

2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management

Developed in partnership with the European Heart Rhythm Association (EHRA) A registered branch of the European Society of Cardiology (ESC), and the Heart Rhythm Society; and in collaboration with the Heart Failure Society of America (HFSA), the American Society of Echocardiography (ASE), the American Heart Association (AHA), the European Association of Echocardiography (EAE) of the ESC and the Heart Failure Association of the ESC (HFA).

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Cardiac resynchronization therapy • CRT • Follow-up • Non-responder • Consensus recommendations

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Background

Cardiac resynchronization therapy (CRT) is one of the most successful heart failure therapies to emerge in the last 25 years and is applicable to ~25–30% of patients with symptomatic heart failure. Since initial approval of the therapy over 10 years ago, there have been hundreds of thousands of implants worldwide. Regulatory approval, largely based on controlled clinical trials, defines a much narrower population of patients for CRT than the patients that are currently implanted with CRT devices. Expert consensus guidelines provide direction as to the population of patients most expected to benefit from CRT, based on the findings, design, and size of prior studies. Updates to indications for CRT are expected in this calendar year and are not the focus of this document.^{1–5}

Cardiac resynchronization therapy can be administered with or without defibrillation therapy. For the purposes of this document, the term CRT applies to either a CRT-pacemaker (CRT-P) or CRT-defibrillator (CRT-D). If the paragraph is relevant to only one type of therapy, the device type will be listed as CRT-P or CRT-D.

The physician responsible for the patients' medical therapy regimen typically refers patients for consideration of CRT. Ensuring an optimal response to CRT requires the implanting physician make an independent assessment of the patient's heart failure status and assure that the patient is on guideline-directed medical therapy demonstrated to improve clinical status, and reduce hospitalization and mortality. The implanting physician should participate in the follow-up care and the monitoring of the patient as well as ensure care coordination with other physicians managing the patient's clinical care. This includes assessment of patient symptoms, as well as diagnostic device data and programming.

Historically, significant attention has been placed on the technical aspects of the implant procedure, particularly placement of the left ventricular (LV) lead. Placement of the transvenous epicardial LV lead is critical to achieving cardiac resynchronization and to garnering the dramatic improvement in symptoms, quality of life, improvement in LV function, hospitalization, and mortality rates in patients with systolic dysfunction, QRS delay, and heart failure. With the increase in operator experience and advancement in implant tools, a successful CRT implant is now achieved in >90% of cases. This allows for additional and updated focus on the patient, device, and lead selection. Further, advances in heart failure diagnostic tests and devices that are independent of or a part of CRT devices require an increasing awareness of the role of CRT in the overall disease management of heart failure patients.

This document represents the efforts of a multi-disciplinary group of physicians with clinical and investigational expertise in CRT for treatment of heart failure. The purpose of this consensus statement is to fill in knowledge gaps with consensus opinion where the clinical evidence is less than certain. The document addresses the pre-implant, implant, and post-implant management of the CRT recipient. The document's recommendations summarize the writing group's consensus opinions supported by 70% or greater of the writing committee by anonymous vote.

The writing group is composed of 28 members representing seven organizations: the American Heart Association (AHA), the American Society of Echocardiography (ASE), the European Heart Rhythm Association (EHRA), the Heart Failure Association of the ESC (HFA), the European Association of Echocardiography (EAE) of the ESC, the Heart Failure Society of America (HFSA), and the Heart Rhythm Society (HRS). Writing group members and peer reviewers provided disclosure statements for all relationships that could be perceived as real or potential conflicts of interest.

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2012 EHRA/HRS Expert Consensus Statement on Cardiac Resynchronization Therapy (CRT) in Heart Failure: Implant and Follow-up Recommendations and Management

1. Pre-implant evaluation

1.1 Pre-implant recommendations (Table 1)

Patients considered for cardiac resynchronization therapy (CRT) should undergo careful pre-implantation evaluation to ensure the likelihood of a successful device implantation, appropriate device selection and programming, and a durable and favourable response to the therapy. The pre-implant assessment begins with a careful evaluation of comorbid conditions that may make implantation difficult or reduce response rates. A careful cardiac anatomic evaluation with imaging techniques is essential for defining left ventricular (LV) size and function and for predicting long-term clinical outcome. In addition to anatomic imaging, an electrophysiological evaluation, including baseline electrocardiogram (ECG) and history of arrhythmias or prior device therapy, is important to guide device selection, lead placement, and programming of the implanted device. Finally, assessment and management of the heart failure medical regimen prior to and after implant is essential to maximize the likelihood of CRT benefit.

1.2 Baseline clinical data

Eligibility for CRT is traditionally based on New York Heart Association (NYHA) Functional Classification of symptoms, the ACC/AHA (American College of Cardiology/American Heart Association) stages of heart failure, QRS duration, left ventricular ejection fraction (LVEF), and, optionally, LV cavity size.^{1,3,4} However, additional information may support the likelihood of successful implantation and improve the clinical response to the therapy.

1.2.1 Optimal medical management

Neurohormonal therapy with angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, and beta-blockers is the mainstay of therapy for patients with an LVEF < 40%.⁶ Aldosterone antagonists and nitrate-hydralazine combinations are indicated for selected patient populations although future guidelines are likely to expand indications for aldosterone antagonists.⁶ Treatment algorithms have been proposed for patients with symptomatic heart failure and reduced LVEF.⁵ Frequently, implanting physicians are required to determine whether medical therapies

are optimized prior to implantation. It is important to assure that patients are getting this maximum benefit from medical therapies and this may require delaying the implant of a referred patient so that therapies can be initiated or dosages titrated upward. The goals of CRT are to improve clinical status, cardiac performance and survival, and it is possible that with sufficient time, appropriate medical therapies may accomplish these goals. Ideally, patients should be treated with guideline-directed medical therapy and stable for at least 3 months before CRT implant.

1.2.2 Routine laboratory/biomarker evaluation

A routine laboratory evaluation including a blood count, serum electrolytes, serum creatinine, glomerular filtration rate (GFR), glucose, liver function tests, urinalysis, and including careful assessment of the international normalized ratio (INR) should be considered pre- and perioperatively in patients, especially those taking oral anticoagulant therapy.¹

Biomarkers that assess heart failure status like the natriuretic peptides BNP and NT-proBNP may be useful in the initial diagnosis of heart failure in patients who present with shortness of breath. The evidence for their use in monitoring and adjusting drug therapy is less clearly established.^{2,5} Cardiac resynchronization therapy has been shown to reduce natriuretic peptide levels substantially and reduction in plasma levels is associated with better outcome.⁷ In the CARE-HF study,⁸ plasma concentration of NT-proBNP was one of the strongest predictors of mortality, regardless of assigned treatment, but it was not an independent predictor of response to CRT.

Other biomarkers and cytokines that are activated in heart failure have been assessed in small studies. Results suggest that Growth differentiation factor-15,⁹ a member of the transforming growth factor- β cytokine superfamily, and amino-terminal propeptide of type III procollagen¹⁰ may predict response to CRT but the data are preliminary.

1.2.3 Functional assessment

Functional assessment endpoints are well studied in clinical trials evaluating the effect of CRT.^{8,11–13} Formal baseline functional testing in clinical practice can be an important part of the pre-implantation assessment. The 6 min hall walk test is an inexpensive and a widely used mechanism to determine functional status along with cardiopulmonary stress testing. The 6 min hall walk test does not require special equipment and allows patients to walk at their own pace as opposed to cardiopulmonary stress testing. Predicting clinical response to CRT using exercise duration on stress testing is unproven. Measurement of peak oxygen consumption on cardiopulmonary exercise testing is well validated as a means of assessing response to CRT. Functional testing at baseline can be repeated after a period of time following implantation (i.e. 3–6 months) to document clinical improvement.^{2,3,5}

1.2.4 Quality of life measurements

Quality of life (QOL) measurements obtained by validated baseline questionnaire also can be helpful when compared with repeated measurements after the therapy is active for a time.^{2,3,5} Assessment of both functional and formal QOL measurements can help patients recognize improvements that may take time to

Table 1 Summary of consensus recommendations

	Is recommended	May be useful	Are not recommended
Pre-implant recommendations	A careful evaluation of comorbidities and an estimate of life expectancy is recommended	Pre-implant formal functional status testing including a QOL measure may be useful for monitoring CRT response	CRT implant should be deferred in patients with acutely decompensated heart failure, who are dependent on inotropes, or who have unstable ventricular arrhythmias until their medical status is improved
	A thorough pre-implant history and physical examination including review of vital signs and laboratory tests is recommended	Cardiac MRI may be useful to assess cardiac function and provide detailed information about viable myocardium in distribution of a CS branch vein considered for LV lead implant	Echocardiographic dyssynchrony assessment should not be used to exclude patients from consideration for CRT
	CRT candidates should have stable heart failure status on guideline-directed medical therapy prior to implant	Venous anatomic mapping using CT angiography may be useful in certain patient populations. These include patients with prior LV lead implant failure or those at risk for abnormal venous anatomy	
	A pre-implant comprehensive echocardiogram for quantification of LVEF and assessment of cardiac size and function is recommended	Development of a pre-implant strategy should be considered to identify and manage atrial fibrillation or frequent PVCs that may impair the ability of CRT to deliver therapy continuously	
	A pre-implant 12-lead ECG including QRS duration measure (>120–130 ms) and characterization of QRS morphology is recommended	In patients at low to moderate thromboembolic risk on oral anticoagulant therapy with warfarin, continuing at reduced dosage (INR 1.5–2) or withholding therapy 3–5 days preoperatively can be useful to minimize bleeding risk	
	In patients at high thromboembolic risk on oral anticoagulant therapy with warfarin, continuing therapy at reduced dosage with close monitoring of INR (INR 2–3) is recommended perioperatively. Post-operative use of heparin is discouraged	In patients at low–moderate thromboembolic risk on direct thrombin or factor Xa inhibitor agents, withholding such therapy 2–3 days before surgery can be useful to minimize bleeding risk	
	Preoperative treatment with an antibiotic that has <i>in vitro</i> activity against staphylococci is recommended for infection prophylaxis		
CRT implant recommendations	Intra-operative haemodynamic monitoring including careful attention of volume status is recommended	General anaesthesia may be considered for CRT implants	It is not recommended to place the LV lead in an apical position.
	The RV lead is recommended as the first intracardiac lead implanted	Controversy exists regarding the value of routine acute defibrillation testing but major CRT trials included DFT testing. The decision to perform DFT testing should be made on an individual basis by the treating physician	
	CS venography is recommended to create a roadmap that guides lead selection and assists with navigation		
	LV lead testing is recommended to assure an adequate safety margin for capture and avoidance of PNS Careful discussion with patients regarding the risk and benefits of CRT-D vs. CRT-P device implant is		

Continued

Table I Continued

	Is recommended	May be useful	Are not recommended
Pre-discharge evaluation recommendations	<p>recommended prior to the decision as to the type of CRT device implanted</p> <p>A physical examination, device interrogation, chest X-ray, and surface ECG is recommended prior to discharge</p> <p>Careful attention to volume status is recommended after the implantation procedure as an acute response to CRT may include significant diuresis</p> <p>A standard echocardiographic assessment is recommended prior to discharge if a procedural complication is suspected on the basis of patient symptoms or clinical findings</p> <p>An assessment to assure 100% biventricular capture is recommended prior to discharge</p> <p>The majority of patients implanted with CRT should remain in the hospital overnight after implant to observe clinical status</p>		
CRT follow-up recommendations	<p>A close degree of cooperation is recommended in the follow-up of the CRT recipient between the heart failure and electrophysiology follow-up physician</p> <p>A minimum in-clinic follow-up interval of 6 months is strongly recommended for CRT recipients</p> <p>Remote monitoring and follow-up in addition to in-clinic follow-up is recommended. Patients should be encouraged to initiate a remote transmission if new symptoms or concerns arise</p> <p>Follow-up visits that include a patient history, physical examination, device interrogation and testing, and systematic analysis of device data is recommended</p> <p>Optimization including upward titration of heart failure drug therapies, if appropriate, is recommended to maximize response to CRT</p> <p>Evaluation of LV function or other adjuncts to assess heart failure progression or regression is recommended during follow-up</p>	<p>Catheter ablation of the AV node in the setting of atrial fibrillation with native conduction can be useful if CRT is not being delivered consistently</p>	
CRT management recommendations	<p>Assessment of patient response to CRT, including an evaluation of symptoms and functional response and echocardiographic measures of cardiac function, is recommended</p> <p>An assessment of potentially reversible causes for non-response is</p>	<p>Echocardiographically directed or empiric AV or VV timing optimization, or LV lead repositioning may be considered in selected patients but their role in improving response has not been proven</p> <p>Discontinuation of CRT by programming off LV stimulation may be considered if</p>	

Continued

Table I Continued

	Is recommended	May be useful	Are not recommended
	recommended in patients without demonstrable improvement in heart failure status after CRT implant	there is no clear evidence of response to therapy or concern exists that LV pacing is introducing risk	
	A device interrogation is recommended to assess for atrial and ventricular arrhythmias, quality of CRT delivery (% effective biventricular capture) and rate response	In patients who do not respond to CRT and continue to experience heart failure symptoms, alternative treatment options should be considered such as placement of a LV assist device or cardiac transplantation	
	Optimization of medical therapy, assurance of appropriate and consistent biventricular pacing and treatment of arrhythmias is recommended		
Special considerations	Pre-implant patient education including information about the need and function of the CRT device and follow-up plan is recommended. There are a variety of digital patient educational tools that can be utilized to fully inform the patient as to the risks and benefits of CRT or CRT-D therapy		

manifest.¹⁴ Often, patients do not remember how they felt prior to CRT implantation and the gradual, but persistent improvements in clinical status are difficult to perceive. Several QOL measurement instruments are available, the Minnesota Living with Heart Failure questionnaire being the most widely used and should be considered as patients are evaluated for CRT.

1.2.5 Determination of heart failure aetiology/coronary angiography

Characterizing the aetiology of heart failure prior to CRT device implantation may be important as heart failure aetiology may influence implantation strategy (Section 2) and response to CRT (Section 5). There is no established definition of ischaemic cardiomyopathy or ischaemic heart failure. The definition most commonly used for clinical research¹⁵ is based on coronary anatomy and defines patients with single-vessel coronary disease as having a non-ischaemic heart failure aetiology unless they have left main or proximal left anterior descending disease or a history of revascularization or myocardial infarction. All other classes of patients with significant epicardial coronary disease are defined as having an ischaemic aetiology. In the general heart failure population, heart failure guidelines^{2,5} indicate that coronary angiography should be considered in patients with heart failure who have angina or significant ischaemia unless the patient is not eligible for revascularization of any kind (class I, level of evidence B).

1.2.6 Comorbidities/life expectancy

An assessment of significant comorbidities that may make implantation difficult or impair the long-term benefit of the CRT is required to select CRT candidates most apt to improve. Patients with significant comorbid conditions were generally excluded

from clinical trials and, as such, CRT should be considered untested in these groups. For example, patients with stage IV–V chronic kidney disease were not included in CRT trials.¹⁶ The Multicenter In Sync Randomized Clinical Evaluation or MIRACLE trial excluded patients with a serum creatinine >3.0 mg/dL, and excluded patients on dialysis.¹¹ Subsequent studies have confirmed that patients with moderate to severe chronic kidney disease at the time of CRT implantation have significantly higher overall mortality compared with those with normal renal function.¹⁷ Therefore, clinical expectation should be tempered in patients with severe chronic kidney disease as these patients also appear to have less robust CRT response.¹² Especially careful consideration should be given to dialysis patients because the benefit of CRT is not well proven in this population.

Pulmonary disorders contributing to chronic dyspnea may influence the outcome and lessen the benefits of CRT.¹⁸ Therefore, pulmonary function testing in patients suspected of having significant lung disease may help provide a better understanding of the potential for CRT benefit. Sleep apnea is also prevalent in CRT candidates and contributes to the malaise and fatigue components of QOL measurements but other than taking a history for sleep apnea symptoms, systematic screening for sleep apnea with a formal sleep study should not be routine. Awareness and treatment of sleep apnea, whether central or obstructive, may improve the overall heart failure syndrome. Meta-analysis evidence suggests that CRT may improve the apnea–hypopnea index patients with sleep apnea primarily by reducing central apnea events.¹⁸ However, systematic screening for sleep breathing disorders cannot be recommended in the pre-implantation evaluation.

Patients with a history of thoracic radiation therapy or previous valve surgery may have altered anatomy and may be at higher risk

for unsuccessful LV lead implantation. Pre-implant assessments in these patients may include special imaging to ensure suitable venous targets are available. Finally, patients with a life expectancy <1 year due to non-cardiovascular disorders are not considered appropriate CRT candidates. Estimating life expectancy in heart failure is based on heart failure severity and severe associated comorbidity. Several scores have been proposed to predict survival in heart failure. The more widely used model is the Seattle heart failure model (SHFM) that provides an accurate estimate of 1-, 2- and 3-year survival with the use of easily obtained clinical, pharmacological, device, and laboratory characteristics.¹⁹ This model also predicts the mode of death.²⁰ The most important limitation of the SHFM is that it does not include the role of major comorbidities that may independently impact prognosis. Results from a recent study investigating the predictive value of the Charlson comorbidity index,²¹ a score widely used as an adjustment variable in prognostic models in chronic diseases²² show that comorbidity is an independent predictor of all-cause mortality in this population. Myocardial infarction, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, peripheral vascular disease, renal failure, and malignancy in any form are the main components of the comorbidity score. These data suggest that a comprehensive assessment of comorbidity is needed along with the estimation of heart failure severity prior to every CRT implant.

1.2.7 Non-ambulatory New York Heart Association class IV

Few patients with ACC stage D refractory NYHA class IV symptoms were enrolled in prospective CRT trials. In fact, >75% of patients enrolled in early trials had NYHA class III symptoms.²³ In addition, patients requiring inotropic support, those characterized by elevated cardiac sympathetic activity (low heart rate variability)²³ or inability to tolerate beta-blocker therapy are more likely to require hospitalization in the year after CRT implantation. Therefore, patients with stage D, refractory class IV heart failure syndromes who require inotropic therapy or cannot tolerate chronic heart failure medications should be carefully evaluated in the context of advanced therapies, as CRT is not generally considered to be a good 'bail-out' or 'last-resort' therapy.

1.3 Imaging techniques

1.3.1 Basic anatomical and functional measures

The quantification of LV dysfunction is a cornerstone for determining candidacy for CRT. An LVEF of $\leq 35\%$ is the most common criterion for candidacy of CRT. Such a key criterion necessitates accurate quantification to ensure optimal effectiveness of therapy. Echocardiography has been considered the single most useful diagnostic test in the evaluation of heart failure patients according to the ACC/AHA.⁶ Other diagnostic modalities such as nuclear imaging, computed tomography (CT), or magnetic resonance imaging (MRI) also are useful for determining EF. However, due to various technical and/or economical limitations, these modalities are far less utilized in clinical practice. Furthermore, echocardiography, as opposed to other techniques, provides additional information such as presence of valvular heart disease, mitral regurgitation (MR) in particular and haemodynamic status. To assure the most accurate determination of LV size and function,

M-mode (only for diameters) and/or 2D measurements and LV biplane volumes indexed to body size using Simpson's method of discs or 3D echocardiography should be utilized.^{24–26} For patients in whom 2D echocardiographic methods are suboptimal (two or more segments unseen), LV opacification using echo contrast agents should be applied to optimize endocardial borders and the measurement of ventricular volumes.²⁷ For patients in whom neither the baseline 2D echo nor a contrast enhanced echo provides accurate diagnostic information, cardiac magnetic resonance (CMR) can be utilized to enhance accuracy of the LV size and functional assessment. Identification of confluent regions of scar that could influence LV lead placement can be identified and analysed with CMR imaging techniques that include late gadolinium enhancement and delayed contraction assessed with tagged imaging.^{28–30} Echocardiography is usually non-diagnostic in determining scar or location even though the presence of end-diastolic myocardial thickness <6 mm is highly suggestive of transmural scar.³¹ Finally, the definitive determination of viability achieved whether by CMR or dobutamine-stress echocardiography may be imperative to a successful outcome.³² The determination of right ventricular (RV) size and function also has been recognized as an important predictor of outcome in patients undergoing CRT.^{33–35}

1.3.2 Dyssynchrony evaluation by imaging/echocardiography

Resynchronization of a portion of the LV that has delayed LV activation is the cornerstone and pathophysiological basis for CRT.^{36,37} It is well demonstrated by various imaging techniques that the acute haemodynamic benefit is associated with both the magnitude of pre-implant mechanical dyssynchrony, as well as with the extent of mechanical resynchronization during CRT.^{38,39} Despite these pathophysiological limitations, the pre-implant quantification of mechanical dyssynchrony, mainly performed by echocardiography, has failed to demonstrate significant predictive value for CRT benefit.^{40,41} It is particularly true if the assessment of dyssynchrony is performed by dichotomous assessment of a single dyssynchrony parameter or dimension.⁴² Such a simplified approach often does not sufficiently characterize the complex mechanical dyssynchrony patterns and may not be sufficiently sensitive to identify the presence of correctable mechanical dyssynchrony.⁴³ On the contrary, significant mechanical dyssynchrony also may be documented in patients with non-viable myocardial segments, where the scar region cannot be sufficiently resynchronized by pacing and the dyssynchrony remains 'non-correctable'.¹¹

Despite all these limitations and pitfalls, there is some evidence that a comprehensive assessment, in expert hands, which integrates several mechanical dyssynchrony parameters, myocardial viability, and sizes, can help at identifying patients with a higher likelihood to respond.^{42–44} Post-implant assessment of CRT efficacy and device optimization is facilitated if pre-implant values are available for direct comparison. Assessing for mechanical dyssynchrony should include conventional Doppler derived measures (LV pre-ejection delay, inter-ventricular mechanical delay) that can be obtained during a pre-implant echocardiogram.⁴⁵ The Doppler parameters characterize both atrial ventricular dyssynchrony (i.e. mitral diastolic filling time) and inter- and intra-ventricular dyssynchrony (i.e. inter-ventricular mechanical delay).

More advanced technology such as the assessment of myocardial deformation patterns by strain imaging techniques or endocardial motion by 3D echocardiography is encouraged wherever the expertise is available and may provide useful information for optimal lead placement by identification of the site of latest contraction.^{46–48} Timing of longitudinal myocardial motion by tissue Doppler velocities has shown value for patient selection in the hands of experienced centres, but have failed to show a consistent benefit in larger prospective multicentre trials⁴⁰ and should not be used for identification of the latest contracting segments.⁴⁹

No patient should be excluded from consideration for CRT solely on the basis of a negative echocardiographic dyssynchrony assessment. However, patients who are scheduled for CRT despite lack of mechanical dyssynchrony by any available parameter require special attention during follow-up.⁵⁰ This practice also applies to patients with a borderline indication for CRT with respect to measures of electrical dyssynchrony that include QRS width and morphology [i.e. QRS < 150 ms and non-left bundle branch block (LBBB) morphology].^{51,52}

1.3.3 Cardiac computed tomography angiography and cardiac magnetic resonance imaging

The roles of cardiac computed tomography angiography (CCTA) and CMR in the pre-implant assessment for CRT are not well

defined. Increased understanding of cardiac anatomy is a goal of using these techniques. Cardiac computed tomography angiography provides detailed assessment of coronary artery and coronary venous branch vein anatomy, but requires X-ray radiation and iodinated contrast. Cardiac magnetic resonance provides myocardial tissue characteristics and timing and degree of segmental ventricular contraction, but requires a gadolinium-based contrast agent, longer scanning times, and the absence of contraindications to the MR environment. With both technologies, the clinical heart failure status of the patient is extremely important, as the studies require the supine position, ability to breath-hold, toleration of a contrast fluid load, and the absence of significant renal dysfunction. Cardiac computed tomography angiography additionally requires patient ability to tolerate pharmacologic heart rate control.

1.3.4 Cardiac computed tomography angiography and cardiac magnetic resonance to define coronary venous anatomy

Cardiac computed tomography angiography can image and quantify the coronary venous system, including individual patient branch vein variability and obstacles to placement prior to a CRT procedure.^{53–60} Preliminary data suggest that pre-procedure knowledge of the 3D coronary venous anatomy can facilitate CRT through decreased procedure time and utilization of guide

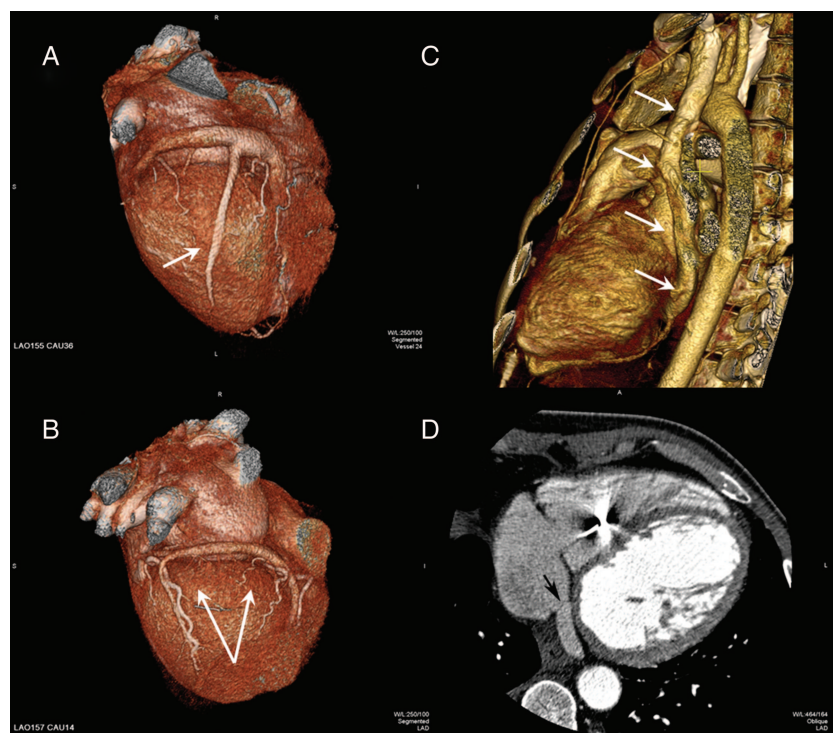


Figure 1 Three-dimensional computed tomography angiograms demonstrating coronary venous variation. (A) Posterior branch vein off of the coronary sinus which courses posterolaterally, without presence of a lateral branch vein. (B) Paucity of coronary venous branch veins in the posterior and postero-lateral myocardial regions. (C) Left-sided superior vena cava coursing into an aneurysmal coronary sinus/great cardiac vein. (D) Thebesian valve covering the coronary sinus ostium. Reprinted with permission. Cao M, Chang P, Garon B, Shinbane JS. Cardiac resynchronization therapy: double cannulation approach to coronary venous lead placement via a prominent Thebesian valve. *Pacing Clin Electrophysiol.* 2012 Mar 20, doi:10.1111/j.1540-8159.2012.03362.x. [Epub ahead of print].

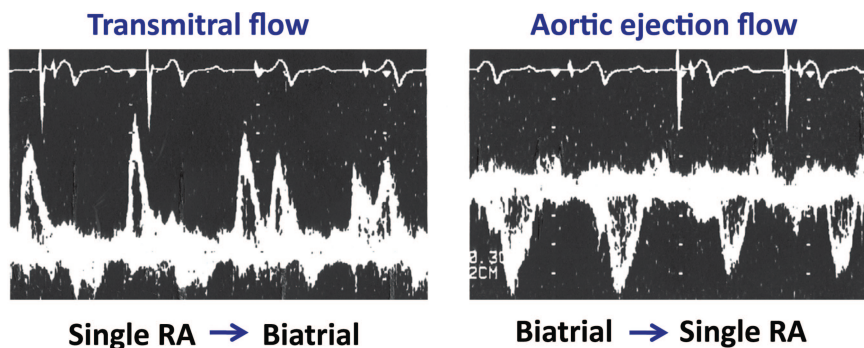


Figure 2 Haemodynamic consequences of long interatrial conduction time: correction with biatrial pacing. Biventricular atrioventricular sequential pacing at 70 b.p.m. with fixed atrioventricular delay of 150 ms. On the left, switching from single right atrium (RA) pacing to biatrial pacing doubles the left ventricular filling time and restores normal left atrial contribution. On the right, switching from biatrial to RA pacing results in instantaneous decrease in aortic ejection flow velocity.

catheters.⁵⁸ Cardiac computed tomography angiography visualized sites of coronary venous branch vein lead placement in areas and echo-derived location of latest mechanical activation has correlated with acute response to CRT, while lack of response occurred with disparity between lead site and area of latest mechanical activation.⁵⁶ Cardiac computed tomography angiography can image the 3D relationship of the phrenic nerve neurovascular bundle to the coronary venous branch veins and requires study to potentially identify high vs. low risk sites for the development of diaphragmatic pacing.⁶¹ Use of 3D coronary venous CCTA images fused with real-time fluoroscopy images is feasible and requires further investigation.⁶² (Figure 1)

Coronary venous angiography has been achieved with CMR whole-heart coronary venography using slow MR contrast infusion protocols.^{63–68} These images can be overlaid with CMR imaging of myocardial infarction scar.^{69,70} The use of real-time magnetic resonance-guided intubation of the coronary sinus (CS) preliminarily is being investigated.⁷¹

1.3.5 Ventricular function and tissue characteristics

Cardiac magnetic resonance can assess dyssynchrony and scar through assessment of wall thickness, wall thickening, wall motion, and latest mechanical activation.^{29,72,73} Functional imaging of scar improves the prediction of response.²⁹ Cardiac magnetic resonance tissue characteristics are predictive of CRT effect in ischaemic cardiomyopathy, with response associated with findings of <15% of total myocardium infarcted and the absence of significant postero-lateral scar.^{74–76} The use of delayed contrast enhancement to guide endovascular LV lead placement away from scarred myocardium resulted in a better clinical outcome regarding heart failure and sudden death compared with lead placement in areas of scar.⁷⁷ Cardiac magnetic resonance can guide decisions as to target sites with latest mechanical activation and no evidence of scar by radial strain or delayed enhancement.^{78–80} Cardiac computed tomography angiography delayed contrast enhancement for myocardial assessment is at an earlier stage of development than CMR and requires additional radiation for delayed imaging.^{81–86}

1.4 Electrical assessment: resting electrocardiogram

Along with LVEF, a 12-lead ECG is the current standard to detect ventricular dyssynchrony as defined by QRS duration and is used to determine eligibility for CRT. Although QRS duration is reproducible, progression may occur over time and repeated ECG evaluations may be warranted.

1.4.1 P-wave and atrial rhythm

In patients in sinus rhythm, it is important to analyse the P-wave morphology and duration. Major inter-atrial conduction delay as indicated by P-wave duration >120 ms is often associated with delayed left atrial contraction. It may result in suboptimal atrioventricular (AV) synchrony in the left heart when programming a standard AV delay during atrio-biventricular pacing. Identification of delay may influence right atrium (RA) lead location and individual programming might be considered in these patients.⁸⁷ (Figure 2)

1.4.2 PR interval

In heart failure, prolonged PR intervals are frequently found and give rise to diastolic MR and prolonged systolic MR time. Cardiac resynchronization therapy can be effective in correcting this prolonged interval by programming shorter (more physiological) intervals, and improving LV filling.

1.4.3 QRS complex duration and morphology

In the current guidelines QRS duration >120 ms is the electrical criteria used to determine eligibility for CRT in NYHA class III–IV patients.^{1–5} While patients with QRS duration >150 ms respond well to CRT, values between 120 and 150 are associated with a more variable response.⁸⁸ There is conflicting evidence from observational studies as to whether patients with a narrow QRS (<120 ms) benefit from CRT. Recent multicentre studies have provided strong evidence that QRS morphology is as important as QRS duration to predict response to CRT. The presence of a typical LBBB morphology is a strong predictor of response while right bundle branch block (RBBB) morphology and non-specific

intra-ventricular conduction disturbances (IVCD) are often associated with a lack of response or even a trend to adverse outcome.^{51,89–91} It also is important to understand that a certain percentage of patients with RBBB on ECG also will have underlying LV electrical delay.

1.4.4 Electrocardiogram criteria for left bundle branch block revisited

Left bundle branch block diagnosis is based on well-established consensus criteria.⁹² Recently, Strauss *et al.*⁹³ provided strong arguments that for a true LBBB, QRS width should be >130 ms for women and >140 ms for men along with mid-QRS notching or slurring in >2 contiguous leads. In further support of the multicentre studies, Sweeney *et al.*⁹⁴ showed that QRS morphology is crucial for recognizing LBBB and that indices derived from QRS morphology, such as LV activation time and scar burden, can be used as positive and negative predictors of CRT response, respectively.

1.4.5 QT interval

Baseline QT or JT interval does not predict response to CRT.⁵¹ There is no clear indication that abnormal QT interval (either absolute value or dispersion) at baseline predicts adverse effects of CRT. In contrast, some small studies demonstrated that prolongation of QT-dispersion upon CRT is associated with life-threatening arrhythmias.^{95,96}

1.4.6 Premature ventricular contractions

Like atrial fibrillation, frequent premature ventricular contractions (PVCs) may reduce the ability to deliver biventricular pacing. Therefore, medical or ablative therapy to reduce PVC burden may be indicated.⁹⁷ A history of life-threatening ventricular arrhythmias and an indication for a primary prevention implantable cardioverter defibrillator (ICD) are additional factors for consideration of a CRT device.

1.4.7 Additional electrophysiological measurements

More detailed electrical measurements can be performed using invasive techniques such as electroanatomic mapping.^{97,98} These techniques demonstrate that the substrate supporting electrical delay in heart failure patients is heterogeneous and these measures may allow detection of LV electrical delay in patient without manifest LBBB on ECG.⁹⁹

1.5 Pre-implantation medical management

1.5.1 Antithrombotics

Implantation of a cardiac rhythm device including CRT during concomitant use of oral anticoagulants or dual antiplatelet therapy poses an increased risk of perioperative bleeding complications (i.e. pocket haematoma), whereas its discontinuation poses a thromboembolic risk. In a recent systematic review,¹⁰⁰ the traditional strategy involving bridging anticoagulation with therapeutic-dose heparin was associated with an incidence of pocket haematoma of 12–20% and should therefore be abandoned. The incidence of pocket bleeding was decreased in patients who continue with warfarin treatment (1–6.6%) or who discontinued anticoagulant therapy (1.1–2%). These strategies did not result in increased incidence of thromboembolic events (0–1%). Patients

at low to moderate thromboembolic risk (i.e. biologic valve, atrial fibrillation with CHADS score <4, no history of thromboembolic event) receiving oral anticoagulant therapy with warfarin should continue with a reduced dose (INR 1.5–2.5) or stop the oral anticoagulant 3–5 days before surgery. Patients at low to moderate thromboembolic risk receiving oral anticoagulant therapy with newer agents (e.g. direct thrombin or factor XA inhibitor agents) should discontinue the oral anticoagulant 2–3 days prior to surgery. Re-initiation of oral anticoagulant therapy can be considered the day after surgery.

In patients treated with aspirin alone or with dual antiplatelet treatment, the risks of bleeding during CRT implantation are two- and four-fold the risk of patients not receiving antiplatelet therapies (3.9 and 7.2 vs. 1.6%; $P = 0.078$ and 0.004 , respectively).¹⁰¹ In most cases, antiplatelet medications can be safely discontinued, for a period of 5–7 days, specifically when prescribed for primary prevention. Assuming dual antiplatelet therapy is used to prevent in-stent thrombosis following percutaneous coronary intervention, it is reasonable to discontinue clopidogrel for a period of 5 days while continuing aspirin in lower risk patients who are late after stent implantation. High-risk patients (i.e. those soon after stent implantation), should continue dual antiplatelet therapy.^{102,103}

1.5.2 Antibiotics

In a multicentre registry of 6319 consecutive recipients of pacemakers or defibrillators in 44 medical centres, device-related infections were reported in 0.68% within 12 months of implantation.¹⁰⁴ Infections occurred more frequently with use of temporary pacing or other procedures before implantation, early reintervention and without antibiotic prophylaxis. A meta-analysis of antibiotic prophylaxis using a regimen of pre-procedure and post-procedure administration suggested a significant reduction in the incidence of infection.¹⁰⁵ A recent large-scale, randomized, double-blind, placebo-controlled trial¹⁰⁶ established the benefit of 1 g intravenous cefazolin administered immediately before the procedure in tolerant patients in reducing the incidence of procedure-related infections and systemic infections from 3.28% in patients not receiving antibiotics to 0.63% in those receiving antibiotic ($P = 0.016$). Systemic perioperative antibiotic prophylaxis should be provided to patients undergoing implantation of a CRT device. A recent AHA/ACC/HRS (Heart Rhythm Society) scientific statement recommends using an antibiotic that has *in vitro* activity against staphylococci. If cefazolin is selected for use, it should be administered intravenously within 1 h before incision; if vancomycin is given, it should be administered intravenously within 2 h before incision.¹⁰⁷

1.5.3 Contrast-induced nephrotoxicity

Implanting the LV lead usually involves contrast administration to define the coronary venous anatomy and to help identify and cannulate the CS ostium. Because of the high prevalence of renal dysfunction, diabetes and low blood pressure in candidates for CRT, contrast nephropathy following CRT may occur despite the modest amount of contrast media used (i.e. <1 tenth of that used for coronary angiography). Published reports of contrast nephrotoxicity following CRT procedures are not available. Hydration and consideration of treatment with renal protective agents such as acetylcysteine may be considered.¹⁰⁸

Table 2 Methods of patient assessment prior to CRT implant

	Assessment	Goals
Basic requirements	ECG	QRS duration and morphology rhythm, PR interval, P-wave morphology
	Echocardiogram	Ejection fraction, LV size, MR, RV function
	Functional testing (6 min hall walk test or CPX)	Baseline objective functional status
	History and physical exam	NYHA symptom class, comorbidities, life-expectancy, risk for altered venous anatomy, suitability for procedure
Additional evaluations: optional	Serum chemistries	Electrolytes and renal function, coagulation tests
	Medication usage	Maximally tolerated doses for appropriate duration. Include diuretic evaluation for volume status
	Mechanical dyssynchrony by echo	Type and extent of dyssynchrony
	Stress echocardiography	Assess 'recruitable' myocardium
	Cardiac CT angiography	Great cardiac vein and branch mapping, CS ostium, LVEF, chamber sizes
	CMRI	Great cardiac vein and branch mapping, CS ostium, LV tissue characteristics including infarct area, LVEF
	QOL measurement	Baseline measurement for future comparison

1.6 Summary

Table 2 summarizes the pre-implant assessment methods for patients prior to CRT implantation. Careful attention to the patient prior to implant helps assure implantation success and long-term beneficial clinical outcomes.

2. Cardiac resynchronization therapy implantation

2.1 Cardiac resynchronization therapy implantation recommendations (Table 1)

2.2 Operative environment

Cardiac resynchronization therapy implants should be performed in operative environments that adhere to institutional guidelines to assure sterile operative technique equivalent to any other operative suite.¹⁰⁹

2.3 Anaesthesia: conscious sedation vs. general anaesthesia

The CRT implant often takes considerably longer than other pacemaker and ICD procedures, and is undertaken in a patient group at increased risk of haemodynamic compromise. The prolonged supine position predisposes to pulmonary oedema, while severe hypotension may result from intravenous sedation and opiates in a dehydrated patient. The choice between general and local anaesthesia (with or without conscious sedation) reflects standard institutional practice, patient preference and psychological factors, and possibly whether ventricular fibrillation (VF) induction is to be performed. General anaesthesia is not medically necessary for the majority of CRT implants. However, it is imperative to closely monitor the haemodynamic status and fluid balance of the patient during the implant procedure.

2.4 Lead implant sequence

2.4.1 Side of chest

Although pacing systems can be implanted on either side of the chest, the left side is generally preferred for CRT-defibrillator (CRT-D) systems for two reasons. First, the left-sided approach follows a relatively continuous curve from subclavian vein to CS, while from the right side two opposing angulations are encountered [entering the superior vena cava (SVC) and then the CS itself]. Secondly, the defibrillation threshold (DFT) is generally lower with a left-sided generator.¹¹⁰ If a right-sided implant is chosen, the system should permit programmable shock vectors in the case of a high threshold.

2.4.2 Venous access

It is often challenging to obtain access for three leads via the cephalic vein, which is not desirable as a single port of entry because it can make lead manipulation difficult. For this reason, the LV lead is generally implanted via the subclavian vein and preferably accessed by axillary venous puncture to minimize the risk of pneumothorax even if the other two leads can be inserted via the cephalic route. In many instances, all three leads may be implanted via the axillary or subclavian veins.

2.4.3 Order of lead implant

The RV lead should be positioned first as most CRT patients have LBBB and trauma to the right bundle during CS cannulation commonly results in complete heart block and an urgent need for RV pacing. Furthermore, an LV lead easily may be displaced during RV lead positioning, while the converse is rare.

An RA lead should always be implanted in patients with sinus rhythm or when there is a chance for conversion from atrial fibrillation to sinus rhythm. Even in patients with persistent atrial fibrillation, a small but significant proportion of patients cardiovert to sinus rhythm, either during DFT testing, or as a consequence of haemodynamic improvement in the months following CRT.¹¹¹ If atrial sensing is >1 mV during atrial fibrillation, then both pacing

and sensing following resumption of sinus rhythm are likely to be adequate.^{112,113} The RA lead can be positioned before or after the LV lead, but it is prudent to complete all right-sided lead positioning before withdrawing the CS sheath to avoid dislodging the LV lead. There is no consensus regarding the best position of the atrial lead and the position is usually guided by the need for stability, with optimal sensing and pacing parameters.

2.4.4 Right-sided lead location

Practice varies regarding the optimum RV lead location. While septal pacing may be preferred in conventional pacemakers, in CRT systems it is not necessarily the case. The location of the RV lead and the impact on the efficacy of the delivery of CRT is unclear.¹¹⁴ However an apical location may have some ancillary benefits such as: permitting the entire distal coil to lie in the RV, thus potentially yielding a lower DFT¹¹⁵ and reducing the likelihood of damage to the tricuspid valve.¹¹⁶ However, in patients with severe myocardial disease, pacing threshold and sensing may be the main determinants of lead location.

2.5 Peripheral and coronary sinus venography

Venography is an invaluable tool to guide CRT implantation. The operator must balance the benefits of multiple subclavian and CS venograms in differing projections against the risk of contrast nephropathy in patients with impaired renal function.

2.5.1 Peripheral venography

Contrast injection via the brachial vein is frequently performed prior to the start of the procedure to locate the subclavian vein and its branches. Contrast venography is of particular value when planning CRT upgrade or revision procedures. Contrast venography can identify subclavian or innominate vein stenosis/occlusion and congenital abnormalities (e.g. persistent left SVC) that can complicate implant procedures. Although stable cannulations of the CS followed by detailed angiography are key components to successful LV lead placement, it can present considerable

anatomical challenges. The location and take-off of the CS ostium varies considerably and can be further distorted by right atrial enlargement and prior surgery. The Thebesian valve, which guards the ostium, may be a vestigial structure, a tightly closed flap requiring a kinked pathway for passage of a sheath, a reticular obstruction to the ostium, continuous with a Chiari network or occasionally absent. An early bifurcation of the CS may favour cannulation of a large posterior branch over the true CS. Finally, the valve of Vieussens, typically 3–5 cm from the CS ostium, may hinder cannulation of the distal vessel.¹¹⁷

Multiple strategies can be used to cannulate the CS. Most commonly, a guide sheath with a J-shaped curve is used in combination with a multipolar electrophysiology catheter, an angiography guide catheter, and/or an 0.038" guide wire. The use of sheaths or catheters with a secondary Amplatz-type curve (usually AL-3), and hydrophilic guide wires may help negotiate a difficult CS ostium. A number of simple or sophisticated tools, including electrophysiology catheter with or without intracardiac electrogram recording, deflectable sheaths, and imaging techniques, are available to assist in difficult cases.

The CS can be cannulated in >95% of patients, so a low-volume operator's failure should prompt referral to a more experienced implantor or surgeon.

2.5.2 Coronary venography

Following CS cannulation, retrograde angiography is performed using a balloon occlusion catheter and hand injection of contrast. Great care must be taken at this stage to obtain full anatomical information permitting selection of the target branch and lead for LV pacing, while avoiding complications. Full occlusion of the CS is necessary and may require careful positioning of the balloon, and sometimes over-inflation to avoid contrast and the catheter being washed back by antegrade CS blood flow. Fluoroscopic acquisition should continue for several seconds after the end of contrast injection as branches proximal to or occluded by the balloon could fill-in late secondary to the collateral flow.

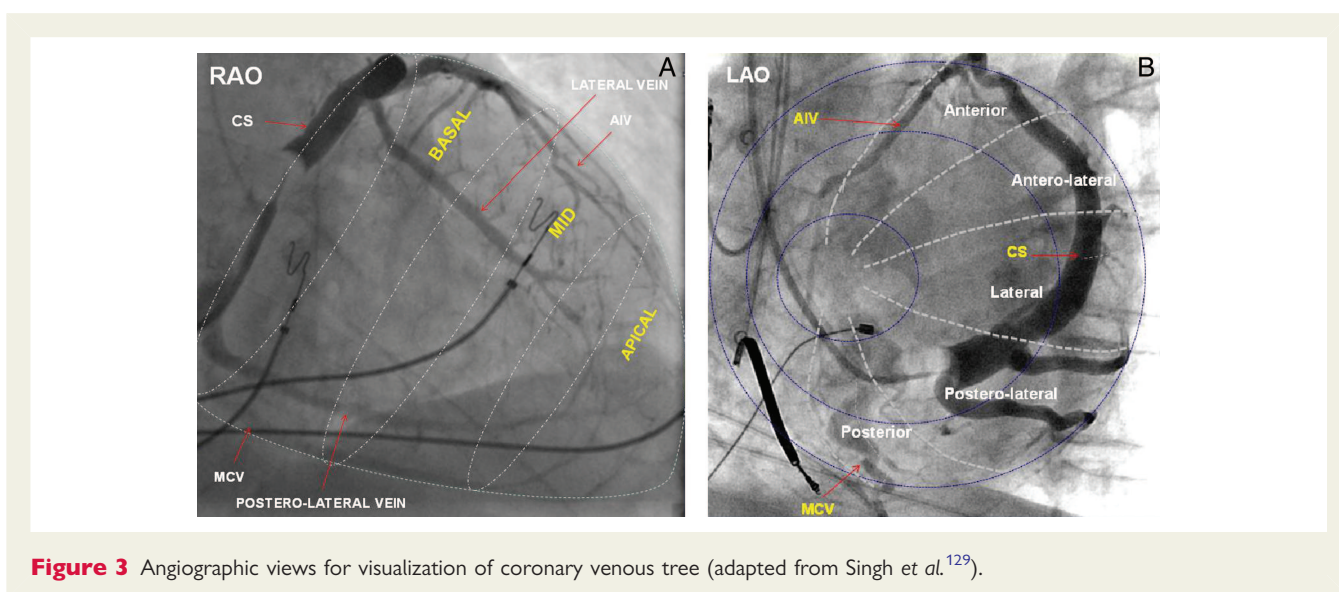


Figure 3 Angiographic views for visualization of coronary venous tree (adapted from Singh *et al.*¹²⁹).

While single-view venography may suffice for more experienced operators, two orthogonal views [right anterior oblique (RAO) 30–45° and left anterior oblique (LAO) 30–45°] are preferred for better visualization of the venous tree and appropriate targeting of the LV lead (Figure 3). The LAO projection ‘opens up’ the CS along its whole path, and differentiates the course of free wall vs. septal branches. However, in this view, the longitudinal course of these veins from base to apex may be foreshortened. Venography in the RAO projection overcomes this problem, and demonstrates second-order branches along the long axis of the heart. Other views may be necessary to aid the cannulation of branches with posterior and tortuous origins. A minority of centres perform rotational venography, which may provide more detailed viewing of the coronary venous anatomy over a range of angles.¹¹⁸

The balloon occlusion catheter has a stiff tip and its manipulation is likely the most common cause of CS dissection. When identified early, this complication does not usually lead to tamponade, but it can significantly hinder or prevent successful CRT implantation. The balloon catheter should therefore be handled with care, and if difficulties are encountered in advancing the catheter within the CS, it is advisable to advance the guide catheter over a J wire to reach the required location.

2.6 Left ventricular lead selection: unipolar, bipolar, or multipolar

Left ventricular lead selection may address some of the challenges posed during implantation of the CRT system as well as facilitate an optimal clinical outcome. As alluded to previously, occlusive venography is recommended to create a roadmap that guides lead selection and assists with navigation. Venous tributaries should be assessed for location, angle of take-off, caliber, tortuosity, and extent of reach. The operator should then select a lead that ‘fits’ the given venous anatomy.

Over-the-wire leads are preferred but may not be required in all cases. Tip design may affect navigability in smaller and more tortuous veins. An isodiametric tip is often more effective in these situations. Lead stability is determined by interaction of the selected lead with the targeted vein. Leads with preformed curves tend to exhibit improved stability by creating more points of contact between the lead and vessel wall. Preformed leads must be deployed with adequate distal penetration, such that the most proximal preformed element is within the target vessel.^{119,120}

Obtaining an adequate capture threshold and avoiding phrenic nerve capture is a significant challenge, a challenge that is partially addressed by lead selection. Only consider unipolar leads when alternative bipolar or multipolar leads cannot be placed. Increasing the number of electrodes on the LV lead increases the number of available pacing polarities in modern devices, and results in increased options for obtaining an acceptable capture threshold.^{120,121} Quadripolar leads confer the maximum number of pacing configurations in currently available devices. The clinical benefit of this new technology has not been evaluated.¹²¹ Similar arguments have been made for avoiding phrenic nerve stimulation (PNS). When a vein has been selected for placement of an LV lead, that vein should be carefully mapped to determine the course of the phrenic nerve. Bipolar and multipolar leads offer various

pacing configurations to minimize phrenic nerve capture detected during LV lead placement.^{121–124} Phrenic nerve stimulation is often detected post-operatively due to patient positional changes or lead migration. Multipolar leads may allow reprogramming to an alternate polarity to ameliorate this problem without invasive intervention.

Left ventricular lead selection may affect the long-term goal of improvement of heart failure symptoms in candidate patients. During long-term follow-up, CRT is interrupted in up to 36% of patients.¹²⁵ Reasons include atrial arrhythmias, PNS, and loss of LV capture. The increased number of pacing polarities afforded by multipolar leads may enhance maintenance of continuous CRT delivery.

There is increasing evidence that selection of specific LV sites for pacing may improve CRT outcomes.¹²⁶ Early acute studies suggested that the LV free wall should be routinely targeted to optimize haemodynamic response,¹²⁷ but more recent trials evaluating long-term response to CRT show a good clinical response with a range of LV lead locations.^{128,129} In two major studies, apical LV lead positions were associated with an unfavourable outcome.¹²⁹ Smaller trials have studied methods to select pacing sites during the operative procedure. These include determination of LV lead electrical delay and maximization of ventricular interlead distance.^{130–133} The Writing Committee recommends venography to evaluate candidate venous tributaries and consideration of electrical and fluoroscopic methods to help select optimal sites. Preformed leads may provide more effective proximal fixation to help avoid apical locations. Multipolar leads provide more pacing options, which may further enable the operator to pace from a non-apical optimal site.

2.7 Perioperative imaging

Preprocedural left heart catheterization with observation of levophase filling of the cardiac veins and CT angiography may clearly define distal venous anatomy as well as confirm the location and other characteristics of the CS ostium.^{55,134}

In the operative setting, imaging may facilitate CS cannulation when traditional methods have proven ineffective. In this setting, transoesophageal echocardiography has again proven useful.¹³⁴ However, in difficult cases intracardiac echocardiography is more tolerable in patients under conscious sedation. Early experience demonstrates reliable imaging of the CS and associated structures, facilitating cannulation when fluoroscopy alone had failed.^{135,136} Fiberoptic endoscopes are also commercially available and have been used to define right atrial and CS ostial anatomy.^{137,138} Preliminary studies show proof of concept in facilitating CS cannulation, but there is not widespread use of this technology. Routine use of intraprocedural imaging is not warranted and is not recommended by the Writing Committee. However, when CS cannulation has failed or when structural anomalies are suspected, imaging techniques may provide information that facilitates successful CS entry.

Imaging in the perioperative setting may help operators select specific sites for LV pacing based on anticipated optimization of electromechanical effects and clinical outcomes.^{48,139–144} The most promising methods have utilized echocardiographic techniques such as Doppler myocardial imaging, velocity vector

imaging, or tissue synchronization imaging to determine target LV sites demonstrating marked mechanical delay.^{141–143} The investigators demonstrate that pacing LV sites that showed the greatest mechanical delay result in greater ventricular remodelling and improved clinical outcomes. Peri-procedural multi-modality imaging with image integration to facilitate individualized pacing therapies still remains investigational.¹⁴⁵ The pros and cons of targeted pacing are discussed in greater length in the subsequent section.

2.8 Left ventricular lead placement: standard lead placement vs. targeted left ventricular lead placement

The optimal placement of an LV lead represents one of the most challenging aspects of CRT device implantation. The final position of the LV pacing lead depends on the anatomy of the cardiac venous system, the performance and stability of the pacing lead, and the absence of PNS. Current CRT strategies involve placement of the pacing leads ‘anatomically’ rather than using more patient-specific physiological approaches. There is controversy regarding the best lead positioning strategy and the choice between an optimal anatomical position, targeting either the segment with maximal mechanical dyssynchrony or a region with maximal electrical delay is uncertain. Much of the earlier published work has suggested that targeting the lateral or postero-lateral wall either by way of an appropriate CS branch or surgical (epicardial) placement is a determinant of improved clinical outcomes.^{127,146} This strategy is based on the contention that most patients eligible for CRT usually have a LBBB, where typically the latest activated site of the ventricle is along the lateral or postero-lateral wall.⁹⁸ However, studies have indicated that there is considerable variability in the ventricular activation pattern¹⁴⁷ and distribution of mechanical dyssynchrony even in the LBBB patient resulting in inter-individual variability in the most optimal pacing site.^{98,126,146–150} Importantly, a significant percentage of patients do not have the typical LBBB morphology or have an indeterminate ventricular conduction defect indicating a more heterogeneous activation sequence making the most effective LV pacing site less predictable to restore LV synchrony. Another alternative LV pacing strategy such as multisite ventricular stimulation has been proposed to improve the clinical and echocardiographic outcomes. In a small multicentre study, despite no differences in clinical outcome, triple-site stimulation further promoted a significantly higher increase in LVEF and reduction in LV end-systolic volume when compared with conventional strategy.¹³³ Further studies are warranted to confirm the superiority of multisite over conventional LV pacing. Notably, lead placement via the endocardial^{126,151} and epicardial approach may have the potential to provide individualized targeted pacing. Other pacing manoeuvres such as triangular and quadrangular pacing are investigational.^{152,153} Table 3 summarizes the different lead implantation strategies.

Recent reports, including those from the MADIT-CRT¹²⁹ and REVERSE-HF¹¹⁴ study, have shown that an apically positioned LV lead location is associated with a worse clinical outcome. The LV depolarization wavefront in most conduction disturbances activates the apex relatively early during the course of the activation sequence, whereby an apical position results in pacing a region

of the heart with less delayed electrical and mechanical activation. Also, CRT involves synchronizing the ventricles via electrical stimulation from RV and LV pacing sites that ideally should be positioned as far away from each other as possible.¹⁵⁴ An apical LV lead location is often in close proximity to the RV lead, which is usually positioned in the RV apex, thereby resulting in reduced inter-electrode distance and inter-lead electrical separation. The COMPANION¹²⁸ and MADIT-CRT¹²⁹ studies recently showed a comparable response between lateral, anterior, or posterior LV lead locations, while recent data from the REVERSE-HF¹¹⁴ maintain the potential benefit of a lateral lead location.

An improvement in cardiac contractility, cardiac output, pulse pressure, or other haemodynamic variable at the time of LV lead implantation has been used by clinicians to help define an optimal LV pacing site. While this approach may have some merit,¹⁵⁵ there are no randomized data to support its use in clinical decision making. There also is insufficient data on the reproducibility of these acute haemodynamic measures; no consensus of what defines a significant increase in these parameters or; if the relevant comparison is the change in the haemodynamic variable during LV pacing or biventricular pacing vs. atrial pacing or sinus rhythm. It also is not clear, what impact if any, the amount and type of anaesthetic has on these measurements. Finally, it is uncertain if these measures, performed in a resting, supine state during an implant procedure, reliably reflect the real-world, ambulatory state of patients.

Retrospective studies have shown that targeted placement of the LV lead over the segment of maximal mechanical dyssynchrony can improve the magnitude of reverse remodelling and clinical outcomes.^{48,143} In these studies, the assessment of the lead-segment relation was a retrospective assumption without true image integration.⁴⁸ The same limitation exists in a recent prospective randomized bicentric study where the targeted approach was shown superior to the conventional approach as regards to the echocardiographic and clinical response. In this study, LV lead positioning was attempted as close as possible to the last deforming region by radial strain in the short axis.¹⁵⁶ Besides the inherent limitations in the echocardiographic imaging of mechanical dyssynchrony, there can be significant variability in the region of delayed mechanical activation. With recent innovations and refining of echocardiographic techniques and technology, areas of greatest delay may be targeted and used for guiding lead placement. Notably, the presence of a coronary vein in close proximity to the target region may be unpredictable.¹¹⁸ The implantation of the LV lead at an area with myocardial scar may result in ineffective CRT. Besides ineffective capture, pacing within myocardial scar is associated with slow conduction or block and less LV haemodynamic improvement. Both scar location and burden can be associated with poor clinical outcome.¹⁵⁷

2.8.1 Phrenic nerve stimulation testing

Phrenic nerve stimulation can be an important challenge to the successful early and long-term delivery of LV pacing. Phrenic nerve stimulation has been reported in 15–37% patients at the time of LV lead implantation,^{120,121,158–160} but occurs less frequently post-operatively when the LV lead is selectively placed in a site free of PNS at the time of lead implant.¹⁶¹ The presence of PNS may require the lead be placed in a very basal site, with a higher risk of lead dislodgement.

Table 3 LV lead implantation approaches

Approach	Advantages	Disadvantages
Transvenous		
Anatomical placement	Abundant data on outcomes Tool set available High implant success Greater choice of implant sites	Individual variability in response Technical challenges Unpredictable implant times Need for fluoroscopy
Targeting electrical delay	Individualized approach May prolong procedural time	Limited data available Clinical outcome favourable
Targeting mechanical delay	Individualized approach Clinical outcome favourable	Limited data available May prolong procedural time Imaging strategies to delineate site of mechanical delay are not robust
Multisite	Recruit more myocardium ? maybe useful in non-responders	Limited data
– Dual LV pacing		More hardware, more complex
– Triangular pacing		Procedure
– Quadrangular pacing		Prolonged procedure time
Endocardial		
Direct	Individualized approach Greater choice of target sites	Limited data Risks from invasive approach Anticoagulation a must Potential challenges with extraction Impact on mitral valve unclear
Transapical	Potential reduction in implant time	Limited data Embolic risk Apical puncture
Epicardial		
Surgical	More predictable implant times	Risk of invasive procedure
Thoracotomy	Minimal fluoroscopy	Higher morbidity
Minimally invasive	Greater choice of target sites	Longer recovery
Robotic		Specialized equipment needed
Percutaneous	Minimal fluoroscopy Greater choice of target sites	Limited data Tool set still investigational Lead fixation strategies in development

The presence of PNS is identified as movement of a hemidiaphragm on fluoroscopy or contraction of the diaphragm by palpation that coincides with the pacing rate. It is optimal that PNS be absent when pacing through the LV lead at maximal voltage (10 V and 0.5 ms pulse width). A safety margin of two times between the LV capture threshold and the PNS capture threshold may be acceptable where coronary venous anatomy, the stability of the LV lead, or an elevated LV capture threshold require placing the LV lead in a region where PNS cannot be completely avoided.

Where possible, PNS should be assessed in all relevant LV pacing configurations for that lead (i.e. true bipolar, integrated bipolar LV cathode to RV, and integrated bipolar LV cathode to device for a dual cathode or bipolar lead). Although, the introduction of multi-polar LV leads makes it cumbersome given the number of potential configurations available, it provides the opportunity to more successfully electrically reposition the lead. In this situation, a representative subset of configurations should be tested (i.e. some bipolar configurations and some integrated bipolar configurations based on the location of the LV lead within the coronary venous branch).

2.8.2 Electronic configuration for stimulation

Dual cathode and multi-polar leads provide greater flexibility in pacing select regions of the LV, obtaining a lower capture threshold, and avoiding PNS. Electronic reprogramming, altering the pacing/sensing configuration to change the electrical vector and reducing the LV capture threshold or avoiding PNS, is available in most contemporary CRT devices.

Recently, the ELECTION study showed that with standard bipolar LV leads, electronic programming could lower pacing threshold in 35% of patients, with complete resolution of PNS in 77% of the patients who had phrenic nerve pacing at the lowest pacing threshold with standard bipolar configurations at the time of the implant.¹⁵⁹ Multi-polar leads offer additional vectors to reduce the chronic LV pacing threshold, minimize PNS, reduce the risk of LV lead dislodgement, and potentially enhance response to CRT. However, at this time, there is only limited, single-centre data regarding the utility of these leads.^{162,163} Electronic repositioning is a potentially useful adjunct to reducing the LV capture threshold, avoiding PNS, and possibly reducing the risk of LV lead dislodgement.

2.9 Right ventricular defibrillation lead selection (single coil vs. dual coil)

Dual-coil defibrillation leads systems often are considered to have lower DFTs as compared with single-coil defibrillation lead systems. Dual-coil defibrillation lead systems also provide additional far-field electrograms that may yield diagnostic information. However, these potential advantages of dual-coil lead systems should be balanced with the increased complexity of dual-coil defibrillation leads.^{164–167}

Multiple small randomized and observational studies have compared DFT values with single-coil vs. dual-coil defibrillator leads.^{164,166–172} Some of these studies have shown statistically significant reductions in DFT with dual-coil vs. to single-coil lead systems, but the differences were modest (<5 J). A very low DFT (<15 J) is more readily achieved with a dual-coil (>95% of the tested patients) vs. single-coil lead system (80–90%). However, it has been shown that a safety margin of at least 10 J can be obtained in the vast majority of patients with contemporary defibrillator single-coil lead systems across multiple manufacturers.¹⁷² The data indicate that single-coil and dual-coil defibrillation lead systems provide defibrillation at comparable energy levels and that the inclusion of a third, SVC electrode, increases system complexity and fragility with little defibrillation advantage.

2.10 Defibrillation testing

Controversy exists regarding the value of routine defibrillation testing at the time of CRT defibrillator implantation. Inducing VF at the time of defibrillator implantation is useful to assess sensing and the reliability of defibrillation.¹⁷³ A recent survey of 57 European Heart Rhythm Association centres found that only one-third of respondents reported performing defibrillation testing post-implantation or prior to discharge and the induction of multiple VF episodes to assess DFT more accurately was only performed by one in eight respondents.¹⁷⁴ Recent data from Canada found that defibrillator testing was performed in approximately two-thirds of both primary and secondary implants.¹⁷⁵ In one large dataset of over 55 000 CRT recipients implanted in the USA, defibrillation testing was performed in >85% of CRT implants.¹⁷⁶ It is important to note that pivotal CRT clinical trials that proved improvements in hospitalization and survival rates with CRT did require defibrillation testing as part of the CRT-D implant.

In the past, a failure of defibrillation was more common. Recipients had a higher risk of sustained life-threatening arrhythmias (e.g. secondary prevention recipients), and defibrillator systems exclusively relied on high-voltage shocks to terminate arrhythmias. In the present era, failure of defibrillation is rare; the risk of sustained life-threatening arrhythmias is less common (e.g. primary prevention recipients); alternatives to high-voltage shocks are often used (e.g. anti-tachycardia pacing therapies for ventricular tachycardia); and a safety margin of at least 10 J can be obtained in the vast majority of patients.¹⁷²

It is essential to recognize that defibrillation testing is by its nature probabilistic and is not a definitive assessment. Defibrillation success is influenced by both predictable and unpredictable factors related to the patient (e.g. concurrent illness, changes in

medications) and the defibrillator system. Since most patients' defibrillator systems will successfully treat a sustained ventricular arrhythmia without modification, most of the patients who fail implant testing may have false negative tests and could undergo unnecessary revision of their defibrillator system.¹⁷³ Further, there is no data to support the notion that system modification in these individuals will alter the real-world success of their arrhythmias being successfully treated in the future. Since defibrillator testing carries risk (e.g. circulatory arrest) of adverse outcomes, many centres have moved away from routine testing in CRT recipients, who may be at higher risk given the severity of their LV dysfunction and heart failure.¹⁷⁷

There are sparse data to base clinical decision making in this area. Defibrillation testing was required in SCD-HeFT. Of 711 patients with defibrillation testing data in that study, 98% were successfully defibrillated with a single shock of < 20 J. Survival and first shock efficacy was similar in the 77% of patients with values < 10 J vs. the 23% with higher values.¹⁷⁸ Data from a cohort of 2173 patients from Ontario found similar risks of adverse events among those who underwent (8.7%) vs. did not undergo (8.3%) defibrillation testing.¹⁷⁵ The data for defibrillation testing in the heart failure patient receiving CRT devices are even more scant, with these patients at a higher risk from testing at the time of implant. Based on the data available to date, it is not possible to make a firm recommendation on whether defibrillation testing should be performed.¹⁷⁹ This decision should be made on an individual basis by the implanting physician, reflecting on usual practice and the risks vs. benefits of testing in a given patient. The shockless implant evaluation study is an ongoing randomized trial comparing the use vs. non-use of intra-operative defibrillation testing. This trial will provide additional evidence and guidance in this area.¹⁸⁰ Defibrillation testing can be safely deferred for a second procedure after recovery from the initial implant.¹⁸¹ Although anecdotal, lead dislodgement may occur during defibrillation testing due to intense muscle contractions; this risk has to be considered if the defibrillation testing is deferred to a second procedure.

2.11 Device upgrade procedures, lead burden and vein occlusion, lead tunnelling

Upgrading an existing device to deliver CRT may pose difficulties due to the necessity to operate in a previously operated area and the presence of previously implanted leads in the venous system. The 6-month major complication rate was very high, 18.7% in the REPLACE registry in patients undergoing upgrade to a CRT device with addition of a new endocardial LV lead to the existing leads.¹⁵⁰ The risk of subclavian vein thrombosis is related to the number of leads implanted and among recipients of CRT devices severe obstruction or occlusion can be observed in 30%.¹⁸² Subclavian venography with injection through the upper extremity veins is a simple and effective technique to evaluate venous anatomy prior to an upgrade or lead revision. Venoplasty may be attempted even in cases with total occlusion, the efficacy is high and the risk of clinically significant complications or lead damage is low.¹⁸³

Extraction of non-used leads during an upgrade or revision should be considered as the risk of long-term complications

from abandoned leads is not negligible and correlates with the number of leads implanted and the number of prior procedures performed.^{184,185}

Implantation via the jugular or contralateral subclavian vein, with subcutaneous tunnelling is required if the anatomy does not permit ipsilateral addition of a new lead. Although primary transvenous device implantations are routinely performed using conscious sedation without much patient discomfort, deep sedation or general anaesthesia may be required for lead tunnelling.¹⁸⁶ If lead extraction has to be performed prior to the upgrade, general anaesthesia, invasive monitoring, and availability of immediate surgical backup are recommended.¹⁸⁷

It is preferable that the physician attempting a complex implantation or a device upgrade is well trained and current in the appropriate interventional and surgical techniques, or a physician with this training is immediately available. The incidence of unsuccessful implantations is declining, which is partly due to the advances in lead technology and implanting tools. However, interventional cardiology techniques also have been increasingly utilized with excellent efficacy and safety records, as is discussed in Section 2.12.

2.12 Considering the non-coronary sinus approach and future lead technologies

Implantation of the transvenous LV lead is highly successful but the anatomical challenges and operating time are unpredictable. Several reasons account for either long implantation time or implantation failure. *Table 4* summarizes conditions that limit transvenous LV lead placement. New attempt from the opposite side, the use of different pre-shaped guiding catheters, guide wires that provide different degree of mechanical support to CS guiding catheter(s) and to LV lead(s), and differently shaped LV leads significantly reduce the likelihood of implantation failure while permitting an optimal match with CS and vein anatomy and maintaining optimal mechanical and electrical lead performance.

To minimize implantation failure, it is advisable to have available guiding catheters and LV leads of at least two different manufacturers whose shape and mechanical performance may be complementary. A frequent debate is whether the implantation of the LV lead in any coronary vein is advisable before abandoning the transvenous approach; although population-based study showed no major difference in symptoms, QOL, LVEF and ventricular volumes, and survival, there are anecdotal reports of significant worsening of symptoms and LV performance when pacing from the anterior or inferior vein.¹²⁸ If no response to CRT is seen at 6 months using a transvenous approach, an LV lead revision can be reasonably considered.

The decision to abandon the LV lead implantation attempt should be taken early on in the implantation procedure by setting a general time limit (*Figure 4*). A time limit ranging from 20 to 40 min should be selected based on operator experience and the implantation equipment portfolio, recognizing that long implantation procedures increase the risk of local, cardiac, and systemic complications. There is limited data pertinent to stopping the LV implantation and the frequency of complications related to implantation time. Based upon operator experience and

Table 4 Conditions limiting transvenous LV lead placement

Anatomical limitations	<ul style="list-style-type: none"> • Subclavian or SVC occlusion • Very dilated RA • Abnormal position of CS ostium • Abnormally small (<2 mm in diameter) and/or short CS (<1 cm in length) • Prominent and/or rigid Eustachian valve impeding CS access • CS valve • Severe CS dissection • Severely dilated CS due to congenital or acquired cardiac disease • Angulated take-off of target vein • Short vein (<1 cm in length) • Tiny vein (<1.2 mm in diameter) • Significant vein tortuosity • Vein stenosis or significant narrowing with inability to perform venoplasty • Vein thrombosis • Vein dissection • Chronic vein occlusion • Persistent Left SVC
Lead-related issues	<ul style="list-style-type: none"> • Lead instability with repeated dislodgment • High pacing threshold (pacing safety margin <1 V) • PNS despite electronic or physical repositioning
Systemic conditions	<ul style="list-style-type: none"> • Lack of significant response to resynchronization therapy

possible support from outside, a second implantation trial may be attempted (*Figure 4*). However, once the decision to abandon the CS approach is taken, the case should be reviewed with a more experienced operator to refine the management strategy. This may involve referral to a higher volume centre.

Surgical placement of LV epicardial leads for CRT delivery is currently performed in a minority of cases and therefore single centres generally have limited experience. It is important to emphasize that the implanting physician should be familiar with epicardial lead implantation technology and should have sufficient background in the field of CRT. The range of epicardial LV lead implantation procedures has included approaches ranging from median sternotomy or limited open or endoscopic thoracotomy to a totally endoscopic procedure with the use of robotic technology. Comparative safety and efficacy data among the different surgical techniques, or related information on procedural complication rates do not exist. Similarly, there are no comparative outcome data on whether the guided approach is superior to conventional pragmatic approach of LV lead implantation on LV free wall. There are small, observational series comparing CRT effectiveness between transvenously implanted vs. surgical LV lead placement showing a trend towards slightly better outcomes that are associated with a greater post-procedural morbidity in surgically treated patients.¹⁸⁸ Steroid eluting sew-on leads have better electrical and mechanical performance than leads with a different type of fixation mechanism, and bipolar leads should be preferred to unipolar ones. Special care in lead tunnelling and manipulation

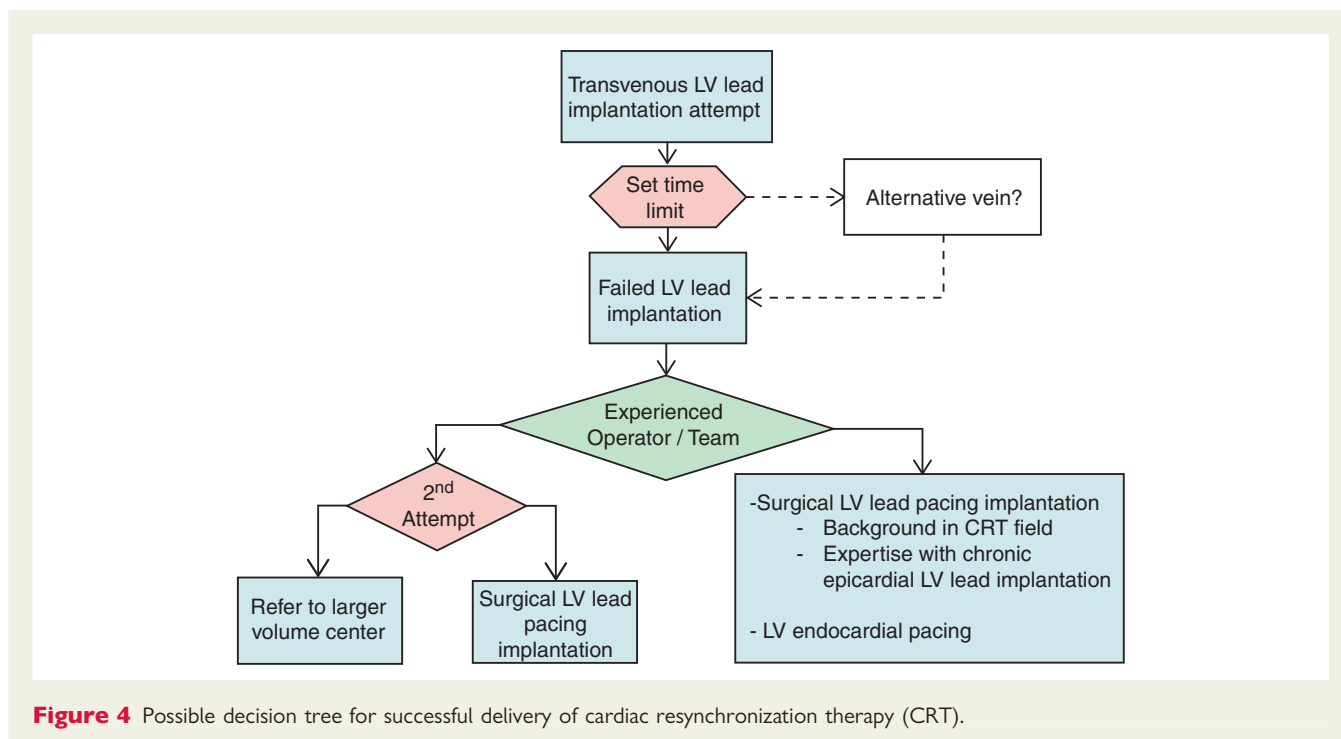


Figure 4 Possible decision tree for successful delivery of cardiac resynchronization therapy (CRT).

should be taken; lead fracture occurs most frequently in high mechanical stress regions within the rib and intercostal muscles. Those patients with previous cardiac surgery deserve special consideration including the location of coronary bypass grafts.

Left ventricular endocardial pacing is a novel approach for CRT delivery and is at a preliminary clinical stage. Procedural safety, clinical efficacy, and effectiveness are limited to small, observational, single-centre experience with limited follow-up time.¹⁸⁹ Endocardial pacing may be technically delivered using conventional pacing leads or by using novel pacing devices either at pre-clinical development stage or the early clinical evaluation phase (Figure 4) [e.g. Wireless Stimulation Endocardially for CRT study (WISE-CRT)]. Numerous pre-clinical studies using different heart failure models have provided robust evidence that endocardial pacing confers significantly greater improvements in cardiac function and mechanics compared with conventional epicardial pacing. Similarly, preliminary data in patients have indicated that temporary endocardial pacing usually increases cardiac function more than epicardial pacing and in a more predictable manner.¹²⁶ However, chronic LV endocardial stimulation also carries potential disadvantages and some risks (see Section 5) (Table 3).

2.13 Interventional techniques to facilitate coronary sinus lead implantation: angioplasty and stenting

Unfavourable CS or vein anatomy, such as valves, tortuosity, or focal stenosis may make LV lead implantation very difficult. In some cases these obstacles can be overcome with the use of conventional interventional cardiology techniques. The instrumentation required is the same as for coronary artery angioplasty.¹⁹⁰ In the majority of cases with focal stenosis, balloon angioplasty is a safe method to

facilitate passage of the lead.^{191,192} In selected cases, stent implantation may be required.¹⁹³ Venoplasty may also be used as a rescue when dissection of the CS or the target vein is observed during implantation, which would otherwise prohibit further attempts for lead placement.^{194,195} In case of unfavourable coronary vein anatomy in the target area, dilatation and use of collateral veins may be considered.^{196,197} Complications from venoplasty are rare; however, venous rupture has been reported.^{190,197}

Coronary stents also can be used to stabilize the position of the LV lead and may be considered if either the lead position is unstable or when an exact location is preferred. One example is where an optimal pacing site is close to the phrenic nerve. This method was shown to be safe and efficient in a large case series, without clinically relevant vein or electrode injury, even lead extraction with conventional techniques was possible.¹⁹⁸ Although newer LV leads have better manoeuvrability and improved fixation mechanisms, interventional techniques are useful adjuncts if difficult anatomy is encountered and prompt access to them may facilitate a challenging implantation.

3. Pre-discharge evaluation and device programming (24–72 h post-implant)

3.1 Pre-discharge evaluation recommendations (Table 1)

3.2 Post-operative clinical evaluation

Overnight observation after CRT implant is prudent to observe recovery after general anaesthesia or conscious sedation and to

assess fluid status as CRT may result in marked and immediate diuresis. Overnight observation also provides another opportunity, while the patient is still hospitalized to assure lead stability.

Assessment after CRT implantation should include an examination of vital signs and auscultation of cardiac and respiratory sounds, looking for any evidence of pneumothorax, haemothorax, or pericardial effusion or heart failure worsening. Examination of the pocket may detect presence of haematoma.

3.3 Chest radiography

Upright postero-anterior (PA) and lateral chest X-rays should be obtained prior to discharge.¹⁹⁹ Chest radiographs typically can rule out pneumothorax and haemothorax and are useful to document lead position. Acute LV lead dislodgement occurs in ~2% of patients who undergo CRT-D implantation,²⁰⁰ and chest radiographs can easily identify early macro-dislodgement of the LV lead. Chest X-rays are less useful to detect micro-dislodgement, especially since full-inspiration upright PA and lateral films may be difficult to compare with angulated views obtained in supine position during device implantation.

Postero-anterior and lateral chest X-rays are not optimal for identifying the exact anatomical position of the LV lead if position was not well established at implant. Comparison with perioperative CS angiography²⁰¹ or post-operative multi-detector CT²⁰² suggests misclassification of LV lead position by PA and lateral chest X-rays in up to 60–70% of cases. Chest X-ray assessment of leads may predict acute haemodynamic response to CRT. Heist *et al.*¹⁵⁴ showed that the horizontal distance between LV and RV lead tips measured on lateral chest X-ray correlated with LV $\Delta P/dt$ measured by Doppler echo 6–12 h after CRT implant.

3.4 Surface electrocardiogram

A 12-lead surface ECG during biventricular pacing should be recorded after implantation, and repeated if significant changes are made to the programmed AV and ventriculoventricular (VV) delays. The ECGs serve as templates for future comparison, as the biventricular paced QRS remains stable over time unless a ventricular lead ceases to capture or is significantly displaced.²⁰³ It is also useful to document the QRS morphology during RV and LV pacing separately (possibly in temporary VVI or VOO mode to avoid the possibility of fusion) (Figure 5). Aside from predicting the morphology that would result from loss of capture, single-site pacing occasionally demonstrates significant latency, giving an early indication that VV delay adjustment may be useful to ensure resynchronization.²⁰⁴

3.4.1 Documentation of biventricular capture

Clinical response to CRT depends on the proportion of effective biventricular capture during daily activity, and this cannot be assumed from a resting ECG. There are various conditions that may lead to loss of biventricular capture during activity: atrial fibrillation with an increased proportion of short RR intervals; accelerated AV conduction; increased ventricular ectopy; upper rate limit behavior; and increased pacing threshold due to change in posture or myocardial ischaemia.

The percentage of biventricular pacing recorded by the device may be an inaccurate guide due to QRS fusion: the presence of

a pacing stimulus does not imply full capture. Prior to hospital discharge or at 2–3-month follow-up, ambulatory Holter ECG or exercise ECG testing, with careful examination of QRS morphology may help to verify constant biventricular capture.

3.4.2 Acute change in paced QRS duration

Although in clinical trials the average QRS duration has been shown to shorten by 20–40 ms with CRT, this effect is not seen uniformly in individual patients.²⁰⁵ Few studies have shown a relationship between the degree of QRS shortening and clinical response to therapy. Indeed, clinical improvement may be seen despite QRS lengthening, especially when the left ventricle is paced alone or significantly earlier than the right ventricle (193). However, the paced QRS morphology can be a useful guide to the presence and site of RV and LV capture.

3.4.3 Paced QRS morphology in chest leads

A dominant R wave in V1 is almost invariably present in successful CRT and exceptional in RV apical pacing.²⁰⁶ It follows that a negative paced QRS complex in V1 should prompt full investigation, as LV lead displacement or lack of capture due to threshold rise is likely. Other causes include LV lead placement in the middle or anterior cardiac veins, or inadvertently in the right ventricle, significant latency or conduction delay from the LV pacing site, or fusion with a spontaneously conducted QRS. All of these conditions may require reprogramming or re-intervention to achieve effective CRT. QRS morphology in the lateral chest leads (V4–6) reflects the LV pacing location, with a positive deflection typical in basal lead positions, and a negative deflection if the site is apical.

3.4.4 Paced QRS axis in the frontal plane

The biventricular paced QRS complex is a fusion between the LV only and RV only pacing complex which is reflected in its axis. Left ventricular pacing (e.g. from a free wall branch of the CS) results in an extreme rightward QRS axis (up to 180°). Typically, the axis in RV apical pacing is directed to the left superior direction (–60 to –120°), and fusion with LV pacing moves this to the right superior quadrant (–90 to –180°). Right ventricular outflow tract and midseptal pacing generally gives an inferior axis (+30 to +120°), and fusion with LV pacing moves this to the right inferior quadrant (+120 to +180°).²⁰⁷

3.4.5 Algorithms to detect loss of left ventricular capture

Loss of LV capture is a recognized complication of CRT implantation. Changes in QRS morphology and axis observed on ECG recorded can be confirmed by device threshold testing. A number of ECG algorithms, with sensitivity and specificity ~95% for the identification of loss of LV capture, have focused on the QRS polarity in lead V1 and the presence of a q/Q wave in lead I.^{208,209}

3.5 Early device programming

At early device programming, attention and focus on pacing mode, pacing rate, and intervals are important. In patients with sinus rhythm, a VDD/DDD pacing mode without rate responsiveness (i.e. at least as first intent) is recommended. The large CRT studies were performed in VDD mode programming at a low

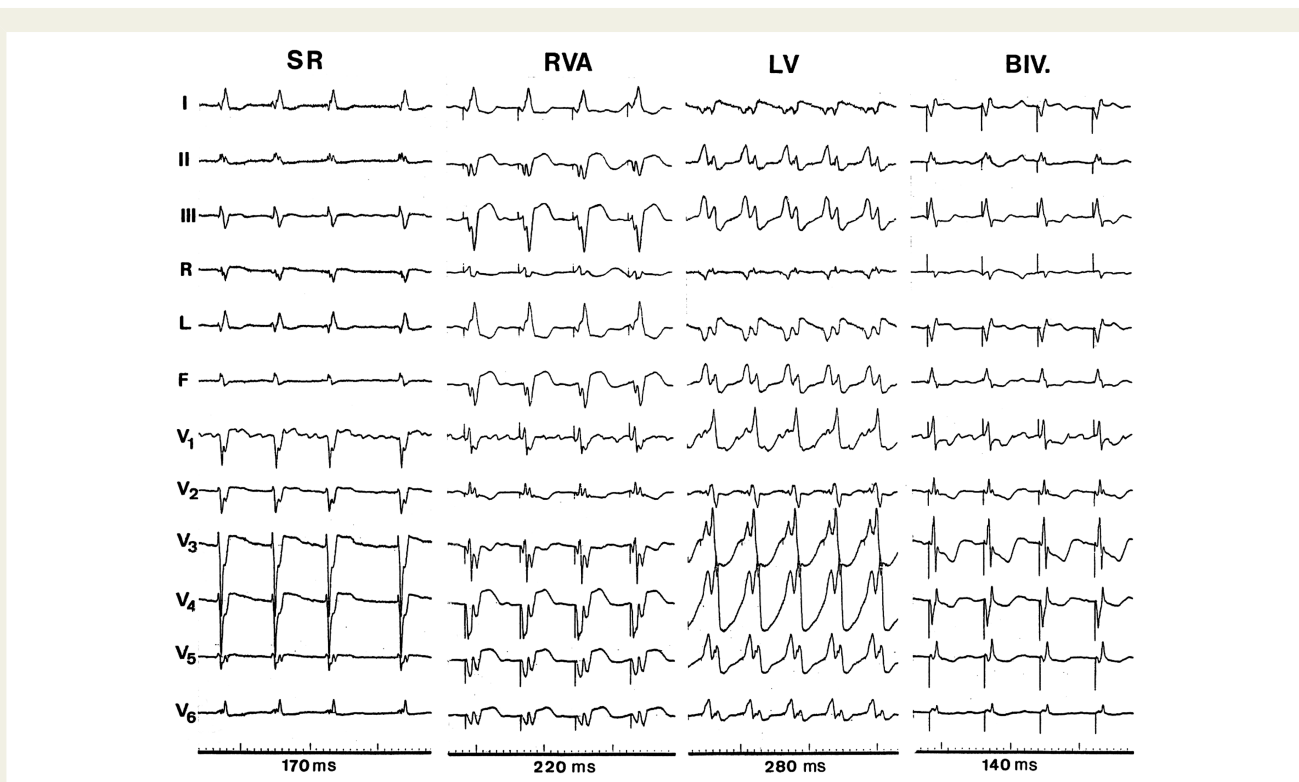


Figure 5 Electrocardiogram sample. Change in paced QRS morphology and duration during right ventricular (RV) apical (RVA), left ventricular (LV) lateral (LV) and biventricular (BiV) pacing with complete ventricular capture in a patient with permanent AF, QRS width = 170 ms and left bundle branch block at baseline.

basic rate, 35–40 b.p.m., to ensure permanent or nearly permanent atrial sensing and to avoid the confounding influences of atrial support.^{210,211} An important objective of heart failure medical treatment is to lower the atrial rate at the lowest tolerated value >50 b.p.m.⁵ Regarding the upper rate limit, it is reasonable to consider programming a rate that is 80% of the maximal age-predicted heart rate. Programming a low maximal tracking rate in a patient with intrinsic conduction may lead to a high risk of symptomatic loss of biventricular capture during exercise.

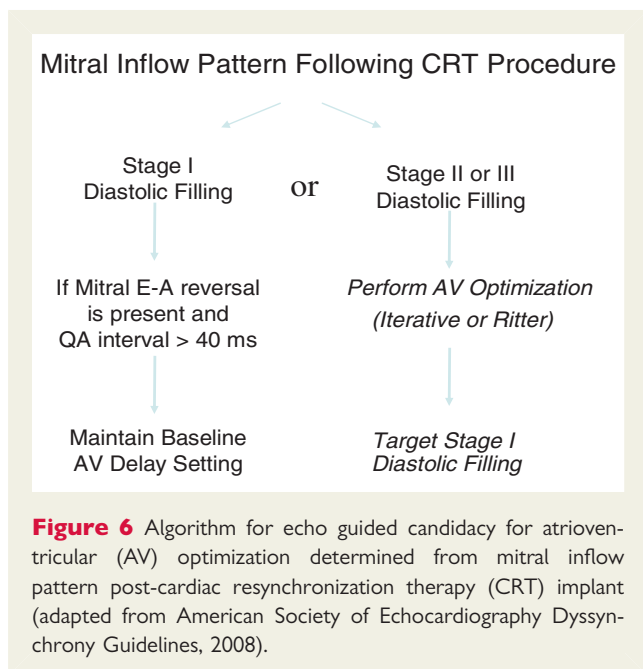
In patients with permanent atrial fibrillation, inhibited rate responsive pacing modes are preferred; DDIR if an atrial lead has been implanted or VVIR, if there is not an atrial lead. The DDDR mode should be reserved for patients with paroxysmal atrial fibrillation. The optimal basic atrial pacing rate has not been determined but there is general agreement that it should not be programmed at rates >60 b.p.m. in the absence of symptoms of chronotropic incompetence at that rate. Similarly, excessive atrial rate response programming with exercise is not recommended.

3.6 Atrioventricular and ventriculoventricular optimization

Although the importance of AV synchrony is unquestioned, the need for routine, systematic AV delay optimization in all patients undergoing CRT remains controversial. Haemodynamic studies have clearly demonstrated the importance of optimal AV delay on cardiac function in the context of CRT.^{212–214} Empirically

setting the sensed AV interval to a standard ‘out-of-the-box’ AV delay of ~100–120 ms in patients undergoing CRT has been the preference for many device implanters, and recent studies suggest that it is a reasonable approach for most patients undergoing CRT. The Smart AV delay trial was a controlled trial that randomized patients to three different methods of AV delay setting: empiric, device algorithm based, and echo-guided when inter- and intra-observer variability in measurement is unsatisfactory.²¹⁵ The study showed no significant difference in the primary outcome between the three strategies and concluded that routine use of AV optimization techniques as assessed in this trial is not warranted. However, these data do not exclude possible utility in selected patients who do not respond to CRT. Notably, patients with prolonged AV conduction due to inter-atrial or AV nodal conduction delay have been reported to derive benefit from echo-guided AV delay optimization.^{216–218} Baseline PR prolongation is a measure of heart failure severity and may predict a lesser outcome after CRT, but the PR prolongation is also correctable with CRT and response rates are still significantly improved.^{217,218}

A consensus statement from the American Society of Echocardiography in 2008 recommended that patients undergo an echo-guided AV optimization procedure following CRT only if the post-implant mitral inflow pattern by pulsed Doppler demonstrates sub-optimal filling patterns, defined as stage II (pseudonormal) or stage III (restrictive) diastolic dysfunction. When the post-implant echocardiogram demonstrates stage I (E-A reversal) on transmitral



inflow at a given, empiric AV delay setting, no further changes to the AV delay are warranted.⁴⁵ (Figure 6).

The role for routine VV optimization is even less clear. Most patients appear to benefit from LV pre-excitation or simultaneous activation.²¹⁹ Hence, many would consider routine VV optimization unnecessary and restrict interrogations to those considered non-responders to therapy. Central to the utility of routine VV timing assessment is widespread agreement on a non-invasive parameter and surrogate of global function most sensitive and representative of subtle changes related to VV timing offsets. Pulsed Doppler interrogation of the LV outflow as a measure of stroke volume is commonly utilized as a global LV function parameter.

3.7 Early echocardiographic assessment

Post-implant echocardiography may be considered to assess the acute response of CRT. The mechanical effects of CRT on the ventricular contraction patterns and the associated haemodynamic changes are immediate and can be monitored on a beat-to-beat basis by transthoracic Doppler echocardiography.²²⁰ Patients in whom reduced mechanical dyssynchrony, together with an improved haemodynamic status and contractile function, can be demonstrated before discharge are likely to benefit in the long term from CRT. In a recent analysis from MADIT-CRT, each 20 ms decrease in LV dyssynchrony by peak transverse strain was associated with a 7% reduction in the primary endpoint of death for any cause or a new heart failure-related event.²²¹

It is recommended to compare the post-implant echocardiographic measures with the baseline values without active pacing, obtained either briefly before implantation or (ideally) during the same post-implant session with temporary inactivation of the device. For practical purposes, the post-implant assessment should focus on a few key measures, which include markers for AV dyssynchrony (transmitral filling profile), inter-ventricular dyssynchrony (difference of the RV and LV pre-ejection intervals,

Table 5 Perioperative complications: summary of rates observed in clinical trials

Perioperative complication	Rates (11,13,91,224–230) (%)
Failure to implant LV lead	4.5–8.5
Pocket haematoma	1.3–3.3
Haemo/pneumothorax	0.4–1.7
CS dissection	0.5–2.1
Cardiac perforation/tamponade	0.3–2.1
Extracardiac stimulation	0.8–4
Complete heart block	0.3–1
LV lead dislodgement	2.8–6.9
Exacerbation of CHF	0.4
Acute renal failure	0
Death	0.01–0.3

inter-ventricular mechanical delay) and inter-ventricular dyssynchrony (by 2D strain or 3D echocardiography).^{45,221} Long-term response depends on multiple factors, and there is no single measure, which predicts a beneficial outcome with sufficient reliability. However, a significant reduction of the inter-ventricular mechanical delay, a disappearance of a presystolic septal flash with a normalized septal contraction pattern,²²² a reduction in MR,^{140,223} and an improvement in intra-ventricular dyssynchrony by deformation imaging (speckle tracking, 2D strain) or 3D echocardiography are changes that have been found to be associated with a beneficial outcome.^{36,221} In contrast, the long-term response to CRT is more uncertain in patients in whom no such improvement can be documented.⁵⁰

3.8 Peri and post-operative complications

A perioperative complication is defined as any event the day of implantation or subsequent 30 days requiring treatment with intravenous fluids or medications or by invasive intervention.²²⁴ Using this definition, the most recognized perioperative complications are failure to successfully implant the LV lead, pocket haematoma, hemo/pneumothorax, CS dissection, cardiac perforation or tamponade, extracardiac stimulation, complete heart block, LV lead dislodgement (including loss of capture), exacerbation of heart failure, acute renal failure, and death. Data from large clinical trials provide a range of incidences for these adverse events (Table 5).^{11,13,91,224–230} Overall perioperative complication rates range from 4% in more recent trials to as high as 28% in earlier CRT trials.^{224,229}

3.8.1 Recommendations to avoid perioperative complications

Many perioperative complications relate directly to patient selection and preparation as well as operative technique. Heart failure status must be optimized medically to avoid instances of acute perioperative decompensation (see Section 1). Death is a rare

perioperative complication and is usually related to implantation attempts in unstable patients. Patients with acutely decompensated heart failure, dependence on inotropes, or unstable ventricular arrhythmias are not acceptable candidates until their medical status is improved.

3.8.2 Diagnosis of perioperative complications

During the implant procedure and in the immediate perioperative period, the operator and team must give careful attention to the potential for implant-related complications. Post-operative chest X-ray is recommended in all patients to rule out hemo/pneumothorax and to assess stability of intracardiac lead position. In cases where venous access was difficult, additional pre-discharge chest films should be considered to assess for development of a late pneumothorax. Pre-discharge laboratory assessment of renal function is recommended in patients with baseline renal dysfunction or in patients that required high amounts of contrast during the implant procedure. The operative site must be carefully assessed to evaluate wound integrity and rule out pocket expansion due to a haematoma prior to discharge. In addition, lead function should be carefully reassessed. At this time, extracardiac stimulation should be evaluated in various patient positions, lead polarities, and ventricular outputs. This may help detect the potential for extracardiac stimulation that would otherwise go unrecognized until post-discharge.

3.8.3 Management of perioperative complications

Use of meticulous technique in the implantation laboratory reduces the chance of perioperative complications. However, a management strategy is required when adverse events are encountered.

Left phrenic nerve stimulation When PNS (see also Section 2.8) is encountered in the perioperative period, chest radiography should be performed to evaluate LV lead position, and electrical parameters of the LV lead should be obtained. In many patients, left PNS is observed without radiographic evidence of lead migration or frank dislodgement. In these cases, phrenic nerve capture is often positional and related to changes in the relative positions of the LV lead electrode and phrenic nerve. Changes in polarity and/or reduction in pacing output may ameliorate this problem. It is important to realize that a large capture 'safety margin' is not required for the LV lead in all patients. Pacing just above the LV capture threshold (and below the phrenic nerve capture threshold) is often needed to resolve this problem. When phrenic nerve capture cannot be reliably prevented while maintaining LV capture, lead repositioning is required.

Haemo/pneumothorax Pneumothorax requires chest tube drainage if significant lung collapse, dyspnea, or desaturation results.^{231,232} Early post-operative chest films must be carefully reviewed and repeated if necessary to rule out the possibility of a late or expanding pneumothorax. Haemothorax usually requires chest tube drainage and reversal of anticoagulants. Transfusion and surgical consultation may be required.

Coronary sinus dissection Most cases of CS trauma produce no adverse sequelae due to low pressure and the direction of flow in the cardiac venous system. The occurrence of coronary

dissection raises the problem of the continuation of the procedure. It is only in the case of a stable patient without significant pericardial extravasation that the operator can consider continuing the procedure. It is recommended to defer a new attempt for 4–6 weeks.

Cardiac perforation or tamponade Cardiac perforation or tamponade should be considered in the event of haemodynamic deterioration, when contrast extravasation or the unusual courses of the tools are observed. As with standard pacemaker and defibrillator implant procedures, the operator must be aware that any lead, particularly the RV lead may perforate and cause haemopericardium. In all cases, immediate echocardiography is indicated. A pericardiocentesis tray and an experienced operator must be available to perform pericardiocentesis, if indicated by haemodynamic status or echocardiographic evidence of impending tamponade.

Exacerbation of heart failure and acute renal failure Exacerbation of heart failure may occur in relatively unstable patients, in those who receive excessive intravenous fluids intra-operatively, after prolonged procedures, or as a result of DFT testing, anaesthetic agents, or other medical adverse reactions. Treatment with diuretic may be required. Intensive care unit monitoring or intravenous inotropes may be required in rare cases.

Renal failure, particularly due to intravenous contrast has been reported.²³³ Prevention of acute renal failure by minimizing contrast and haemodynamic stress is critical, due to the morbid nature of the complication. Evaluation of renal function post-operatively is required. In some patients, gentle rehydration and/or manipulation of the medical regimen is indicated.

4. Cardiac resynchronization therapy follow-up

4.1 Cardiac resynchronization therapy follow-up recommendations (Table 1)

4.2 General objectives of heart failure follow-up in the cardiac resynchronization therapy patient

The main goal of CRT follow-up is to assess and assure that the device recipient's heart failure status is optimized and that the device is programmed to maximize the chance of a positive response to device therapy. Response to therapy occurs if the patient has improvement in heart failure symptoms and functional status, signs of anatomic and other markers of improved cardiac function, and a reduction in hospitalization and death.

4.3 Treatment models

Ideally, the CRT recipient receives follow-up care, either in the form of reviewing remotely transmitted data and/or with in-clinic visits by a care team with expertise in the management of CRT devices and heart failure. It is especially important if the clinical course after CRT is not characterized by improvement in disease status. In these instances careful attention to factors that influence worsening heart failure status or device function is required.

4.4 Physical examination and symptom assessment

A thorough physical examination including vital signs is a key component of the clinical follow-up assessment. Special attention should be given to the site of implantation. Early after device implantation or change out, attention should be focused on any evidence of infection such as fever, pain, swelling, erythema, warmth, oozing, or haematoma formation which may in turn increase the risk of device infection. Later in follow-up, attention should be focused on signs of device migration, skin thinning, bruising, or discoloration that may indicate a higher risk of device erosion through the skin. Arm swelling and/or the appearance of superficial skin veins on the chest or shoulder, ipsilateral to the device may indicate the occlusion of the subclavian vein on that side, which may be important to know in the event of the need for additional leads. Although rare, signs and symptoms of SVC syndrome have to be recognized and addressed promptly.

Knowing the patient's baseline heart failure status prior to implant provides a basis for evaluation of symptoms and functional status after the device is implanted. Formal QOL assessments may be helpful in objectifying patient response.¹⁴ Functional assessments of activity such as the 6 min walk or cardiopulmonary exercise testing also may be useful (Table 6).

4.5 Evaluating improvement in cardiac function

An echocardiogram at 3 or 6 months after implant showing reverse structural remodelling and improvement in LV function indicates a positive response to CRT, likely translating into long-term reduction in risk of morbidity and mortality.¹² Biomarker assessment and heart rate variability measures also are likely to be improved by 3 months post-implantation but were not shown as independent predictors of response after CRT.^{7,8}

4.6 Optimization of heart failure medical therapies

It is important to reevaluate medical therapy following CRT as improvement in blood pressure and clinical symptoms may allow up titration of neurohormonal blocking agents in patients who did

not tolerate maximal recommended doses prior to CRT.¹³ In addition, clinical improvement following CRT may improve the effectiveness of diuretics and permit lowering the dosage of these agents.

4.7 Surface electrocardiogram

The 12-lead surface ECG can play a role in the follow-up for CRT recipients. While representing only a snapshot in time, the ECG provides adjunctive information to a device evaluation (Table 7). If atrial fibrillation is discovered and represents a new finding, management decisions regarding anticoagulation, antiarrhythmic drug therapy, and cardioversion need to be considered. Furthermore, the ECG reveals whether atrial fibrillation or other atrial arrhythmia is tracked by the device causing rapid and irregular ventricular pacing, or in the presence of intact native AV conduction, leads to inhibition of biventricular pacing or fusion beats.

4.8 Long-term event monitoring

Outpatient ECG monitoring can be valuable to document atrial or ventricular arrhythmias that may not have been detected by the device and to confirm device-detected arrhythmias (e.g. frequent PVCs). It also is useful to document intermittent symptoms that the patient is experiencing that are not explained during device interrogation.

4.9 Exercise testing

Exercise testing can be used to quantify the exercise functional capacity, help in detecting intermittent sensing or pacing problems, and rhythm changes that interrupt CRT such as sinus tachycardia above upper tracking limit, rapid ventricular response in atrial fibrillation (above lower rate or sensor rate), shortening of the intrinsic PR interval during exercise, frequent PVCs or ventricular bigeminy sinus rate increase with loss of tracking due to P waves in the post-ventricular atrial refractory period (PVARP).^{23,4}

4.10 In-clinic device follow-up

Routine device interrogation and testing should be performed according to guidelines for device-based therapy of cardiac arrhythmias. Since CRT recipients have advanced heart failure, bi-annual or quarterly visits should be considered unless the patient's clinical condition necessitates more frequent visits.

Device testing includes interrogation of battery status, lead impedances, amplitudes of intrinsic cardiac signals in atrium, right

Table 6 Indications for selective follow-up testing in the CRT patient

Indication	Test
Increasing functional impairment	6 min walk distance
Worsening QOL	QOL tool
Functional assessment	Exercise EKG
Transplant/VAD evaluation	Cardiopulmonary exercise testing
Assess extent of lung disease	Pulmonary function tests
Arrhythmia	Ambulant 24 h EKG
Haemodynamic evaluation	Right heart catheterization
Ischaemia	Perfusion scan/ stress echo
Revascularization? (CABG/PCI)	Coronary angiography

Table 7 Electrocardiogram evaluation of the CRT recipient

Atrial rhythm—NSR or atrial paced vs. atrial fibrillation
Evidence of appropriate atrial sensing or capture
Presence of ventricular pacing
Presence, frequency, and morphology of PVCs
Evidence of appropriate ventricular sensing or capture
Morphology of paced QRS—evidence of LV capture
Paced QRS width
Evidence of pacing fusion or pseudo-fusion in QRS

and left ventricle, and pacing threshold testing in these three chambers. Loss of left or RV pacing capture that can be restored by reprogramming occurs in ~12% of patients and constitutes an important cause of CRT interruption.¹²⁵ Testing of the LV pacing threshold can be challenging; pseudo-fusion in intrinsic AV conduction and bundle branch block as well as RV anodal capture can obscure ineffective pacing and must be excluded.²³⁵ Testing of ventricular pacing thresholds should be performed separately for right and LV leads. In patients with intrinsic AV conduction, ventricular asynchronous mode (VVI) instead to dual-chamber pacing (DDD) may be used for easier ECG interpretation (to avoid pseudo-fusion).

Interrogation and analysis of device stored memory data is essential to verify if CRT is being continuously applied (Table 8). Percentage of biventricular pacing should be as close as possible to 100%. Studies have shown that biventricular pacing for >92% and >98% offers the highest survival probability free of heart failure hospitalization.^{236,237} It is particularly important in patients with atrial fibrillation. There is data to suggest that in permanent atrial fibrillation patients, AV node ablation, when necessary to facilitate biventricular pacing, is associated with an improved response to CRT suggesting that it should be considered earlier rather than later during follow-up.^{238,239}

Device counters, while useful, also have limitations. In certain instances ineffective sensing and pacing cannot be detected directly from counter data. For example, intermittent atrial under sensing may mistakenly appear as sinus tachycardia in case of atrial flutter with 2:1 under sensing (Figure 7), so-called '2:1 lock-in'²⁴⁰ and T wave oversensing may appear as PVCs.

4.10.1 Device detected arrhythmias and therapies

If atrial or ventricular stored electrograms indicate a sustained or significant non-sustained arrhythmia, it is essential to give attention to potential treatments and precipitating factors. Atrial fibrillation complicates the course of up to 40% of patients with CRT devices after implant, carries significant associated independent risk, may explain symptom worsening or may compromise CRT delivery and, is the most common cause of inappropriate shock.²⁴¹

Ventricular tachycardia/fibrillation requiring shock therapy is associated with worsened prognosis²⁴¹ and should trigger an evaluation of heart failure status.

4.11 Device programming optimization (Table 9)

Similar to programmable parameters in single- and dual-chamber pacemakers and ICDs, atrial, and biventricular pacing outputs should be programmed to assure consistent capture and not programmed excessively high. Automatic capture verification algorithms are useful to minimize pacing energy requirements.

In CRT systems, atrial pacing vs. atrial sensing may result in ineffective AV synchrony due to atrial conduction delay. Unnecessary atrial pacing and competition between sinus rhythm and atrial pacing should be avoided by reducing the lower pacing rate. If chronotropic response is adequate, the preferred pacing mode is for CRT devices is VDD/DDD.

If intrinsic AV conduction is present and causes pseudo-fusion, the AV delay should be shortened. Specific device-based algorithms may be useful to secure a high percentage of ventricular pacing.

Table 8 Use of device diagnostic data in CRT patients

Diagnostic data	Description and rationale
Ventricular pacing (VP)	Estimate of the percentage of paced ventricular events <ul style="list-style-type: none"> Should be >95% (ideally near to 100%)
Biventricular (BiVP), right (RVP), and left ventricular pacing (LVP)	Dedicated counters available in some devices <ul style="list-style-type: none"> May indicate VP without resynchronization (%RVP < %BiVP)
Biventricular pacing via resynchronization algorithm	Counter for LVP after RV sensing <ul style="list-style-type: none"> LV capture questionable
Ventricular sensing (VS)	Estimate of the percentage of sensed ventricular events <ul style="list-style-type: none"> Should be close to 0% VS episodes (continuous ventricular sensing) may indicate intrinsic AV conduction (programmed AV delay too long) or atrial undersensing with intrinsic AV conduction
Premature ventricular complexes (PVCs)	Number of PVCs and per cent of ventricular events that are PVCs <ul style="list-style-type: none"> PVCs reduce the time in effective CRT; should be suppressed May represent atrial undersensing with intrinsic AV conduction, ventricular oversensing (QRS, T wave) or ventricular exit block
Mode switch, atrial high rate episodes, AT/AF episodes	Number of AF episodes and percentage of time in mode switch <ul style="list-style-type: none"> May explain non-response to CRT May represent inappropriate mode switch due to atrial oversensing (resulting in VVI pacing with pacemaker syndrome)
VT/VF	Evaluate for triggers of VT/VF events (e.g. atrial fibrillation)
Non-sustained VT	High grade non-sustained VT may result in significant loss of BiV pacing <ul style="list-style-type: none"> Can represent ventricular oversensing or atrial undersensing

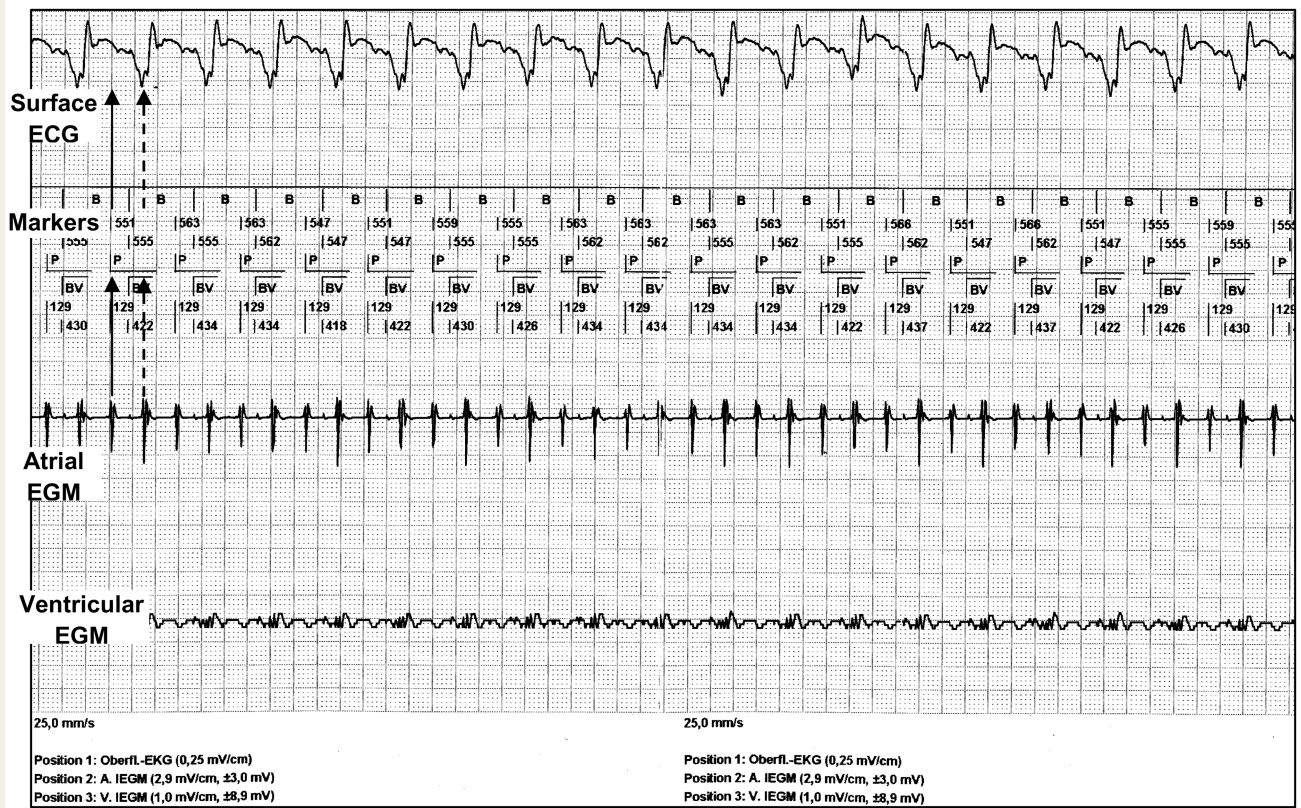


Figure 7 2:1-undersensing of atrial flutter ('2:1 lock-in'). Alternating flutter potentials are sensed (marker P, arrow with solid line) or not sensed (no marker, arrow with dotted line) because they occur at the time of post-ventricular atrial blanking.

Sinus rate above upper tracking limit can occur in patients with heart failure and patients with CRT should receive programming that provides tracking of sinus rhythm as much as possible. Programming optimization in the presence of atrial fibrillation with AV conduction can be challenging. Device-based strategies that trigger LV or biventricular pacing during native AV conduction are unproven and often result in fusion vs. true biventricular paced beats.

Frequent PVCs reported by device counters may represent ventricular oversensing or atrial under sensing with native ventricular conduction and may compromise the amount of biventricular capture. In the case of T wave oversensing decreasing ventricular sensitivity is important but may require repeat VF testing depending upon the original implant defibrillation testing programmed sensitivity.

Inappropriate mode switching, usually due to ventricular far field oversensing in the atrium can also significantly reduce the response to CRT. In this situation, the device will revert to VVI CRT pacing but can cause retrograde VA conduction with the risk of pacemaker syndrome. It usually can be prevented by a programming a post-ventricular atrial blanking period (PVAB) of at least 150 ms.

Conversely, under sensing of atrial fibrillation can lead to absence of mode switching and irregular, fast tracking of atrial fibrillation. Adjusting atrial sensitivity to a more sensitive value can minimize it. Additionally, the detection rate of atrial

tachyarrhythmias can be reduced (e.g. to 170–180 b.p.m.) to allow atrial fibrillation detection in the presence of intermittent atrial fibrillation under sensing. Under sensing of atrial flutter in the PVAB (Figure 7) can be avoided by device-specific algorithms, programming a shorter AV delay, and/or reducing the upper tracking limit.

If sinus rhythm tracking is not occurring consistently, it may be due to under sensing during PVARP prolongation after PVC. Similarly, automatic algorithms to terminate pacemaker-mediated tachycardia (PMT) may misinterpret sinus tachycardia as PMT and interrupt sinus rhythm tracking. In this case, sinus tachycardia with intrinsic AV conduction and long first degree AV block can occur with P waves in the PVARP resulting in persistent interruption of CRT.²³⁴ If interruption of CRT is observed, PVC or PMT intervention algorithms should be programmed off or, if available, utilize dedicated algorithms to regain sinus rhythm tracking.

4.12 Remote monitoring and follow-up

4.12.1 Summary of current clinical data to date

Remote monitoring offers the advantage of earlier detection of clinical problems (e.g. ventricular tachyarrhythmias, atrial fibrillation) and technical issues (e.g. lead fracture, insulation defect) than conventional in-hospital follow-up. In one study, remote monitoring detected arrhythmias as much as 154 days earlier than with an in-clinic follow-up performed at 6-month intervals. In the

Table 9 Problems that may be detected during follow-up and proposed solutions

Problem	Solution
Loss of right or LV capture	Reprogramming of pacing parameters (activation of automatic capture verification) Lead revision
Undesirable atrial pacing	Reduction of the lower rate limit
Intrinsic AV conduction	Shortening of the AV delay (sensed, paced) Activation of sensing reaction algorithm
Sinus rate above upper tracking limit	Increase upper tracking limit Beta-blocker therapy
Atrial fibrillation with rapid conduction	Increase lower rate limit Activate rate responsive pacing Activate early CRT pacing algorithms Pharmacologic prolongation of AV conduction AV node ablation
Very short sensed AV delay	Pharmacological prolongation of AV conduction AV node ablation
Frequent PVCs	Check for ventricular oversensing and adapt ventricular sensitivity/activate specific algorithms Check for atrial undersensing and adapt atrial sensitivity/activate specific algorithms
Inappropriate mode switching	Prolong PVARP as long as necessary to blank out ventricular farfield signals
Intermittent undersensing and tracking of atrial fibrillation	Increase atrial sensitivity Reduce atrial tachyarrhythmia detection rate
Functional atrial undersensing of atrial flutter (2:1 lock-in)	Shorten sensed AV delay and PVAB Reduce upper tracking limit (e.g. to 110 b.p.m.)
Functional atrial undersensing of sinus tachycardia	Deactivate PVC reaction and/or PMT intervention algorithms Activate specific algorithms shorten AV delay and/or PVARP

AV, atrioventricular; PMT, pacemaker mediated tachycardia; PVAB, post-ventricular atrial blanking period; PVARP, post-ventricular atrial refractory period; PVC, premature ventricular complex.

TRUST trial, the median time to detection of an arrhythmic event was <2 days with remote monitoring compared to 36 days with conventional follow-up.²⁴²

A number of trials involving >100 000 remotely monitored patients as well as other remote registry data have confirmed the advantages of remote follow-up compared with conventional in-hospital follow-up.^{241–246} Compared with no remote monitoring, outcomes appear to be improved with remote follow-up resulting in reductions in heart failure hospitalization.^{241,243,246,247} The reasons for these improvements may also relate to the ability of the patient to trigger a transmission in the event of new symptoms.

There are other measures, intrinsic to CRT devices that can be continuously monitored remotely to detect possible heart failure deterioration. Heart rate and rhythm, heart rate variability, and intrathoracic impedance or a combination of these measures may be helpful in the assessment of heart failure status. The PARTNERS HF trial has shown that the combination of parameters provided by CRT devices can improve the prediction of heart failure deterioration significantly.²⁴⁸ Whenever two measured criteria were positive, the risk of heart failure hospitalization within the next month showed a 5.5-fold increase: atrial fibrillation of long duration, rapid ventricular rate during atrial fibrillation, low trans-thoracic impedance, low patient activity, abnormal values for night heart rate or heart rate variability, or abnormalities of device therapy (low percentage of biventricular pacing or shock therapy).

In addition to these parameters that do not require additional hardware, other parameters that require specific implantable sensors (e.g. to measure haemodynamics) or wireless technology (e.g. blood pressure, body weight) can be used to monitor heart failure (Table 10). While multiple parameters are monitored that may assist in disease management and earlier identification of cardiac decompensation, single measures such as thoracic impedance are overly sensitive and may result in a high rate of false positive alerts.²⁴⁹ However, current parameters are not likely utilized to their fullest extent and improvements are required for future devices to make interpretation of the data, especially using blended sensors, more convenient and efficient for the clinician.

4.12.2 European and US differences

Clinical application of remote monitoring is widespread in North America with data from ~1 million patients with implanted devices transmitting data remotely. Acceptance of remote monitoring is particularly high due to availability of reimbursement for remote follow-up and accumulating evidence that outcomes are better compared with standard in-clinic follow-up and long distances that some patients have to travel in many parts of North America.

Remote monitoring has a highly variable penetration in Europe, mostly due to highly variable reimbursement systems.²⁵⁰ There are different components of remote monitoring costs including: (i) the devices capable of remote monitoring (typically 'premium segment' devices); (ii) the transmitters; (iii) the telephone connection and

Table 10 Heart failure diagnostic methods and parameters

Heart-rhythm-related parameters	Heart rate (during sinus rhythm and atrial fibrillation) Heart rate variability Atrial fibrillation (AF burden, number/duration of episodes) Ventricular arrhythmias (%/number of PVCs; nsVT, VT, VF)
Device-related/calculated parameters	Percentage of biVP Number of shocks Intrathoracic impedance Patient activity level
Parameters transmittable via wireless technology	Blood pressure Body weight
Parameters from specific hardware sensor technology	Intracardiac pressure: RV, pulmonary artery, left atrial Third heart sound (via peak endocardial acceleration)

AF, atrial fibrillation; nsVT, non-sustained ventricular tachycardia; PVC, premature ventricular complex; VF, ventricular fibrillation; VT, ventricular tachycardia.

calls; (iv) the database (company or service provider); (v) the messages to the follow-up physician(s) (e.g. electronic mail, fax, text); and (vi) the calling costs to the patient if there are significant events. One or more of these components are not reimbursed in many European countries. Additionally, travel distances to the follow-up centre are short in many parts of Europe. Finally, legal aspects of remote monitoring (e.g. data safety) are highly heterogeneous in Europe. Therefore, while some European countries have started to establish a nationwide database (e.g. UK), remote monitoring is less utilized and organized in other European countries.

4.13 Continuous implantable haemodynamic monitoring/pulmonary artery pressure or left atrial pressure monitoring

Most heart failure deteriorations are due to fluid overload. It is increasingly clear that fluid accumulation may develop weeks before the development of weight increases and symptoms. While none of the direct pressure sensors are Food and Drug Administration (FDA) approved, the expectation is that in the future the direct haemodynamic pressure sensors will be incorporated into CRT devices.

The implantable haemodynamic monitor first tested for heart failure patients is the Chronicle® device (Medtronic) that continuously measures RV diastolic pressure to estimate LV filling pressures from a lead implanted in the right ventricle.^{251–254} In a randomized trial (COMPASS-HF) the use of these pressures compared with non-use to tailor heart failure medication failed to significantly lower the primary endpoint of total heart failure events in patients with advanced heart failure and was not FDA approved.²⁵² The results from the Chronicle study provided confirmatory data

that intracardiac pressure increases precede clinical deterioration of heart failure as much as 5–6 weeks in advance of a clinical event.

In the CHAMPION study (CardioMEMS) patients in NYHA III who also had a previous heart failure hospitalization were implanted with a leadless and wireless implantable haemodynamic monitor implanted as a stent system placed in the distal part of the pulmonary artery.²⁵⁵ Medical therapy guided by daily transmission of pulmonary artery pressure was compared with standard medical management. A significant 39% reduction in hospitalization for heart failure was seen in sensor patients vs. controls.²⁵⁵ To date, the device has not received FDA approval. A direct left atrial pressure sensor is in under active investigation in the randomized LAPTOP-HF trial. This study has several randomization arms, including a no LAP device arm and includes the LAP device in both ICD and CRT device randomization arms. The patient takes the left atrial pressure daily and is given a remotely transmitted ‘dynamic prescription’ depending on the pressures measured. Study endpoints include mortality and hospitalization.²⁵⁶

These studies may indicate the addition of central pressures to CRT or incorporation of the technology in CRT devices might further enhance CRT by providing continuous data regarding heart failure status to assist in follow-up of the CRT patient from a clinical and programming perspective.

The direct pressure monitoring systems would also require active engagement of implanted patients in their own care, an aspect of heart failure care management that allows patients and physicians to partner in the continuous management of the patients’ clinical status. As the use of continuous pressure monitoring today is investigational, clinical use should await positive trials showing these features cause more benefit than harm.

4.13.1 Advantages and disadvantages of remote monitoring to follow heart failure patients with cardiac resynchronization therapy devices

Although initially it was asserted that it would be disadvantageous to forego the regular face-to-face encounters between patient and device clinic caregivers, several factors indicate that there is less of a concern. Most clinics maintain a link with patients either with infrequent visits to the device clinic and contact by phone or other mechanisms. The psychological reassurance that many patients have by knowing there is more constant surveillance of their device appears to outweigh the importance of seeing and talking to a caregiver on a regular basis. Patients also express the practical advantages of minimizing travel, travel costs, schedule, and the absence of required in-clinic visit schedule.

There were early concerns that the amount of data received on a regular basis would overwhelm the management capabilities of the caregivers. Although there is considerable data, the ability to customize alerts and notification techniques has helped to streamline prioritization of data analysis.

Another expressed issue is the potential for litigation if a clinical event had been remotely transmitted and not acted upon with the patient subsequently experiencing an adverse clinical event. The more rapid detection of, and response to, clinical events by remote monitoring as determined by randomized clinical trials may minimize physicians’ legal concerns.

4.14 Late complications: detection and management

In patients with CRT, long-term complications are more frequent than in single- or dual-chamber pacemaker/ICD systems since these patients usually have advanced heart disease, implantation is more complex, and there is more hardware, particular leads at risk. The annual risk of CRT system infection detected during follow-up averages between 1 and 3%²³⁹ and tends to increase over time and is associated with prolonged hospitalization stay and increased cost.²⁵⁷ Recommendations for diagnosis of CIED infection, antimicrobial management, removal of infected material, and eventual new device implantation are reported in the 2010 AHA scientific statement.¹⁰⁷

Renal failure, device replacements, device size, and re-interventions increase infection risk.^{104,258} In most patients with device system infection, the complete system including all leads should be explanted. The Heart Rhythm Society policy statement on lead extraction from 2000 allowed retention of a lead if it can be cut through a sterile incision separate from an infected pocket,²⁵⁹ but a significant risk of re-infection remains with this approach.

Lead extraction can be difficult in CRT systems due to lead burden and the underlying condition of the patient. Laser and other technologies that reduce risk of explants as well as experienced operators will help reduce explant risk.

Apart from system infection, long-term lead abnormalities play a dominant role in late complications detected during follow-up. The risk of lead problems (e.g. insulation failure, conductor fracture) is recognized to be higher with high energy vs. pacing leads.

Even for experienced implanters, hardware complications requiring surgical revision are significantly more frequent for CRT-D systems compared with single- or dual-chamber ICDs.²⁶⁰ In a recent meta-analysis of randomized trials and a registry, the dislodgement rate in CRT-D systems was ~3-fold compared with single- and dual-chamber ICDs (1.8 vs. 5.7%,²⁶¹ odds ratio 2.92 for CRT-D²⁰⁰). The only independent predictor for LV lead dislodgement was high pacing threshold at the time of implant.²⁵⁸

5. Response to cardiac resynchronization therapy-management of the non-responder

5.1 Response to cardiac resynchronization therapy management recommendations (Table 1)

A critical component of CRT follow-up is to identify the predictors of favourable clinical outcomes and strategies for treating non-responders. This component includes appropriate patient selection, implantation strategies, and programming to maximize the benefit of this therapy.

5.2 Assessment of response to cardiac resynchronization therapy in clinical trials and in the naturalistic practice

There is a lack of consensus on the definition of prevalence and treatment strategies to approach the patient who does not respond to CRT. Randomized trials and clinical practice definitions of non-response are not uniform. Typically, clinical trials evaluate event-driven endpoints such as heart failure hospitalizations and mortality as primary clinical determinant of response to therapy and measures of cardiac function and functional status as important secondary endpoints. The most commonly used measures are volumetric changes of the left ventricle, typically LV end-systolic volume index, or end diastolic index. In real life outside of clinical trials, patients overall well being is a more relevant measure; less well-defined criteria are used to assess response. Definition of response to CRT is also a matter of expectation. Patients in advanced heart failure seek symptom relief; many patients at this stage of disease are willing to trade off months of life against even some time with a better QOL. However, when a patient feels significantly better after CRT, his or her attention may be directed towards less frequent admission to the hospital, greater need for social life and activities, and finally prolongation of quantity of life.²⁶²

5.2.1 Quality of life and functional endpoints

Assessment of multiple aspects of well being, including QOL, symptoms, and functional capacity to demonstrate consistency of effect, is preferable in choosing one arbitrary aspect of well being. In the context of pragmatic evaluation of elderly people with heart failure, a heart failure symptom questionnaire, a general QOL questionnaire, and a walk-test (e.g. 6 min walk) would appear appropriate.¹⁴ Cardiopulmonary exercise tests are a useful assessment of pathophysiology but relatively impractical for large-scale clinical trials or for the clinic setting.

5.2.2 Event-driven endpoints

There are many clinical measures of CRT response used in clinical trials.^{2,6,8,11,13} There are some advantages and disadvantages of the categories of CRT response measures (Table 11). Measures that include all-cause deaths will undoubtedly include events unlikely to be influenced by CRT. However, it is the most unbiased method to compare the effect of CRT on mortality when used in large-scale randomized controlled trials. It is easy to interpret and has major impact on health economics. The outcome measure of heart failure hospitalization is an appropriate measure to address the effect of CRT on patient's heart failure status deterioration needing hospitalization. However, it still can be influenced by adjudication bias, especially in open labelled clinical trials when treatment allocation is not concealed. The use of event-driven measures is appropriate to be used for large-scale, long-term clinical trials, but in the determination of an individual in clinical practice, it may not be as meaningful.

5.2.3 Composite endpoints

Composite endpoints are frequently used in clinical trials of CRT.²⁶³ Such composites are only valid when each component is of similar importance, or one component of the endpoint

Table 11 Measures of response to CRT

Category	Example	Advantage	Disadvantage
Outcome measures	Mortality cardiac transplant HF hospitalization	Well-defined measures Easy to access Objective Less susceptible for bias	Need large number of patients Need long-term follow-up Need comparison group (best with randomized controlled trial) Differences in outcomes could be attributable to other factors than CRT
Remodelling measures	LV volumes LVEF	Standardized measures Objective Related to CRT effect	Susceptible to inter-observer variability Affected by incomplete data/loss of follow-up Can be affected by attrition and detection bias Need less patients Need short-term follow-up
Clinical measures	NYHA functional class 6 min walk test Peak VO ₂ QOL Score patient global ass.	Easy to assess Clinically relevant Need less patients Need short-term follow-up	Subjective Can be affected by performance, attrition and detection bias Susceptible to inter-observer variability Affected by incomplete data/loss of follow-up
Clinical composite measures	Composite of above categories	Include hard outcome, remodeling, and clinical measures Clinically relevant	Affected by the proportion of individual measures

(usually death) precludes the patient attaining other components. For the latter reason, composite endpoints should generally include death since it is one way of a patient avoiding non-fatal events. Composite endpoints should not generally be used to inflate event rates (typically by adding blood or imaging tests as part of the composite) for statistical purposes but should be clinically valid.

5.2.4 Comparisons of measurements of cardiac resynchronization therapy response

Different methods to assess CRT response often do not yield similar response rates since they may be assessing different aspects of heart failure status.^{2,3,6} In addition, they all have potential weaknesses that may influence results and therefore must be interpreted accordingly. *Figure 8* demonstrates CRT response pooled from major CRT clinical trials. Response rates are highest when functional measure endpoints are used. Structural and event-driven endpoints resulted in response rates between 40 and 60%.^{8,13,74,75,89,91,144,203,213,229,230,264–304}

5.3 Predictors of cardiac resynchronization therapy response

A number of clinical, ECG, and cardiac function characteristics have been shown to predict CRT response.⁸ Notably, end-stage heart failure patients, including those who are inotropic drug-dependent appear to have a poor response rate. Thus, CRT should be used carefully and with less expectation of clinical response in patients with ACC/AHA stage D, refractory NYHA class IV syndromes.^{2–6} Patients with non-ischaemic aetiologies of heart failure often have a better response to CRT, particularly with regard to reverse remodelling.² Some studies have stratified patients with ischaemic heart failure aetiology in part by an evaluation of scar burden.^{50,65–76} Those with extensive scar, usually

measured by MRI, have a lower response rate to pacing therapy.³² Several studies have also shown an interaction of gender with CRT, as women tend to respond more frequently.¹² The mechanism of this effect is still unclear, but it appears independent of the clinical differences between sexes, such as aetiology of heart failure and ECG parameters.¹

It is evident that both baseline QRS duration and morphology are predictors of long-term outcome and response to CRT (see Section 1 and subsequent sections). As noted previously, measures of cardiac function are fundamental to understand the response to CRT, even if they are not always appropriate as a measure of response rate. The value of mechanical dyssynchrony assessment and of biomarkers is addressed in Section 1.

The potential value of a multi-parameter approach to predict response to CRT was recently evaluated in MADIT CRT.¹² Seven factors were identified as associated with echocardiographic response at 1-year and made up the response score: female gender, non-ischaemic origin, left bundle-branch block, QRS ≥ 150 ms, prior hospitalization for heart failure, LV end-diastolic volume ≥ 125 mL/m², and left atrial volume < 40 mL/m². Multivariate analysis showed a 13% ($P < 0.001$) increase in the clinical benefit of CRT-D per one-point increment in the response score and a significant direct correlation between risk reduction associated with CRT-D and response score quartiles.²⁶⁴

5.4 Evaluation of the non-responder

It is important to adopt a criterion of response to CRT and apply it to the post-operative follow-up in assessment of CRT recipients.^{2–6} Objective criteria such as 6 min walk or cardiopulmonary testing in addition to LV volumes and function by echocardiography in combination with symptoms assessment are accepted and validated measures of response. If a patient is defined as a non-responder, a systematic effort to identify and treat reversible

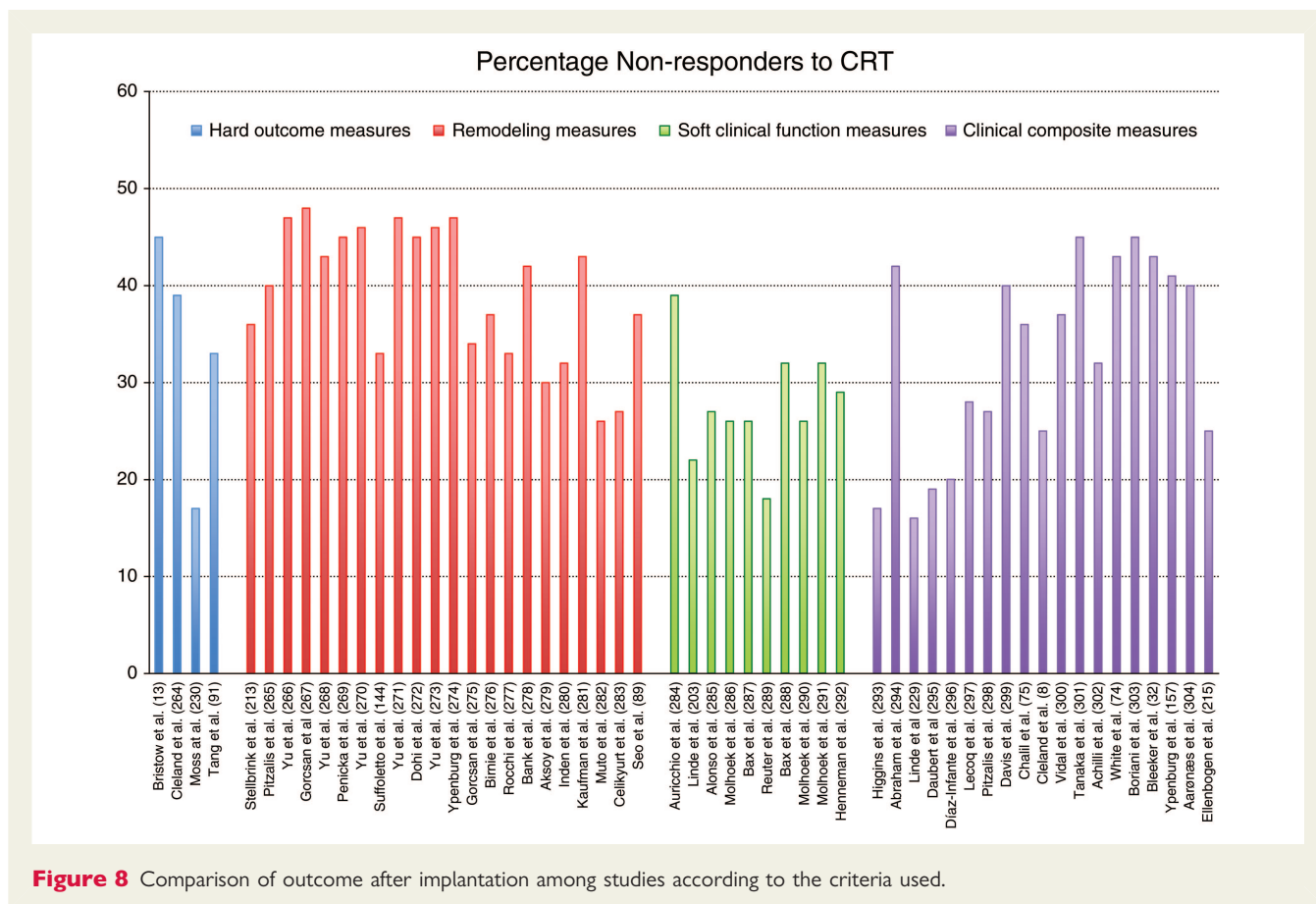


Figure 8 Comparison of outcome after implantation among studies according to the criteria used.

causes is recommended. This process should be step-wise process to make efficient use of interrogation methods and to ensure a comprehensive evaluation.²⁶⁶

The assessment should begin with a physical examination, review of medical regimen, and assessment of lead location and device function. A device interrogation to assess for atrial and ventricular arrhythmias, satisfactory sensing and pacing, rate response, and presence and frequency of continuous BiV capture is recommended. A device-guided or echo-guided AV optimization is a reasonable and relatively simple and rapid next step, although the benefit of this approach appears small from prospective multicentre studies (see Section 3).

One reason for non-response may be insufficient conduction delay at baseline. In a series reported by Mullens *et al.*,⁵⁰ 9% of patients had a baseline QRS duration of 130 ms or less. Further, an unpaced QRS duration of 120–140 ms suggests a lower likelihood to achieve an improved outcome whether defined by reduced LV end-systolic volume, hospitalizations, or mortality.^{13,91,213,230,264} Intrinsic QRS morphology is also of major importance. Both the RBBB and IVCD conduction patterns have been associated with worse outcome. The MADIT-CRT and RAFT trials^{91,230} demonstrated that patients with RBBB were at a higher risk of death compared with the control group, with a borderline reduction in frequency of hospitalizations. Patients with IVCD had an increased risk of hospitalizations and death. If the baseline ECG shows a narrow or non-LBBB configuration and worsening

clinical status or clear evidence of non-response is present after implant, consideration may be given to discontinuing CRT.

5.5 Treatment of the non-responder

5.5.1 Reprogramming

Reprogramming, whether by modifying the AV/VV delays or rate, only should be considered after a thorough device interrogation. Performing an echocardiographic assessment of global and regional LV function with or without pacing can assist in determining if the physician can document an objective difference between the two conditions. The findings of this evaluation could result in several different combinations of modifications in device settings, multiple follow-up visits and adjustments, and potentially the determination to discontinue CRT.²⁶⁶

5.5.2 Optimization of medical therapy

Optimization of medical therapy should be a goal for all heart failure patients; but in particular, patients who are non-responders to CRT (see Section 1). Life-saving medicine doses often are limited in patients with heart failure by hypotension and renal dysfunction. A hallmark of CRT is a rise in systolic blood pressure and theoretically, this rise should permit up-titration of life-saving pharmacological therapies. It is certainly the case for some individuals. However, in general, there is limited evidence that medication doses are increased after CRT and some evidence of a decrease after CRT. Since CRT systems also provide bradycardia

support more aggressive titration of beta-blockers may be better tolerated after implant.

5.5.3 Pacing lead position/configuration

The role of pacing lead position to treat or prevent non-responders remains controversial, as the optimal location of the lead is a matter of debate.^{305,306} Some authors suggest that providing more pacing sites in the right or left ventricles would improve the correction of cardiac dyssynchrony and the response to CRT. In an acute study in 21 patients, Yoshida *et al.* compared conventional biventricular pacing with triple-site pacing using one LV lead and two RV leads, one at the apex and one at the right outflow tract.¹⁵² Left ventricular dP/dt and cardiac output were significantly improved with triple-site pacing when compared with biventricular pacing. They also found an acute reduction in LV end-systolic volume and an acute increase in LVEF; though significant, the differences were small. Finally, authors showed that dual-site RV pacing was superior to biventricular pacing to improve mechanical dyssynchrony, but the finding was not confirmed by Lane *et al.*³⁰⁷ Another triple pacing site configuration with two LV leads positioned through the CS was studied. Lenarczyk *et al.*³⁰⁸ and Leclercq *et al.*³⁰⁹ demonstrated the feasibility of the implantation of two leads into the CS. Acute haemodynamic studies designed to assess the superiority of dual LV pacing sites have showed conflicting results. Mid-term follow-up studies provided encouraging results: Lenarczyk *et al.*³⁰⁸ in a preliminary non-randomized study comparing 27 patients with biventricular pacing and 27 with dual LV pacing sites showed that the magnitude of improvement in symptoms and LVEF was greater with triple-site resynchronization. In a randomized cross-over trial including 42 patients with permanent atrial fibrillation and an indication for CRT, Leclercq *et al.* showed that triple-site pacing yielded a significant improvement in LVEF and LVESV after 3 months while there was no significant change in NYHA class, six MWT and QOL.³⁰⁹ The real value of multisite ventricular pacing needs further assessment in randomized trials. At least two trials are ongoing. TRUST is a trial conducted in *de novo* CRT patients.³¹⁰ The V3 trial designed to assess the potential efficacy of a second LV lead in non-responders patients is ongoing.³¹¹

5.5.4 Endocardial left ventricular pacing

Pre-clinical studies showed consistent haemodynamic benefit of LV endocardial over LV epicardial pacing.^{312,313} Endocardial LV pacing is currently under investigation. One system paces the LV using ultrasound technology that does not require an LV lead. It has been performed in some patients in whom transvenous LV pacing has been unsuccessful.^{314–316} In these studies, access to the LV endocardium for pacing typically requires transseptal puncture that may increase risk of systemic embolization and³¹⁷ mitral valve dysfunction as the leads pass through the mitral valve. A recent report described the feasibility of a transapical approach for endocardial LV placement.³¹⁸ The potential attraction of LV endocardial pacing is that it allows greater options for LV pacing, with sites not limited by CS anatomy, with reduced likelihood of PNS. Preliminary data are conflicting regarding whether response rates to CRT differ between endocardial and epicardial LV pacing.^{126,151,312,319}

5.5.5 Treating arrhythmias

Poor response to CRT may be due to arrhythmias, including atrial fibrillation and frequent PVCs. Aside from loss of AV coordination, the main problem that atrial fibrillation presents is a fast ventricular response that exceeds the pacing rate, leading to loss of resynchronization therapy in the ventricles. Atrioventricular nodal blocking agents are rarely adequate to ensure that a high percentage of beats are paced without fusion.³²⁰ Catheter ablation of the AV node has emerged as an attractive adjunctive therapy for CRT recipients with atrial fibrillation, particularly for those with permanent atrial fibrillation or high atrial fibrillation burden, to ensure 100% ventricular pacing. Gasparini *et al.* showed that in CRT patients with permanent atrial fibrillation, those who underwent AV node ablation showed increased LVEF, reverse remodelling effect, and improved exercise tolerance, while those treated with nodal blocking drugs did not. These investigators and others also found that AV node ablation might lead to improved survival among CRT recipients with atrial fibrillation.^{238,321} In summary, CRT patients with permanent or frequent atrial fibrillation should be considered for AV node ablation.

A more controversial issue is whether CRT recipients with atrial fibrillation should undergo pulmonary vein isolation (PVI) or other left atrial ablation procedure with the goal of eliminating atrial fibrillation or reducing the arrhythmia burden. In the absence of device therapy, there are somewhat disparate findings regarding the success rate of PVI in patients with reduced EF. In separate studies, De Potter *et al.*³²² and MacDonald *et al.*³²³ both reported atrial fibrillation-free survival of 50% after PVI in patients with heart failure and atrial fibrillation, even though patients were older and had more advanced heart disease in the latter study. In contrast, Khan *et al.*³²⁴ reported PVI patients derived greater improvement in EF, 6 min walk distance, and Minnesota Living with Heart Failure score than those who received nodal ablation and CRT. Since no patients received both PVI and CRT, it remains unknown whether these therapies offer additive benefits. At least two multicentre studies addressing the value of PVI in CRT recipients, the AMICA (NCT00652522) and CASTLE-AF (NCT00643188) trials, are currently enrolling patients.

The role of catheter ablation in CRT patients with high burden of PVCs is less well studied. With sufficient frequency of ectopic beats, CRT may become ineffective due to high fraction of non-paced beats. When a CRT non-responder has unifocal PVCs in sufficient number to enable catheter mapping of the origin, ablation of the ectopic focus may allow a greater response to CRT to emerge. Herczku *et al.*³²⁵ reported a case in which this occurred. While intuitively attractive, this approach awaits further study.

5.6 Treating associated conditions

Certain concomitant cardiac conditions contribute to heart failure so may counteract or minimize the benefit of CRT. These include ischaemia, anemia, thyroid disorders, and valvular heart disease. Accordingly, correcting or treating these conditions may enhance the effect of CRT. For instance, treatment of active ischaemia either medically or with revascularization (percutaneous or surgical) should be an important component of the overall treatment of patients. Similarly, it was recently shown that reducing MR with a

percutaneous mitral clip procedure resulted in marked improvement of the response to CRT.³²⁶

5.7 Haemodynamic monitoring

Cardiac resynchronization therapy devices record and provide important information from measured electrical and impedance data that are designed to predict heart failure status^{241,327} (see Section 4). The role of these measures in optimizing response to CRT is unproven.

5.8 Summary

Despite the consistent finding of structural, clinical, and survival benefit of CRT from large clinical trials of patients with LV dysfunction and QRS prolongation, there are patients that do not appear to respond to therapy using one or several measures of response. In clinical practice, it is important to use several measures of response prior to declare a patient a non-responder. These measures should include functional tests aimed at symptom assessment, imaging studies to assess LV function and neurohormonal activation encompassing biomarkers and heart rate variability.

Once it is determined that a patient has a suboptimal response to CRT, a systematic effort should be utilized to identify and treat reversible causes. This effort includes optimization of medical therapy, assurance of appropriate and consistent pacing, treatment of arrhythmias and reversible causes of deterioration. The role of adding or repositioning leads, as well as modifying paced rate, AV of VV timing on response is less clear. In patients who do not respond to interventions, alternative treatment options should be considered such as placement of a LV-assist device or cardiac transplantation.

6. Special considerations

6.1 Special consideration recommendations (Table 1)

6.2 The cardiac resynchronization therapy patient with atrial fibrillation

Atrial fibrillation is the most common arrhythmia and its prevalence increases in the presence of heart failure. Patients with CRT often have concomitant atrial fibrillation that may be diagnosed before or after the implantation of the CRT device.

There are three special considerations that are pertinent to the CRT patient with atrial fibrillation: (i) if patients with atrial fibrillation extract similar survival, symptomatic, and echocardiographic benefit from CRT compared with patients in normal sinus rhythm (NSR); (ii) how to ensure a high percentage of biventricular pacing in CRT patients with atrial fibrillation and to understand the role of AV nodal ablation in the management of the CRT patient in atrial fibrillation; and (iii) the effect of CRT on changing the burden of atrial fibrillation.

From a total survival perspective, there are no randomized prospective trials examining the effect of CRT on morbidity–mortality endpoints in patients with atrial fibrillation. Prospective non-randomized observational data³²⁸ suggested no difference in

total mortality after CRT in 96 patients with chronic atrial fibrillation compared with 167 patients in NSR. Retrospective analyses²⁶⁴ of the CARE-HF trial identified 124 out of 813 (15%) patients with a diagnosis of atrial fibrillation. In that analysis, the presence of atrial fibrillation did not diminish the benefits of CRT on all-cause mortality. A more recent meta-analysis³²⁹ suggested an attenuated survival response to CRT in atrial fibrillation patients compared with patients in NSR.

From the symptomatic perspective, CRT has established benefits in patients with atrial fibrillation. In the MUSTIC AF trial,²⁰³ 41 patients with slow chronic atrial fibrillation of >3 months in duration and with a paced QRS of >200 ms were randomized in a single-blinded cross-over study design to RV vs. biventricular pacing (3 months for each phase). At the end of 6 months, 85% of patients preferred biventricular pacing over RV pacing. With the preferred mode of pacing adopted for the following 6 months (85% biventricular pacing), patients had significant improvement in their 6 min walk test, QOL score, and NYHA class compared with baseline. Other studies^{330,331} also have documented improved patients symptoms after CRT in heart failure patients with chronic RV pacing undergoing upgrade to biventricular pacing. A more recent meta-analysis³²⁹ suggested an attenuated symptomatic response to CRT in atrial fibrillation patients compared with patients in NSR.

Echocardiographically, CRT also improves systolic function and induces reverse remodelling in patients with atrial fibrillation. Prospective non-randomized observational data³²⁸ demonstrated similar rates of LV reverse remodelling (defined as >10% decrease in LV end-systolic volume) between CRT patients with chronic atrial fibrillation vs. NSR. Similarly, in heart failure patients who are chronically paced in the right ventricle, upgrading to CRT increases the LVEF³³⁰ and reduces the LV end-systolic diameter and the severity of MR.³³¹ However, a more recent meta-analysis³²⁹ suggested an attenuated echocardiographic response to CRT in atrial fibrillation patients compared with patients in NSR.

Even in patients with chronic atrial fibrillation but no heart failure or reduced LVEF, CRT pacing after AV nodal ablation seems to prevent a decline in LVEF and improve measure of the 6 min walk test and peak myocardial oxygen consumption compared with RV pacing.³³² It was also recently shown³³³ to reduce the rates of worsening of heart failure and of hospitalizations for heart failure.

In patients with atrial fibrillation, it is imperative to ensure a high rate of biventricular pacing for the patient to extract maximum benefit from CRT. Unlike in NSR, in atrial fibrillation patients this task may be challenging. Relying on the per cent biventricular pacing data stored in the CRT device may be misleading as these rates would include fusion and pseudo-fusion between pacing from the device and conduction through the patient's intrinsic conduction system. This is one of the reasons implicated in the improved outcomes of CRT patients with atrial fibrillation with AV nodal ablation compared to rate control with medications.²³⁸ Other mechanisms implicated in the improved outcomes after AV ablation include more complete rate control and regularization without the need for medications that may induce fatigue and tiredness and exacerbate other symptoms of heart failure.³²⁹

The question as to whether CRT can decrease the burden of atrial fibrillation by virtue of improving the haemodynamics of heart failure has been considered. Despite some reports suggesting less atrial fibrillation in the months after comparing with before CRT,³³⁴ analyses from the CARE HF trial²⁶⁴ and other studies³³⁵ suggest no change in atrial fibrillation burden after CRT. In the CARE HF trial, the 15% of patients who were diagnosed with atrial fibrillation after randomization were equally distributed between the CRT and optimal medical therapy arms of the study. Therefore, CRT is not currently indicated for reducing the burden of atrial fibrillation.

6.3 The renal dialysis patient

There is a paucity of data about the role of CRT in end-stage renal failure patients on dialysis therapy. Dialysis patients have been excluded from all large prospective randomized trials that examine the role of CRT in HF patients.^{13,230,264}

Few studies have examined the effect of renal function in CRT patients. In one analysis³³⁶ of 64 patients with CRT who had a GFR rate <30 mL/min, total survival was significantly worse than that of patients with better renal function and similar to that of patients with GFR <30 mL/min and a standard non-CRT defibrillators. Also, in patients with GFR <30 mL/min, the increase in LVEF and decrease in LV end-systolic diameter were greatly attenuated compared to patients with more preserved renal function. Another report¹⁷ confirmed worse survival rates in CRT patients with renal dysfunction (GFR <60 mL/min) compared to patients with normal renal function.

Paralleling the marginal benefits of CRT in patients with advanced kidney dysfunction, the risks of device-related infections is significantly higher in dialysis patients. In one report,²⁸³ dialysis was one of four independent predictors of device-related infections; the remaining included the need for surgical re-intervention, the implantation of a CRT device as compared with a device without CRT, and length of procedure times.

Based on the available data, these diminished benefits and increased risks should be taken into consideration when considering the implantation of a CRT device in a dialysis patient. More research in this field is needed to guide appropriate clinical decision.

6.4 Cardiac resynchronization therapy-defibrillator/cardiac resynchronization therapy-pacemaker upgrade, downgrade considerations

Special attention to device tachycardia programming also is indicated, particularly as the majority of CRT-D recipients have a defibrillator for primary prevention indications (NCDR Database update 2009 HRS).³³⁷ Recent data, analysing programming in thousands of ICD recipients, indicate that both mortality outcomes and risk of inappropriate shock therapy is reduced dramatically if two-zone tachycardia programming is utilized and lower rate tachycardia detection zones >170 b.p.m.³³⁸

For those with CRT-pacemaker (CRT-P) devices, worsening or stabilization in heart failure clinical status that is maintained for >6 months may merit consideration for upgrading to a CRT-D device.^{339–341} For patients with CRT-D devices who experience

complete reverse remodelling with CRT and who do not receive a device shock, downgrading to a CRT-P device could be considered at the time of device replacement due to battery depletion. However, in the absence of clinical data it seems advisable to continue CRT-D therapy in these situations.³⁴²

The demographics of patients receiving a CRT-P differ from those receiving a CRT-D; they are older, more frequently male and, have more comorbid conditions. They also have a higher prevalence of atrial fibrillation and a poorer prognosis.³⁴³ The decision concerning which type of device should be implanted involves assessment of the individual and long-term prognosis.

Patients with reduced LVEF and worsening heart failure under chronic RV pacing (ICD/pacemaker) may be considered candidates for an upgrade to a CRT-P or CRT-D device.³⁴⁴

6.5 Device replacement considerations

In patients with heart failure with an existing device, elective device replacements provide the opportunity to reevaluate the patients' clinical status and determine whether the patient's status and needs merit the same type of device or another with more or less capability. Careful thought as to the technical and anatomic issues inherent in upgrading or downgrading device or leads should be well considered in advance of the procedure so that patient safety and procedural success are optimized.

6.6 Patient's end-of-life considerations

The decision to inactivate the defibrillation function of a CRT-D device to defer treatment of a tachyarrhythmia is one that only should be made after a thorough discussion between the patient and the caregivers. If the patient has intractable heart failure symptoms associated with very poor QOL, the decision to inactivate shock therapies may be an appropriate choice. First and foremost, the physician responsible for inactivating the device should serve as the patient advocate after careful discussion of what it means to defer shock therapy in the context of end-of-life planning.^{345,346} Identification of the appropriate palliative care team is important in these settings.

6.7 Patient education and engagement

As with any attempt to engage patients for the purpose of compliant follow-up, it is crucial that patients understand their required actions and the clinical importance of their involvement. It is equally important that the physician and allied professionals involved in the care of the CRT recipient, understand the benefits of remote follow-up from both a patient and caregiver perspective.^{237,241,338,347}

Although remote monitoring is passive for the patient subsequent to the set-up of the equipment, ensuring the equipment is connected can be a challenge for many patients. Caregivers staffing remote monitoring centres report a myriad of reasons why remote monitoring equipment is not functional. It is critical that patients are educated about the importance of monitoring and the advantages of remote monitoring.

Depending on the age and awareness of the patient, it is critical to engage caregivers in the education process. Raising awareness about the importance of remote monitoring and highlighting technical issues about device installation is critical in specific

circumstances. Patient and caregiver education should include multiple dimensions:

- Basic understanding of the disease process and the factors that contributed to the necessity for a CRT device.
- Overview of the clinical advantages of remote monitoring; (e.g. superior and more timely detection of abnormalities resulting in faster caregiver reaction to clinically significant events).
- Understanding of the greater convenience of remote monitoring over repeated in-clinic visits.
- Constant surveillance afforded by remote monitoring.
- Ability to initiate an immediate download of information for most systems if the patient has concerns about device function or if new symptoms develop.
- Thorough description of how to install the remote monitoring equipment and offer to walk the patient through installation by phone when the patient is at home with the equipment.

Patients should be provided with as much educational material as possible depending on their ability to access and understand the specific, provided information. Written information summarizing remote monitoring techniques, benefits, and technical aspects of the required equipment should be offered to allow the patient to refer to the material, as needed. Caregivers that are familiar with the educational material should review the material with the patient. This can be done pre-implant or post-implant and ideally is done more than once.

Referring the patient to manufacturer-specific information, either paper- or web-based source is recommended. Steering 'tech-savvy' patients to reliable non-manufacturer web-based sources of information, e.g. patient education sites, patient support groups, patient blogs, may be positive for those patients who request information from other patients and independent sources.

Patients also may benefit from anecdotal accounts of remote monitoring advantages that may be communicated during patient support groups. Technical or installation nuances of a specific monitor may emerge when a group of patients have the opportunity to share their collective experience.

6.8 Cost effectiveness

There has been great interest in and discussion around whether CRT is cost effective. This is due to the significant up-front cost of the devices and the limited life expectancy of patients with advanced heart failure and QRS delay.^{348–350}

Cost effectiveness analysis of three clinical trials of CRT for both CRT-D and CRT-P devices that have medical therapy only randomization arms and measures of hospitalization and mortality as primary endpoints provide important data.

The COMPANION trial, that compared CRT-P and CRT-D therapy with optimal medical therapy, demonstrated significant improvements in the primary endpoint for both devices over a 12-month follow-up. Using quality-of-life adjusted survival analysis (QALY), assuming therapy over a 7-year follow-up interval, both devices were associated with cost effectiveness (CRT-P \$19 600, CRT-D \$43 000 QALY) compared with optimal medical therapy. This trial, performed in the USA, utilized Medicare cost data and

assumed a cost-effective benchmark of \$50 000–100 000 per QALY.³⁴⁹

Additional cost-effectiveness analysis was performed using data from the UK. In this study, cost data were based on the CARE-HF trial data for CRT devices (performed largely in Europe) also utilized the COMPANION data for CRT-D devices and similarly found very favourable incremental cost effectiveness per life year gained and per QALY gained for both devices when compared with medically treated patients over a 6–7-year follow-up after implantation.^{348,350}

Cardiac resynchronization therapy has also demonstrated to be a cost-effective intervention when applied to patients with less advanced symptom class heart failure.³⁵¹

Both CRT and CRT-D devices demonstrate cost effectiveness compared with internationally accepted benchmarks for other therapies, including medical therapies when analysis is performed over the battery life of the devices. The addition of ICD therapy to the CRT device increases cost because the device is more expensive but cost effectiveness is still within accepted standards as it has been demonstrated in the USA and Europe.

7. Conclusions

The clinical evidence, collected over the last 15 years, establishes CRT as an important heart failure therapy in a broad range of patients with systolic heart failure, reduced LV function, and QRS delay. The emergence of CRT as a therapy that improves symptoms, cardiac function, hospitalization rates, and mortality is profound considering it has filled a major therapeutic void for patients with QRS delay and advanced heart failure status. The consensus recommendations in this document aim to advise the implanting physician on issues regarding CRT patient care, and are intended to help maximize response to therapy acutely and chronically. Additional consideration is given to problem solving in select patient populations where device management and programming are particularly important. There is a review of the role of ancillary testing, advances in programming and device technologies, and devices that impact the CRT recipient. The document is intended for use as a resource for physicians seeking to provide the highest quality of care to the CRT patient.

Conflict of interest: Please see the appendix.

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Appendix

Table A1. EHRA/HRS Expert Consensus Statement on Cardiac Resynchronization Therapy Implant and Follow-up Considerations

Expert	Type of Relationship with Industry
Adamson Philip	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <p>- Medtronic : ICD's and Pacemakers (2011)</p> <p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <p>- St Jude Medical : ICD's, pacemakers, hemodynamic monitors (2011)</p> <p>C - Receipt of royalties for intellectual property.</p> <p>- Cardiomems : Hemodynamic monitors (2011)</p>
Auricchio Angelo	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <p>- Biologics Delivery Systems, Cordis Corporation a J&J company : Biological Therapy (2011)</p> <p>- Daiichi Sankyo : Cardiac Imaging (2011)</p> <p>- Merck Sharp & Dohme : Drugs (2011)</p> <p>- Abbott : implantable Cardiac Electronic Device (2011)</p> <p>- Medtronic : implantable Cardiac Electronic Device (2011)</p> <p>- Sorin Group : implantable Cardiac Electronic Device (2011)</p> <p>- St Jude Medical : implantable Cardiac Electronic Device (2011)</p> <p>- Biotronik : implantable Cardiac Electronic Device (2011)</p> <p>- Impulse Dynamics : implantable Cardiac Electronic Device (2011)</p> <p>- EBR Systems : implantable Cardiac Electronic Device (2011)</p>
Berger Ronald	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <p>- Boston Scientific : Rhythm management devices (2011)</p> <p>C - Receipt of royalties for intellectual property.</p> <p>- Zoll Medical : external defibrillation (2011)</p>
Beshai John	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <p>- American College of Cardiology : Cardiosource Editorial board member - Atrial Fibrillation Community (2011)</p> <p>- Lifewatch : Physician advisor - ambulatory monitoring (2011)</p> <p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <p>- Medtronic : Resynchronization therapy clinical trial (2011)</p> <p>D - Research funding (departmental or institutional).</p> <p>- St Jude Medical : Ablation catheter clinical trial (2011)</p> <p>- Medtronic : Resynchronization therapy clinical trial (2011)</p>
Breithardt Ole A	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <p>- Boston Scientific : CRT (2011)</p> <p>- Siemens Healthcare : Echocardiography (2011)</p> <p>- GE Healthcare : Echocardiography (2011)</p>

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Table A1. Continued

Expert	Type of Relationship with Industry
Brignole Michele	None
Cleland John	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - CEPHALON : Biologicals (2011) - Teva Pharmaceutical Industries : Biologicals (2011) - BRAHMS GmbH : Biomarkers (2011) - Alere : Biomarkers (2011) - BG medicine : Biomarkers (2011) - Philips : Devices (2011) - St Jude Medical : Devices (2011) - Bayer : Pharmaceuticals (2011) - Boehringer-Ingelheim : Pharmaceuticals (2011) - Novartis : Pharmaceuticals (2011) - Servier : Pharmaceuticals (2011) - GlaxoSmithKline : Pharmaceuticals (2011) - Menarini : Pharmaceuticals (2011) - Johnson & Johnson : Pharmaceuticals (2011) - Torrent : Pharmaceuticals (2011) - Amgen Inc : Pharmaceuticals (2011) - Genzyme : Pharmaceuticals (2011) - Merck Sharp & Dohme : Pharmaceuticals (2011) - National Institute for Health Research : Research (2011) - BMBF - German Ministry of Research and Education : Research (2011) - Cardiomems : Sensors (2011) - Resmed : Sleep Apnoea (2011) - Baxter : Solutions (2011) - Bosch AG Germany : Telemonitoring (2011) <p>D - Research funding (departmental or institutional).</p> <ul style="list-style-type: none"> - Biosense Webster : Ablation (2011) - CEPHALON : Biologicals (2011) - Teva Pharmaceutical Industries : Biologicals (2011) - BRAHMS GmbH : Biomarkers (2011) - Alere : Biomarkers (2011) - BG medicine : Biomarkers (2011) - Sorin Group : Devices (2011) - Biotronik : Devices (2011) - Amgen : Pharmaceuticals (2011) - Bayer : Pharmaceuticals (2011) - Boehringer-Ingelheim : Pharmaceuticals (2011) - Novartis : Pharmaceuticals (2011) - Pfizer : Pharmaceuticals (2011) - Servier : Pharmaceuticals (2011) - Menarini : Pharmaceuticals (2011) - Johnson & Johnson : Pharmaceuticals (2011) - Torrent : Pharmaceuticals (2011) - Vifor International : Pharmaceuticals (2011) - Takeda Pharmaceuticals : Pharmaceuticals (2011) - Merck Sharp & Dohme : Pharmaceuticals (2011) - Galenica Vifor : Pharmaceuticals (2011) - Roche Diagnostics : Pharmaceuticals and Biomarkers (2011) - Oxford University Press : Publishing (2011) - National Institute for Health Research : Research (2011) - British Heart Foundation : Research (2011) - Cardiomems : Sensors (2011)

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Table A1. Continued

Expert	Type of Relationship with Industry
Daubert Jean-Claude	<ul style="list-style-type: none"> - Resmed : Sleep Apnoea (2011) - Philips : Telemonitoring and Devices (2011) <p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Boehringer-Ingelheim : Antithrombotics (2011) - Sanofi Aventis : Dronedarone (2011) - Medtronic : Implantable devices (2011) - Sorin Group : Implantable devices (2011) - St Jude Medical : Implantable devices (2011) - EBR Systems : Implantable devices (2011) - Heart.org : Interviews (2011) - Novartis : Medical education (2011) <p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Medtronic : iMPLANTABLE DEVICES (2011)
De Lurgio David	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - St Jude Medical : CRM (2011) <p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Boston Scientific : CRM (2011)
Dickstein Kenneth	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Boston Scientific : CRT (2011) - Medtronic : CRT (2011) - Sorin Group : CRT (2011) - Biotronik : CRT (2011)
Exner Derek	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Medtronic : Device Company (2011) - Hearforce Medical : Noninvasive imaging (2011) <p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - GE Healthcare : Noninvasive imaging (2011) <p>C - Receipt of royalties for intellectual property.</p> <ul style="list-style-type: none"> - Cambridge Heart : Noninvasive imaging (2011) <p>D - Research funding (departmental or institutional).</p> <ul style="list-style-type: none"> - St Jude Medical : Device Company (2011)
Gold Michael R	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Cameron Health : Devices (2011) - Sorin Group : Electrophysiology (2011) - Boston Scientific : Electrophysiology (2011) - Medtronic : Electrophysiology (2011) - St Jude Medical : Electrophysiology (2011) - Biotronik : Electrophysiology (2011) - Thoratec : Heart Failure (2011) <p>D - Research funding (departmental or institutional).</p> <ul style="list-style-type: none"> - Boston Scientific : Devices (2011) - Medtronic : Devices (2011) - Sorin Group : Devices (2011) - St Jude Medical : Devices (2011)
Grimm Richard	None
Hayes David	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Boston Scientific : Implantable devices (2011) - Medtronic : Implantable devices (2011) - Sorin Group : Implantable devices (2011) - St Jude Medical : Implantable devices (2011) - Biotronik : Implantable devices (2011)

Continued

Table A1. Continued

Expert	Type of Relationship with Industry
Israel Carsten W	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Boston Scientific : Pacemakers, ICDs (2011) - Sorin Group : Pacemakers, ICDs (2011) - St Jude Medical : Pacemakers, ICDs, CRT (2011) - Medtronic : Pacemakers, ICDs, CRT, Remote Monitoring (2011) - Biotronik : Pacemakers, ICDs, Remote Monitoring (2011) <p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Boston Scientific : ICDs (2011) - Biotronik : ICDs (2011) - Medtronic : ICDs, CRT, Remote Monitoring (2011)
Leclercq Christophe	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Boston Scientific : CRM (2011) - Medtronic : CRM (2011) - Sorin Group : CRM (2011) - St Jude Medical : CRM (2011) - Biotronik : CRM (2011) - General Electric : CRM (2011)
Linde Cecilia	<p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Medtronic : CRT (2011) <p>D - Research funding (departmental or institutional).</p> <ul style="list-style-type: none"> - Medtronic : CRT (2011)
Lindenfeld Joann	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Cardiomems : heart Failure (2011) - Zona : Hypertension (2011) - Boston Scientific : ICD, CRT (2011) - St. Jude : ICD, CRT (2011) <p>D - Research funding (departmental or institutional).</p> <ul style="list-style-type: none"> - Zensun : Heart failure (2011) - Zona : Hypertension (2011)
Merkely Bela	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Krka : ACS (2011) - Sanofi Aventis : Atrial Fibrillation (2011) - Boston Scientific : CRT (2011) - Medtronic : CRT course (2011) - St Jude Medical : CRT/ICD (2011) - Servier : Heart Failure (2011) - Biotronik : ICD/CRT (2011) - Abbott : STEMI (2011) - GE Healthcare : STEMI networking (2011) - Duke Institute : Trilog Study (2011) <p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Boston Scientific : CRT (2011) - Biotronik : ICD/CRT Heart Failure (2011) - University of Leuven : NOMI trial (2011) - GE Healthcare : STEMI (2011) - Duke Research Unit : Trilog Study (2011)
Mont Lluis	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - St Jude Medical : Atrial Fibrillation, Resynchronization Therapy. (2011) <p>D - Research funding (departmental or institutional).</p> <ul style="list-style-type: none"> - Biosense Webster : Atrial Fibrillation (2011)
Murgatroyd Francis D	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p>

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Table A1. Continued

Expert	Type of Relationship with Industry
Prinzen Frits	<ul style="list-style-type: none"> - Sanofi Aventis : Antiarrhythmic Drug therapy (2011) - Boehringer-Ingelheim : Anticoagulation (2011) - Medtronic : Cardiac Implantable Electronic Devices (2011) D - Research funding (departmental or institutional). - Sorin Group : Cardiac Implantable Electronic Devices (2011) A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - St Jude Medical : pacemakers, resynchronization therapy (2011) E - Research funding (personal). - Medtronic : pacemaker, resynchronization therapy (2011) - Merck Sharp & Dohme : Vernakalant (2011)
Saba Samir	<ul style="list-style-type: none"> A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - St Jude Medical : CRMD (2011) - Spectranetics : Lead extraction (2011) C - Receipt of royalties for intellectual property. - Medtronic : CRMD (2011) D - Research funding (departmental or institutional). - Boston Scientific : CRMD (2011) - Medtronic : CRMD (2011) - St Jude Medical : CRMD (2011) - Biotronik : CRMD (2011)
Saxon Leslie	<ul style="list-style-type: none"> A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Boston Scientific : Consultant (2011) B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Medtronic : Consultant (2011) C - Receipt of royalties for intellectual property. - St Jude Medical : Consultant (2011)
Shinbane Jerold	None
Singh Jagmeet	<ul style="list-style-type: none"> A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Cardiolsight : Advisory board (2011) - Biosense Webster : Consulting (2011) - Respicardia : DSMB committee (2011) - Boston Scientific : Speaker fees and consulting (2011) - Medtronic : Speaker fees and consulting (2011) - Biotronik : Speaker fees and consulting (2011) - Sorin Group : Speaker fees, Steering committee member and consulting (2011) - St Jude Medical : Speaker fees, Steering committee member and consulting (2011) D - Research funding (departmental or institutional). - Boston Scientific : CRT (2011) - Medtronic : CRT (2011) - Biotronik : CRT (2011) - St. Jude Medical : CRT (2011)
Tang Anthony	<ul style="list-style-type: none"> A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Boehringer-Ingelheim : antiOcoagulant (2011) - Biosense Webster : catheter ablation (2011) - Medtronic : PM, ICD, CRT (2011) - St Jude Medical : PM, ICD, CRT (2011) D - Research funding (departmental or institutional). - St Jude Medical : catheter ablation (2011) - Biosense Webster : catheter ablation (2011) - Medtronic : CRT (2011)
Vardas Panagiotis	<ul style="list-style-type: none"> A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Bayer : Honoraria for participation in "ASP Alliance" and "SPAF Advisory Board". Speaker fees. (2011) - Boehringer-Ingelheim : Honorarium for participation in Advisory Board. Speaker fees (2011)

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Table A1. Continued

Expert	Type of Relationship with Industry
<p>Wilkoff Bruce</p>	<ul style="list-style-type: none"> - Menarini : Honorarium for participation in Ranolazine Advisory Board (2011) - Servier : Speaker and article-writing fees (2011) B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Medtronic : Consultancy fee (2011) - Bristol Myers Squibb : Honorarium (2011) - Bayer : Speaker fee (2011) - Boehringer-Ingelheim : Speaker fees and honoraria (2011) D - Research funding (departmental or institutional). - Amgen : ATOMIC AHF study (institutional) (2011) - Novartis : CANTOS study (institutional) (2011) - Medtronic : MORE CARE study (institutional) (2011) - Servier : SIGNIFY study (institutional) (2011) D - Research funding (departmental or institutional). - Medtronic : Ablation and CIED (2011) - St Jude Medical : Ablation and CIED (2011) - Boston Scientific : CIED (2011) - Biotronik : CIED (2011)
<p>Zamorano Gomez Jose Luis</p>	<ul style="list-style-type: none"> B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Abbott Vascular : IMAGING IN HF (2011) - Merck Sharp & Dohme : LIPIDS (2011)

This table represents the relevant relationships of the above experts with Industries and other entities that were reported to us at the time of publication of the Guidelines.

Table A2. EHRA/HRS Expert Consensus Statement on Cardiac Resynchronization Therapy Implant and Follow-up Considerations - Document Reviewers

Expert	Type of Relationship with Industry
Anand Inder	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - CVRx : Carotid sinus stimulation device (2011) - Amgen : Darbepoetin (2011) - Boston Scientific : Devices (2011) - Sanofi Aventis : Donaderone (2011) - BMS : Irbesartan (2011) - Novartis : Pharmaceutical products (2011) - Cybertronics : Vagal stimulation device (2011) <p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Amgen : Darbepoetin (2011) - Novartis : Heart Failure (2011) - NHLBI : Heart Failure Trials (2011) <p>D - Research funding (departmental or institutional).</p> <ul style="list-style-type: none"> - NHLBI : Heart Failure Clinical Trials (2011)
Blomstrom-Lundqvist Carina	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Sanofi Aventis : AF (2011) <p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Biotronik : Arrhythmia (2011) - Medtronic : ICD, AF (2011) <p>D - Research funding (departmental or institutional).</p> <ul style="list-style-type: none"> - Medtronic : AF (2011) - Atricure : AF (2011) - Biotronik : Arrhythmias (2011)
Boehmer John	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Boston Scientific : CRT, ICD therapy (2011) <p>B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Medtronic : CRT therapy, Events Committees (2011) <p>C - Receipt of royalties for intellectual property.</p> <ul style="list-style-type: none"> - St Jude Medical : Atrial fibrillation (2011) <p>D - Research funding (departmental or institutional).</p> <ul style="list-style-type: none"> - St Jude Medical : Hemodynamic monitoring (2011)
Calkins Hugh	<p>E - Research funding (personal).</p> <ul style="list-style-type: none"> - Medtronic : sudden death (2011) - St Jude Medical : sudden death (2011)
Cazeau Serge	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Medtronic : CRM (2011) - Sorin Group : CRM (2011)
Delgado Victoria	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - St Jude Medical : cardiac resynchronization therapy (2011) - Medtronic : Valvular heart disease (2011)
Estes N A Mark	<p>A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc.</p> <ul style="list-style-type: none"> - Boston Scientific : Pacemakers/ ICDs (2011) - Medtronic : Pacemakers/ ICDs (2011) <p>D - Research funding (departmental or institutional).</p> <ul style="list-style-type: none"> - Boston Scientific : Pacemakers/ ICDs Fellowship Support (2011) - Medtronic : Pacemakers/ ICDs Fellowship Support (2011) - St Jude Medical : Pacemakers/ ICDs Fellowship Support (2011) <p>E - Research funding (personal).</p> <ul style="list-style-type: none"> - Boston Scientific : Pacemakers/ ICDs Fellowship Support (2011)

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Table A2. Continued

Expert	Type of Relationship with Industry
Haines David	B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Boston Scientific : catheter (2011) - Medtronic : catheter (2011) - Bard : catheter (2011) - Toray Medical : catheter (2011) - Zoll Medical : defibrillator (2011) D - Research funding (departmental or institutional). - CardioFocus : catheter (2011) - Medtronic : ICD (2011)
Kusumoto Fred M	None
Leyva-Leon Francisco	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Boston Scientific : Cardiac devices (2011) - Medtronic : Cardiac devices (2011) - Sorin Group : Cardiac devices (2011) D - Research funding (departmental or institutional). - Medtronic : Cardiac devices (2011) - Sorin Group : Cardiac devices (2011) - St Jude Medical : Cardiac devices (2011)
Ruschitzka Frank	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Biotronik : Devices (2011) B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Servier : Drugs (2011) C - Receipt of royalties for intellectual property. - Cardiorientis : Drugs (2011) D - Research funding (departmental or institutional). - Pfizer : Drugs (2011)
Torp-Pedersen Christian Tobias	A - Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Sanofi Aventis : Antiarrhythmics (2011) - Merck Sharp & Dohme : Antiarrhythmics, diabetes (2011) - Cardiomeas : atrial fibrillation (2011) B - Payment to your Institution: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. - Sanofi Aventis : Investigator various drugs (2011) - Merck Sharp & Dohme : Investigator various drugs (2011) - Bristol Myers Squibb : Investigator, various drugs (2011) D - Research funding (departmental or institutional). - Bristol Meyer : Atrial fibrillation (2011)
Warner Stevenson Lynne	None

This table represents the relevant relationships of the above experts with Industries and other entities that were reported to us at the time of publication of the Guidelines.