khatib SM, Pu W, Sarkar S, Porter CB, Pavri BB, O'Connor CM; PARTNERS Study Investigators. Combined heart failure device diagnostics identify patients at higher risk of subsequent heart failure hospitalizations: results from PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) study. *J Am Coll Cardiol* 2010;**55**:1803–1810.

147. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, Brachmann J, Lewalter T, Goette A, Block M, Kautzner J, Sack S, Husser D, Piorkowski C, Sogaard P; IN-TIME Study Group. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. *Lancet* 2014;**384**:583–590.
148. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, Phillips CO, Hodshon BV, Cooper LS, Krumholz HM. Telemonitoring in patients with heart failure. *N Engl J Med* 2010;**363**:2301–2309.
149. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Bohm M, Boll H, Baumann G, Honold M, Koehler K, Gelbrich G, Kirwan BA, Anker SD; Telemedical Interventional Monitoring in Heart Failure Investigators. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the Telemedical Interventional Monitoring in Heart Failure study. *Circulation* 2011;**123**:1873–1880.
150. Ong MK, Romano PS, Edgington S, Aronow HU, Auerbach AD, Black JT, De Marco T, Escarce JJ, Evangelista LS, Hanna B, Ganiats TG, Greenberg BH, Greenfield S, Kaplan SH, Kimchi A, Liu H, Lombardo D, Mangione CM, Sadeghi B, Sadeghi B, Sarrafzadeh M, Tong K, Fonarow GC; Better Effectiveness After Transition–Heart Failure (BEAT-HF) Research Group. Effectiveness of remote patient monitoring after discharge of hospitalized patients with heart failure: the Better Effectiveness After Transition – Heart Failure (BEAT-HF) randomized clinical trial. *JAMA Intern Med* 2016;**176**:310–318.
151. Morgan JM, Kitt S, Gill J, McComb JM, Ng GA, Raftery J, Roderick P, Seed A, Williams SG, Witte KK, Wright DJ, Harris S, Cowie MR. Remote management of heart failure using implantable electronic devices. *Eur Heart J* 2017;**38**:2352–2360.
152. Boehmer JP, Hariharan R, Devecchi FG, Smith AL, Molon G, Capucci A, An Q, Averina V, Stolen CM, Thakur PH, Thompson JA, Wariar R, Zhang Y, Singh JP. A multisensor algorithm predicts heart failure events in patients with implanted devices: results from the MultiSENSE study. *JACC Heart Fail* 2017;**5**:216–225.
153. van Veldhuisen DJ, Braunschweig F, Conraads V, Ford I, Cowie MR, Jondeau G, Kautzner J, Aguilera RM, Lunati M, Yu CM, Gerritse B, Borggrefe M. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. *Circulation* 2011;**124**:1719–1726.
154. Timmermans I, Meine M, Szendey I, Aring J, Romero RJ, van Erven L, Kahlert P, Zitron E, Mabo P, Denollet J, Versteeg H. Remote monitoring of implantable cardioverter defibrillators: patient experiences and preferences for follow-up. *Pacing Clin Electrophysiol* 2019;**42**:120–129.
155. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WH, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:137–155.
156. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot NM, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. *J Arrhythm* 2017;**33**:369–409.
157. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
158. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**:1825–1833.
159. Al Halabi S, Qintar M, Hussein A, Alraies MC, Jones DG, Wong T, MacDonald MR, Petrie MC, Cantillon D, Tarakji KG, Kanj M, Bhargava M, Varma N, Baranowski B, Wilkoff BL, Wazni O, Callahan T, Saliba W, Chung MK. Catheter ablation for atrial fibrillation in heart failure patients: a meta-analysis of randomized controlled trials. *JACC Clin Electrophysiol* 2015;**1**:200–209.
160. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bansch D; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–427.
161. Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kenneback G, Rubulis A, Malmborg H, Raatikainen P, Lonnerholm S, Hoglund N, Mortsell D. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. *JAMA* 2019;**321**:1059–1068.
162. Prabhu S, Taylor AJ, Costello BT, Kaye DM, McLellan AJ, Voskoboinik A, Sugumar H, Lockwood SM, Stokes MB, Pathik B, Nalliah CJ, Wong GR, Azzopardi SM, Gutman SJ, Lee G, Layland J, Mariani JA, Ling LH, Kalman JM, Kistler PM. Catheter ablation versus medical rate control in atrial fibrillation and systolic dysfunction: the CAMERA-MRI study. *J Am Coll Cardiol* 2017;**70**:1949–1961.
163. Khan MN, Jais P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibgilla V, Bonso A, Casella M, Raviele A, Haissaguerre M, Natale A; PABA-CHF Investigators. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med* 2008;**359**:1778–1785.
164. Lakkireddy D, Di Biase L, Ryschon K, Biria M, Swarup V, Reddy YM, Verma A, Bommana S, Burkhardt D, Dendi R, Dello Russo A, Casella M, Carbucicchio C, Tondo C, Dawn B, Natale A. Radiofrequency ablation of premature ventricular ectopy improves the efficacy of cardiac resynchronization therapy in nonresponders. *J Am Coll Cardiol* 2012;**60**:1531–1539.
165. Doval HC, Nul DR, Grancelli HO, Varini SD, Soifer S, Corrado G, Dubner S, Scapin O, Perrone SV. Nonsustained ventricular tachycardia in severe heart failure. Independent marker of increased mortality due to sudden death. GESICA-GEMA Investigators. *Circulation* 1996;**94**:3198–3203.
166. Teerlink JR, Jalaluddin M, Anderson S, Kukin ML, Eichhorn EJ, Francis G, Packer M, Massie BM. Ambulatory ventricular arrhythmias in patients with heart failure do not specifically predict an increased risk of sudden death. PROMISE (Prospective Randomized Milrinone Survival Evaluation) Investigators. *Circulation* 2000;**101**:40–46.
167. Solomon SD, Wang D, Finn P, Skali H, Zornoff L, McMurray JJ, Swedberg K, Yusuf S, Granger CB, Michelson EL, Pocock S, Pfeffer MA. Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation* 2004;**110**:2180–2183.
168. Goldenberg I, Moss AJ, Hall WJ, McNitt S, Zareba W, Andrews ML, Cannom DS; Multicenter Automatic Defibrillator Implantation Trial (MADIT) II Investigators. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the Multicenter Automatic Defibrillator Implantation Trial II. *Circulation* 2006;**113**:2810–2817.
169. Moss AJ, Greenberg H, Case RB, Zareba W, Hall WJ, Brown MW, Daubert JP, McNitt S, Andrews ML, Elkin AD. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. *Circulation* 2004;**110**:3760–3765.
170. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, van Veldhuisen DJ. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J* 2015;**36**:2793–2867.
171. Friedman DJ, Upadhyay GA, Rajabali A, Altman RK, Orencole M, Parks KA, Moore SA, Park MY, Picard MH, Ruskin JN, Singh JP, Heist EK. Progressive ventricular dysfunction among nonresponders to cardiac resynchronization therapy: baseline predictors and associated clinical outcomes. *Heart Rhythm* 2014;**11**:1991–1998.
172. Verhaert D, Popovic ZB, De S, Puntawangkoon C, Wolski K, Wilkoff BL, Starling RC, Tang WH, Thomas JD, Griffin BP, Grimm RA. Impact of mitral regurgitation on reverse remodeling and outcome in patients undergoing cardiac resynchronization therapy. *Circ Cardiovasc Imaging* 2012;**5**:21–26.
173. van der Bijl P, Khidir MJH, Leung M, Yilmaz D, Mertens B, Ajmone MN, Delgado V, Bax JJ. Reduced left ventricular mechanical dispersion at 6 months follow-up after cardiac resynchronization therapy is associated with superior long-term outcome. *Heart Rhythm* 2018;**15**:1683–1689.
174. Mathias A, Moss AJ, McNitt S, Zareba W, Goldenberg I, Solomon SD, Kutyifa V. Clinical implications of complete left-sided reverse remodeling with cardiac resynchronization therapy: a MADIT-CRT substudy. *J Am Coll Cardiol* 2016;**68**:1268–1276.
175. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A,

Marx SO, Cohen DJ, Weissman NJ, Mack MJ; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318.
176. Auricchio A, Schillinger W, Meyer S, Maisano F, Hoffmann R, Ussia GP, Pedrazzini GB, van der Heyden J, Fratini S, Klersy C, Komtebedde J, Franzen O. Correction of mitral regurgitation in nonresponders to cardiac resynchronization therapy by MitraClip improves symptoms and promotes reverse remodeling. *J Am Coll Cardiol* 2011;**58**:2183–2189.
177. McMurray JJ, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Belohlavek J, Bohm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukat A, Ge J, Howlett JG, Katova T, Kitakaze M, Ljungman CE, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjostrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;**381**:1995–2008.
178. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;**83**:778–786.
179. Potapov EV, Antonides C, Crespo-Leiro MG, Combes A, Farber G, Hannan MM, Kukucka M, de Jonge N, Loforte A, Lund LH, Mohacsi P, Morshuis M, Netuka I, Ozbaran M, Pappalardo F, Scandroglio AM, Schweiger M, Tsui S, Zimpfer D, Gustafsson F. 2019 EACTS Expert Consensus on long-term mechanical circulatory support. *Eur J Cardiothorac Surg* 2019;**56**:230–270.
180. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, Danziger-Isakov L, Kirklin JK, Kirk R, Kushwaha SS, Lund LH, Potena L, Ross HJ, Taylor DO, Verschuuren EA, Zuckermann A. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: a 10-year update. *J Heart Lung Transplant* 2016;**35**:1–23.
181. Martens P, Vercammen J, Ceyssens W, Jacobs L, Luwel E, Van Aerde H, Potargent P, Renaers M, Dupont M, Mullens W. Effects of intravenous home dobutamine in palliative end-stage heart failure on quality of life, heart failure hospitalization, and cost expenditure. *ESC Heart Fail* 2018;**5**:562–569.
182. Ruwald MH, Solomon SD, Foster E, Kutyifa V, Ruwald AC, Sherazi S, McNitt S, Jons C, Moss AJ, Zareba W. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: results from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial. *Circulation* 2014;**130**:2278–2286.
183. Chatterjee NA, Roka A, Lubitz SA, Gold MR, Daubert C, Linde C, Steffel J, Singh JP, Mela T. Reduced appropriate implantable cardioverter-defibrillator therapy after cardiac resynchronization therapy-induced left ventricular function recovery: a meta-analysis and systematic review. *Eur Heart J* 2015;**36**:2780–2789.
184. Kini V, Soufi MK, Deo R, Epstein AE, Bala R, Riley M, Groeneveld PW, Shalaby A, Dixit S. Appropriateness of primary prevention implantable cardioverter-defibrillators at the time of generator replacement: are indications still met? *J Am Coll Cardiol* 2014;**63**:2388–2394.
185. Nijst P, Martens P, Verbrugge FH, Dupont M, Tang WH, Mullens W. Cardiovascular volume reserve in patients with heart failure and reduced ejection fraction. *J Cardiovasc Transl Res* 2020;**13**:519–527.
186. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, Jackson R, Rahneva T, Wage R, Smith G, Venneri L, Tayal U, Auger D, Midwinter W, Whiffin N, Rajani R, Dungu JN, Pantazis A, Cook SA, Ware JS, Baksi AJ, Pennell DJ, Rosen SD, Cowie MR, Cleland JG, Prasad SK. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. *Lancet* 2019;**393**:61–73.
187. Haugaa KH, Potpara TS, Boveda S, Deharo JC, Chen J, Dobreanu D, Fumagalli S, Lenarczyk R, Hernandez MA, Larsen TB, Sciarrafia E, Taborsky M, Tilz RR, Pieragnoli P, Przybylski A, Dagres N. Patients' knowledge and attitudes regarding living with implantable electronic devices: results of a multicentre, multinational patient survey conducted by the European Heart Rhythm Association. *Europace* 2018;**20**:386–391.
188. Podolecki T, Pudlo R, Mazurek M, Koziel M, Jedrzejczyk-Patej E, Boidol J, Przybylska K, Sokal A, Kowalski O, Kowalczyk J, Lenarczyk R, Kalarus Z. The incidence, clinical significance, and treatment effects of depression in cardiac resynchronization therapy recipients. *Cardiology* 2017;**138**:115–121.
189. Reddy VY, Miller MA, Neuzil P, Sogaard P, Butter C, Seifert M, Delnoy PP, van Erven L, Schalji M, Boersma LV, Riahi S. Cardiac resynchronization therapy with wireless left ventricular endocardial pacing: the SELECT-LV study. *J Am Coll Cardiol* 2017;**69**:2119–2129.
190. Salden FC, Luermans JG, Westra SW, Weijs B, Engels EB, Heckman LIB, Lamerichs LJ, Janssen MH, Clerx KJ, Cornelussen R, Ghosh S, Prinzen FW, Vernooy K. Short-term hemodynamic and electrophysiological effects of cardiac resynchronization by left ventricular septal pacing. *J Am Coll Cardiol* 2020;**75**:347–359.
191. Occhetta E, Bortnik M, Magnani A, Francalacci G, Piccinino C, Plebani L, Marino P. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. *J Am Coll Cardiol* 2006;**47**:1938–1945.
192. Vijayaraman P, Chung MK, Dandamudi G, Upadhyay GA, Krishnan K, Crossley G, Bova CK, Lee BK, Refaat MM, Saksena S, Fisher JD, Lakkireddy D. His bundle pacing. *J Am Coll Cardiol* 2018;**72**:927–947.
193. Upadhyay GA, Vijayaraman P, Nayak HM, Verma N, Dandamudi G, Sharma PS, Saleem M, Mandrola J, Genovese D, Tung R. His corrective pacing or biventricular pacing for cardiac resynchronization in heart failure. *J Am Coll Cardiol* 2019;**74**:157–159.
194. Barba-Pichardo R, Manovel SA, Fernandez-Gomez JM, Morina-Vazquez P, Venegas-Gamero J, Herrera-Carranza M. Ventricular resynchronization therapy by direct His-bundle pacing using an internal cardioverter defibrillator. *Europace* 2013;**15**:83–88.
195. Zanon F, Ellenbogen KA, Dandamudi G, Sharma PS, Huang W, Lustgarten DL, Tung R, Tada H, Koneru JN, Bergemann T, Fagan DH, Hudnall JH, Vijayaraman P. Permanent His-bundle pacing: a systematic literature review and meta-analysis. *Europace* 2018;**20**:1819–1826.
196. Lustgarten DL, Crespo EM, Arkhipova-Jenkins I, Lobel R, Winget J, Koehler J, Liberman E, Sheldon T. His-bundle pacing versus biventricular pacing in cardiac resynchronization therapy patients: a crossover design comparison. *Heart Rhythm* 2015;**12**:1548–1557.
197. Sharma PS, Dandamudi G, Herweg B, Wilson D, Singh R, Naperkowski A, Koneru JN, Ellenbogen KA, Vijayaraman P. Permanent His-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: a multicenter experience. *Heart Rhythm* 2018;**15**:413–420.
198. Huang W, Su L, Wu S, Xu L, Xiao F, Zhou X, Ellenbogen KA. A novel pacing strategy with low and stable output: pacing the left bundle branch immediately beyond the conduction block. *Can J Cardiol* 2017;**33**:1736.e1–3.
199. Keene D, Arnold A, Shun-Shin MJ, Howard JP, Sohaib SA, Moore P, Tanner M, Quereshi N, Muthumala A, Chandresekeran B, Foley P, Leyva F, Adhya S, Falaschetti E, Tsang H, Vijayaraman P, Cleland JG, Stegemann B, Francis DP, Whinnett ZI. Rationale and design of the randomized multicentre His Optimized Pacing Evaluated for Heart Failure (HOPE-HF) trial. *ESC Heart Fail* 2018;**5**:965–976.
200. Shen L, Jhund PS, Docherty KF, Petrie MC, Anand IS, Carson PE, Desai AS, Granger CB, Komajda M, McKelvie RS, Pfeffer MA, Solomon SD, Swedberg K, Zile MR, McMurray JJ. Prior pacemaker implantation and clinical outcomes in patients with heart failure and preserved ejection fraction. *JACC Heart Fail* 2019;**7**:418–427.