5 Cardiac Resynchronization Therapy for Functional Ischaemic Mitral Regurgitation

Marta Sitges and Bàrbara Vidal

Abstract

Functional mitral regurgitation (MR) is a common finding in patients with heart failure (HF). It results from an imbalance between closing and tethering forces that ensure valve competence as a consequence of systolic dysfunction and altered geometry of the left ventricle (LV). In some patients, mechanical asynchrony in chamber contraction might be present and also contributes to the development of MR, either leading to diastolic MR, systolic MR or both.

Cardiac resynchronization therapy (CRT) has the potential to reverse the vicious cycle resulting in MR worsening, specifically in those patients with abnormal electrical conduction leading to disturbances in mechanical contraction. CRT leads to LV reverse remodeling and reduces morbidity and mortality, in addition to symptoms and exercise capacity improvement. CRT can effectively reduce functional MR by improving mechanical dyssynchrony in cardiac contraction, which leads to improve LV systolic and diastolic function, and also by inducing reverse LV remodeling which in turn restores the abnormal geometry of the mitral valve apparatus. There is growing evidence that CRT can be considered as a first line treatment in patients with HF and severe secondary MR who have mechanical dyssynchrony amenable to be electrically corrected with CRT.

Keywords

Functional mitral regurgitation • Cardiac resynchronization therapy • Left ventricle remodeling • Dyssynchrony • Heart failure • Pacing • Cardiomyopathy • Systolic dysfunction • Predictors • Mortality

M. Sitges, MD, PhD (✉) • B. Vidal, MD, PhD
Cardiology Department, Cardiovascular Institute,
Hospital Clinic, Institut d'Investigacions
Biomèdiques August Pi i Sunyer (IDIBAPS),
University of Barcelona, Barcelona, Spain
e-mail: msitges@clinic.ub.es

K.M.J. Chan (ed.), *Functional Mitral and Tricuspid Regurgitation*,
DOI 10.1007/978-3-319-43510-7_5

Abbreviations

CRT	Cardiac resynchronization therapy
ECG	Electrocardiogram
HF	Heart failure
LBBB	Left bundle branch block
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MR	Mitral regurgitation

Principles of Treatment

Pathogenesis of functional mitral regurgitation (MR) involves multiple factors, including increased mitral leaflet tethering due to the outward displacement of the papillary muscles caused by global and regional left ventricular (LV) remodeling, decreased LV closing forces and deformation of the whole mitral apparatus including the annulus [1, 2]. In some patients with heart failure, differences in the timing of cardiac chamber or even between myocardial segments contraction, namely mechanical dyssynchrony, can contribute to the development of more insufficiency of the mitral valve. Dyssynchrony may cause the increase in functional MR in several pathways: the presence of global LV dyssynchrony may decrease the efficiency of LV contraction and thus, decrease the LV closing force acting on the mitral leaflets. Also, dyssynchronous contraction of the papillary muscle insertion sites at the LV free wall may induce geometric distortion of the mitral valve apparatus. Finally, dyssynchronous contraction of the LV basal segments may render a non-simultaneous contraction of the papillary muscles and adjacent LV walls, resulting in uneven timing of leaflet coaptation [3]. Also, the presence of atrioventricular dyssynchrony with abnormal atrioventricular coupling may lead to diastolic MR (Fig. 5.1), as well as the presence of interventricular dyssynchrony, which induces an abnormal motion of the interventricular septum, may provoke the inadequate closure of the mitral leaflets.

Improvement in papillary muscles dyssynchrony [4] together with an increase in the rate of LV pressure increase [5], which counteracts tethering forces and leads to more effective mitral valve closure with the consequent reduction of the MR orifice area, explains the immediate decrease of MR with CRT-activation [6, 7]. It has

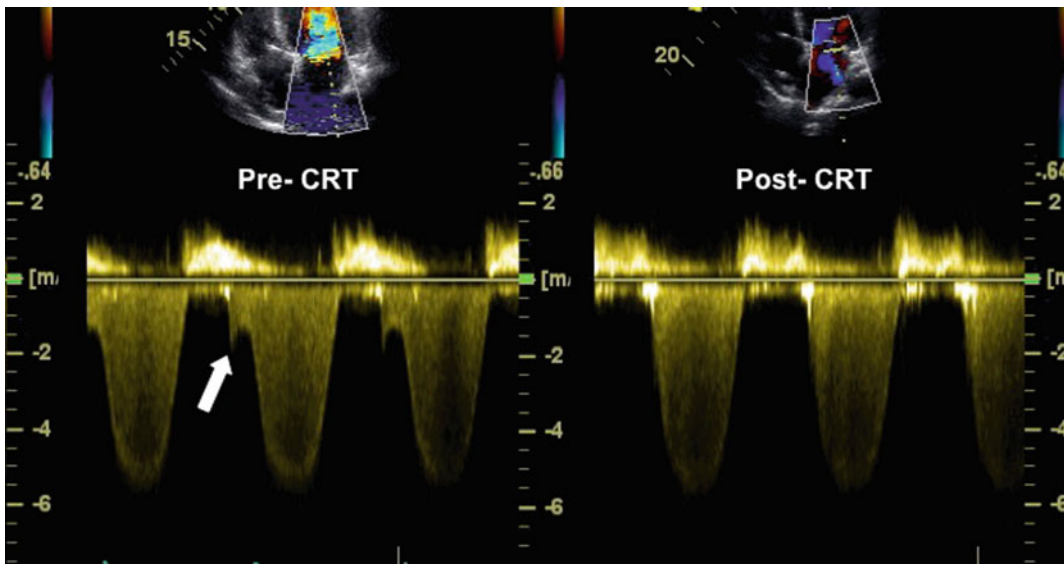

Fig. 5.1 *On the left panel*, a continuous wave Doppler signal of a mitral regurgitation with a presystolic component can be observed that disappears with the pacemaker activation as shown *on the right panel*. On the other hand, the signal intensity is reduced after CRT activation, suggesting an improvement of the regurgitation severity

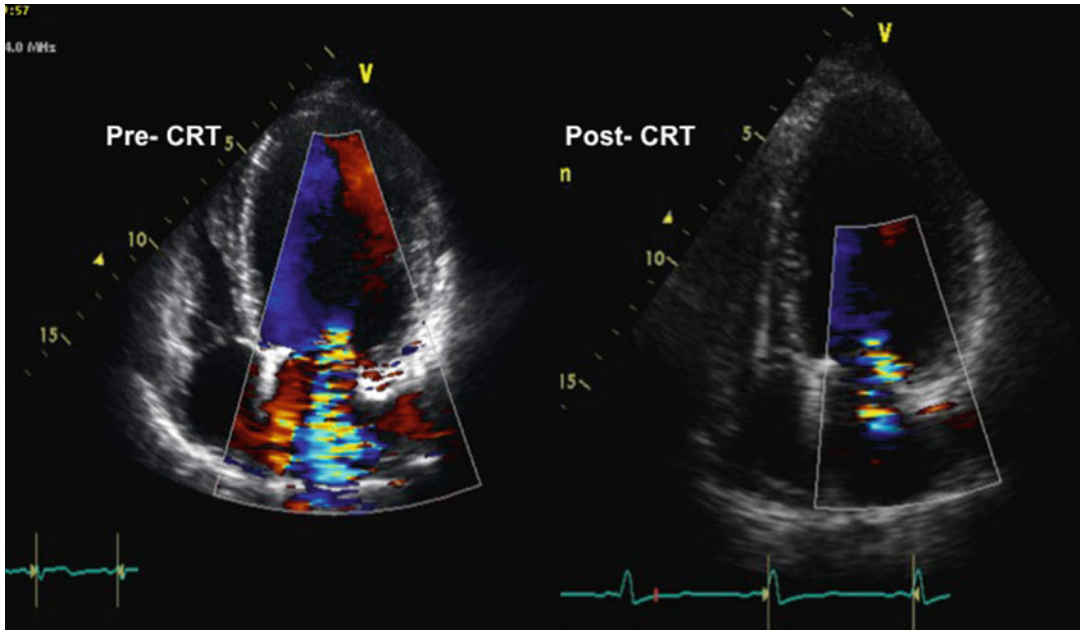

Fig. 5.2 Mitral regurgitation improvement after 6-month CRT. Reduction in the left ventricle volume can also be observed

also been observed an acute beneficial change in MV geometry after CRT in patients who would be responders in the follow-up (defined by echocardiographic criteria as a reduction in end-systolic LV volume >15 %) [5]. This acute effect on the mitral valve is pacing dependent as the interruption of CRT causes an immediate recurrence of MR [4]. Another described acute effect of CRT is the correction of the atrioventricular delay in CRT that eliminates diastolic or pre-systolic MR, when present.

In the mid-long run, the reduction of MR induced by CRT can also extend in relation to a global (LV volumes) and local (mitral valve geometry) resynchronization-related reverse remodeling [7] (Fig. 5.2).

Another factor that has to be considered in the response to CRT, including MR improvement, is the presence of myocardial viability. Traditionally, it has been accepted that patients with ischemic cardiomyopathy, large scar tissue and particularly with severe MR at baseline, present lesser LV reverse remodeling and clinical response at follow-up when treated with CRT [8]. Other studies show that ischemic patients do also respond to CRT but to a lesser extent [9]. This discrepancy between studies suggests that response to CRT is a multifactorial process and that the presence and location of myocardial viability is an important factor together with the presence of a mechanical abnormality that is amenable to be electrically corrected [10]. A direct relationship between the extent of myocardial contractile recruitment during a stress echo and the extent of LV remodeling has been shown. Also, the precise status of the myocardium at the site of the lead placement is important; in this sense some studies have shown that the coincidence of the site of the lead implantation on scar tissue is related to a poorer response to CRT [11].

Indications

According to current Guidelines [12], CRT is indicated in symptomatic HF patients in functional class II-IV despite receiving optimal medical treatment, severe left ventricle systolic dysfunction with a left ventricular ejection fraction (LVEF) $\leq 35\,\%$ and presenting with a wide QRS on the ECG (QRS width ≥ 120 ms) preferably with a LBBB pattern.

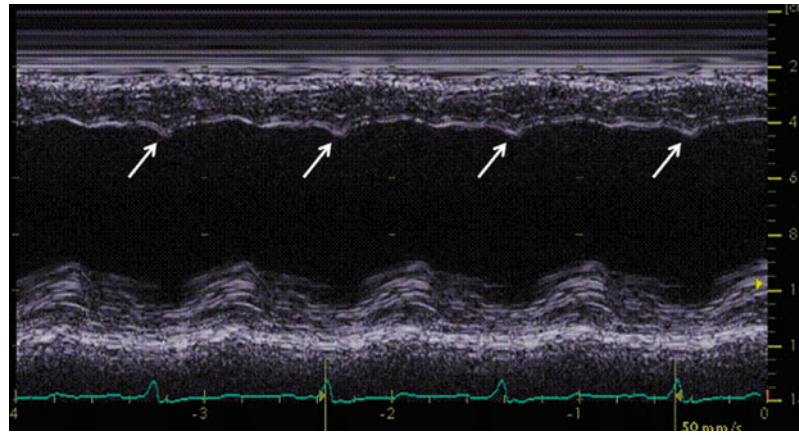

Fig. 5.3 M-mode scan across the left ventricle depicting the typical motion of the septum in patients with intraventricular dyssynchrony that correspond to the septal flash. The septal flash (*arrows*) can be detected in M-mode imaging as an early rapid contraction and relaxation of the interventricular septum. The lateral wall contraction is delayed

Use of CRT to treat functional MR without fulfilling the previous conditions is still not contemplated in the guidelines, although growing evidence exists about the benefits of CRT in reducing the severity of mitral regurgitation by at least one degree, and for this reason, the possibility to postpone surgical treatment in the CRT-responder patients. The pooled data from 5 major studies including more than 350 patients treated with biventricular pacing, followed up for more than 6 months, showed a decrease in the amount of MR by 30–40 % [13].

Identification of patients who will benefit with CRT treatment is still a matter of controversy, despite recent approaches based on understanding the mechanisms leading to cardiac dyssynchrony amenable to be electrically corrected have been proposed. Some studies [10, 14] have demonstrated that the presence of a correctable mechanical abnormality is almost mandatory to obtain a positive response with CRT. The presence of a septal flash (Fig. 5.3) is the mechanical abnormality that can be most easily corrected with CRT and most related to a clear response. Moreover, patients without any mechanical abnormality are largely non-responders. It is important to use an integral approach when assessing cardiac dyssynchrony, taking into account all kinds of possible subtypes of dyssynchrony, since all of them are potentially correctable with CRT and can lead to a substantial improvement in patient outcome. The presence of these mechanical abnormalities is an independent predictor of echocardiographic response and midterm cardiovascular mortality, along with creatinine level and LV diameters, which reflect severity and evolutive status of the disease. A correctable mechanical abnormality not only detects patients with a higher probability of reverse remodeling, but also has a real impact on survival. However, the extent of response will be variable depending on other baseline parameters such as myocardial substrate (viability), underlying disease (renal insufficiency), and clinical status [10].

Some authors have also tried to identify baseline characteristics that may point to the best candidates for CRT regarding MR reduction after CRT. In this sense a very severe MR with a baseline tenting area of >3.8 cm^2 would identify patients in whom CRT would not be effective to reduce MR, suggesting that the more advanced LV remodeling and the more distorted LV geometry, the lower the probability of effective treatment for functional MR [7] (Fig. 5.4). The fact is that response to CRT is modulated by several factors and acute and long-term benefits depend not only on the presence of LV dyssynchrony but also on the extent of residual myocardial viability in ischemic patients and severity of MR.

A less invasive percutaneous approach to treat MR in non-responder patients to CRT using the Mitraclip device has been recently proposed in order to avoid a high-risk surgery in this population of very fragile patients [15].

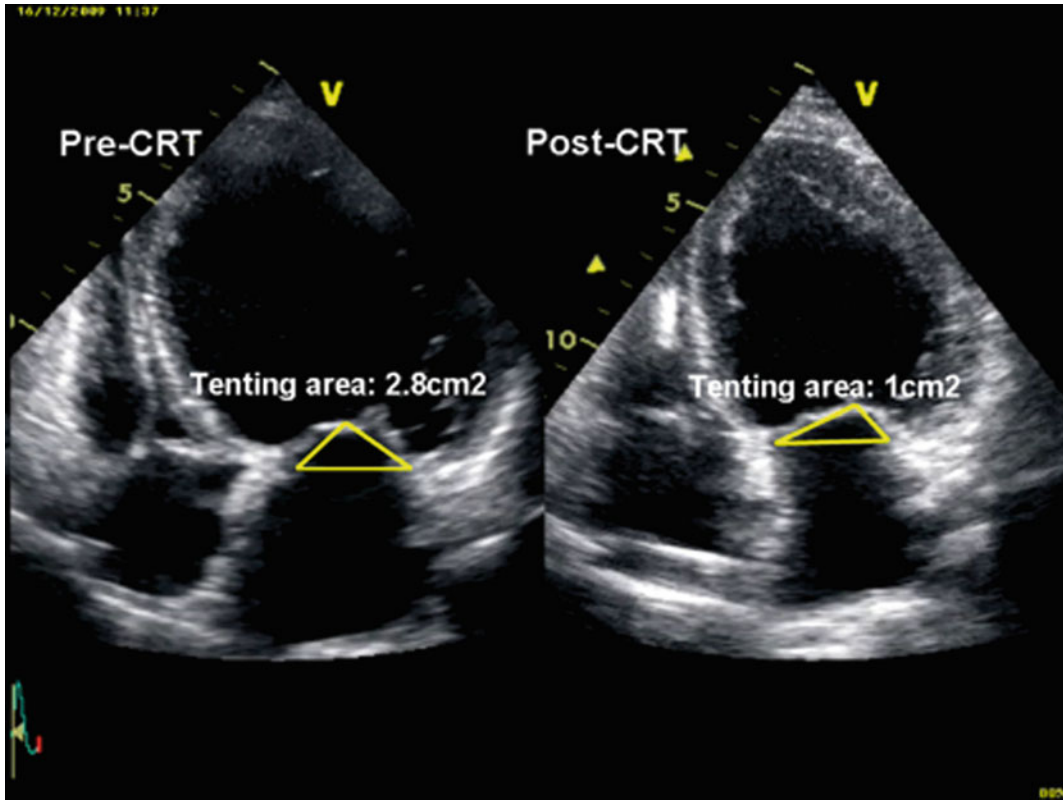

Fig. 5.4 The changes of mitral geometry together with left ventricle remodeling explain the reduction of mitral regurgitation with CRT. A baseline tenting area of >3.8 cm^2 would identify patients in whom CRT would not be effective to reduce MR

Results of Treatment

Large prospective studies have demonstrated the additional clinical benefit of CRT in HF patients medically treated with suboptimum response. CRT results in improvement in symptoms, quality of life and survival in patients with advanced heart failure and wide QRS [16, 17], especially if associated to a cardioverter - defibrillator [18, 19]. Echocardiographically, a progressive LV reverse remodelling (with even normalization of LV dimensions) is found with a reduction in LV volumes and dyssynchrony. Moreover, a significant reduction of MR severity of at least one degree is expected in around 30–40 % of the patients [4] independently of the etiology of the underlying cardiomyopathy [7]. These benefits, which are very congruent in all published studies, have helped to expand the indications of CRT, and nowadays, the tendency is to start CRT in less advanced stages of heart failure patients.

The influence of MR severity on CRT response is also conflicting. Some investigators have shown that patients with severe MR have less chance of a positive response to CRT [13, 20, 21]. Others, like from those participating in the CARE-HF study, which was a randomized trial including a large number of patients, conversely showed that patients who did not respond to CRT were likely to have less MR as compared to responders [22]. Nonetheless, the presence of severe MR at baseline is usually associated with lower response to CRT as it usually indicates a more advance stage of the disease (50 % clinical and 40 % echocardiographic response instead of 70 and 50 %) [7].

The reduction in MR severity with CRT typically occurs within the first days after starting

CRT [6] and can be expected even until the first 3-months follow-up; however, it is very unlikely to happen after that period [4]. This MR reduction behavior has two important implications: firstly, patients who present MR improvement of at least one degree at 3-months with CRT will probably continue to be CRT responders at mid-long term and no further intervention will be required. Secondly, patients who persist with severe MR at 3-months follow-up, and are candidates for surgery, do not benefit from waiting longer because no positive response is expected anymore at mid-long term and another treatment approach should be proposed, if possible.

Which Patient Should Have This Procedure

According to current Guidelines [12], CRT is indicated for patients with symptomatic heart failure in NYHA class II-IV despite receiving optimum medical treatment, with an LVEF <35 % and a wide QRS in the ECG. All these patients could benefit from CRT therapy, specially if they have not achieved the point of no return in the evolution of the heart failure syndrome: what it seems clear, is that patients presenting with too dilated ventricles, specially of an ischemic origin, too severe MR and a very severe reduction of LVEF [9] have a very low chance of improving with the therapy.

Although some discrepancies exist, the presence of a severe MR reduces the probability of clinical response to CRT, which decreases from 70 % back to 50 %. On the other hand, it is also known that around 30–40 % patients with severe MR respond to the therapy. Complementary information about the presence of dyssynchrony, viability of the LV myocardium, magnitude and transmurality of the scar and the functional etiology of MR can help us to better select the candidate patient for CRT.

Once the device is implanted, an acute benefit on MR reduction is expected. Most patients experience acute improvement confirmed echocardiographically at 3–6 months follow-up. At this point, typically no more improvement is to be expected, and if the patient persists with severe MR, surgery has to be planned. In high risk patients a less invasive approach with Mitraclip can be also proposed (Fig. 5.5).

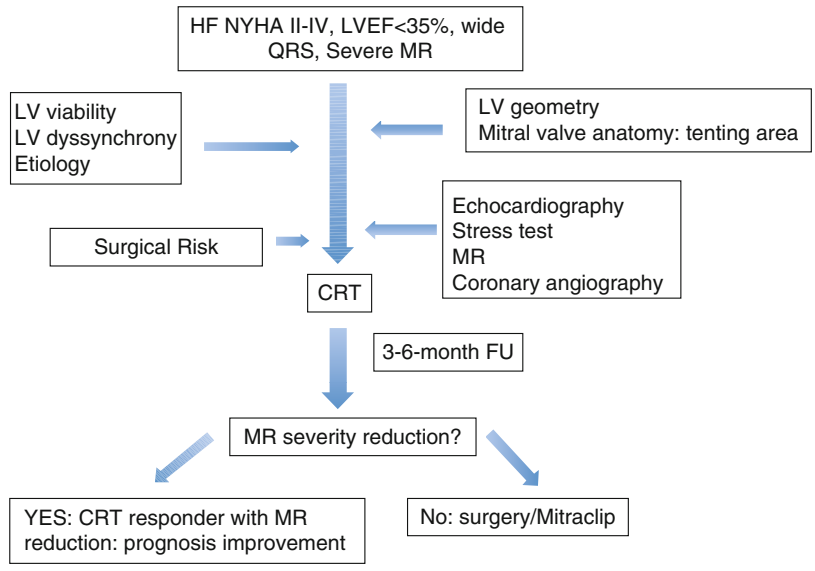

Fig. 5.5 Proposed management algorithm to select which patient should have this procedure

References

1. Levine RA, Schwammenthal E. Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. Circulation. 2005;112(5): 745–58.
2. Otsuji Y, Handschumacher MD, Schwammenthal E, Jiang L, Song JK, Guerrero JL, Vlahakes GJ, Levine RA. Insights from three-dimensional echocardiography into the mechanism of functional mitral regurgitation: direct in vivo demonstration of altered leaflet tethering geometry. Circulation. 1997;96(6): 1999–2008.
3. Liang YJ, Zhang Q, Fang F, Lee AP, Liu M, Yan BP, Lam YY, Chan GC, Yu CM. Incremental value of global systolic dyssynchrony in determining the occurrence of functional mitral regurgitation in patients with left ventricular systolic dysfunction. Eur Heart J. 2013;34(10):767–74.
4. Di Biase L, Auricchio A, Mohanty P, Bai R, Kautzner J, Pieragnoli P, Regoli F, Sorgente A, Spinucci G, Ricciardi G, Michelucci A, Perrotta L, Faletra F, Mlcochová H, Sedlacek K, Canby R, Sanchez JE, Horton R, Burkhardt JD, Moccetti T, Padeletti L, Natale A. Impact of cardiac resynchronization therapy on the severity of mitral regurgitation. Europace. 2011;13(6):829–38.
5. Solis J, McCarty D, Levine RA, Handschumacher MD, Fernandez-Friera L, Chen-Tournoux A, Mont L, Vidal B, Singh JP, Brugada J, Picard MH, Sitges M, Hung J. Mechanism of decrease in mitral regurgitation after cardiac resynchronization therapy: optimization of the force-balance relationship. Circ Cardiovasc Imaging. 2009;2(6):444–50.
6. Verhaert D, Popovic ZB, De S, Puntawangkoon C, Wolski K, Wilkoff BL, Starling RC, Tang WH, Thomas JD, Griffin BP, Grimm RA. Impact of mitral regurgitation on reverse remodeling and outcome in patients undergoing cardiac resynchronization therapy. Circ Cardiovasc Imaging. 2012;5(1):21–6.
7. Sitges M, Vidal B, Delgado V, Mont L, Garcia-Alvarez A, Tolosana JM, Castel A, Berruezo A, Azqueta M, Pare C, Brugada J. Long-term effect of cardiac resynchronization therapy on functional mitral valve regurgitation. Am J Cardiol. 2009;104(3): 383–8.
8. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). Circulation. 2006;113(2):266–72.
9. Vidal B, Sitges M, Delgado V, Mont L, Díaz-Infante E, Azqueta M, Paré C, Tolosana JM, Berruezo A, Tamborero D, Roig E, Brugada J. Influence of cardiopathy etiology on responses to cardiac resynchronization therapy. Rev Esp Cardiol. 2007;60(12): 1264–71.
10. Doltra A, Bijnens B, Tolosana JM, Borràs R, Khatib M, Penela D, De Caralt TM, Castel MA, Berruezo A, Brugada J, Mont L, Sitges M. Mechanical abnormalities detected with conventional echocardiography are associated with response and midterm survival in CRT. J Am Coll Cardiol Img. 2014;7:969–79.
11. Sénéchal M, Lancellotti P, Magne J, Garceau P, Champagne J, Philippon F, O'Hara G, Moonen M, Dubois M. Impact of mitral regurgitation and myocardial viability on left ventricular reverse remodeling after cardiac resynchronization therapy in patients with ischemic cardiomyopathy. Am J Cardiol. 2010; 106(1):31–7.
12. Russo AM, Stainback RF, Bailey SR, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol. 2013;61:1318–68.
13. Vinereanu D. Mitral regurgitation and cardiac resynchronization therapy. Echocardiography. 2008;25(10): 1155–66.
14. Parsai C, Bijnens B, Sutherland GR, Baltabaeva A, Claus P, Marciniak M, Paul V, Scheffer M, Donal E, Derumeaux G, Anderson L. Toward understanding response to cardiac resynchronization therapy: left ventricular dyssynchrony is only one of multiple mechanisms. Eur Heart J. 2009;30(8):940–9.
15. Auricchio A, Schillinger W, Meyer S, Maisano F, Hoffmann R, Ussia GP, Pedrazzini GB, van der Heyden J, Fratini S, Klersy C, Komtebedde J, Franzen O, PERMIT-CARE Investigators. Correction of mitral regurgitation in nonresponders to cardiac resynchronization therapy by MitraClip improves symptoms and promotes reverse remodeling. J Am Coll Cardiol. 2011;58(21):2183–9.
16. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J, MIRACLE Study Group, Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N Engl J Med. 2002;346(24):1845–53.
17. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005;352(15):1539–49.
18. Gold MR, Daubert JC, Abraham WT, Hassager C, Dinerman JL, Hudnall JH, Cerkvenik J, Linde C.

Implantable defibrillators improve survival in patients with mildly symptomatic heart failure receiving cardiac resynchronization therapy: analysis of the long-term follow-up of remodeling in systolic left ventricular dysfunction (REVERSE). Circ Arrhythm Electrophysiol. 2013;6(6):1163–8.
19. Linde C, Gold MR, Abraham WT, St John Sutton M, Ghio S, Cerkvenik J, Daubert C, REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction Study Group. Long-term impact of cardiac resynchronization therapy in mild heart failure: 5-year results from the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study. Eur Heart J. 2013;34(33):2592–9.
20. Díaz-Infante E, Mont L, Leal J, García-Bolao I, Fernández-Lozano I, Hernández-Madrid A, Pérez-Castellano N, Sitges M, Pavón-Jiménez R, Barba J, Cavero MA, Moya JL, Pérez-Isla L, Brugada J, SCARS Investigators. Predictors of lack of response to resynchronization therapy. Am J Cardiol. 2005;95(12):1436–40.
21. Cabrera-Bueno F, García-Pinilla JM, Peña-Hernández J, Jiménez-Navarro M, Gómez-Doblas JJ, Barrera-Cordero A, Alzueta-Rodríguez J, de Teresa-Galván E. Repercussion of functional mitral regurgitation on reverse remodelling in cardiac resynchronization therapy. Europace. 2007;9(9):757–61.
22. Cleland J, Freemantle N, Ghio S, Fruhwald F, Shankar A, Marijanowski M, Verboven Y, Tavazzi L. Predicting the long-term effects of cardiac resynchronization therapy on mortality from baseline variables and the early response a report from the CARE-HF (Cardiac Resynchronization in Heart Failure) Trial. J Am Coll Cardiol. 2008;52(6):438–45.