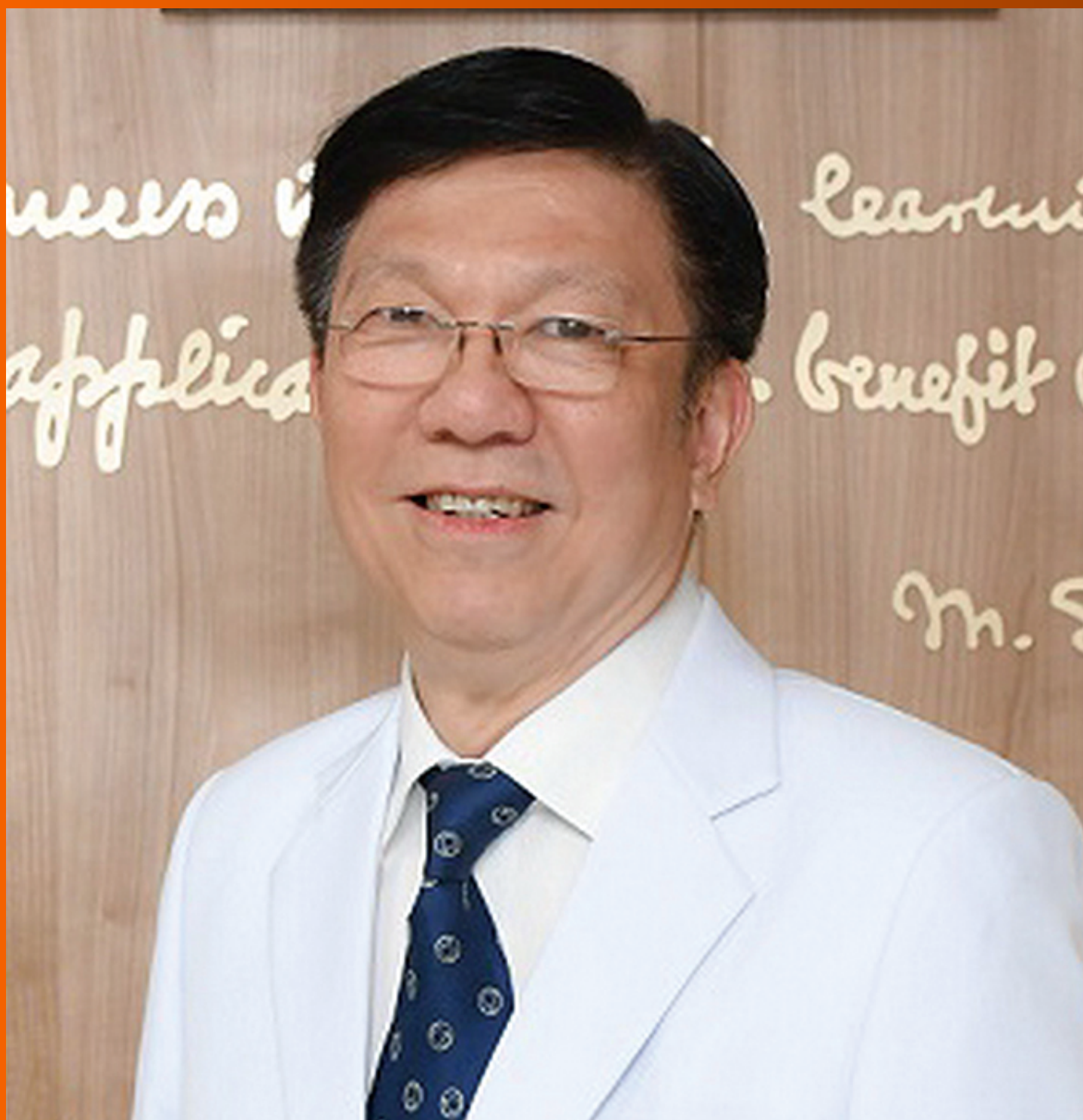


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## Predictors of persistence of functional mitral regurgitation after cardiac resynchronization therapy: Review of literature

Eleonora Russo, Giulio Russo, Maurizio Braccio, Mauro Cassese

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### Abstract

Functional mitral regurgitation is a common finding among heart failure patients with ischemic and non-ischemic dilated cardiomyopathies. The presence of moderate or severe mitral regurgitation is associated with higher morbidity and mortality. Heart failure patients meeting electrocardiogram and left ventricle function criteria are good candidates for cardiac resynchronization therapy, which may reduce the degree of functional mitral regurgitation in the short and long term, specifically targeting myocardial dyssynchrony and inducing left ventricle reverse remodeling. In this article, we analyze data from the literature about predictors of mitral regurgitation improvement after cardiac resynchronization therapy implantation.

**Key Words:** Functional mitral regurgitation; Cardiac resynchronization therapy; Predictors; Mitral regurgitation improvement; Dyssynchrony

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**Core Tip:** Functional mitral regurgitation is a common finding among heart failure patients and, if moderate or severe, is associated with higher morbidity and mortality. Cardiac resynchronization therapy, as a therapy for a subset of heart failure patients, may determine a reduction of the degree of functional mitral regurgitation specifically targeting myocardial dyssynchrony and inducing left ventricle reverse remodeling. Here, we analyze predictors of mitral regurgitation improvement after cardiac resynchronization therapy implantation.

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## INTRODUCTION

Functional mitral regurgitation (FMR) is a common finding of left ventricular (LV) dysfunction and remodeling, occurring both in ischemic and non-ischemic heart disease[1]. The prevalence of FMR varies from 20% to 50% of heart failure (HF) patients[2,3], with 40% of patients presenting with moderate or severe mitral regurgitation (MR)[4]. Data from the literature suggest that any degree of FMR is associated with increased morbidity and reduced survival in patients with LV dysfunction[3-5]. In this setting, there is no conclusive evidence for a survival benefit after mitral valve intervention. The limited data regarding FMR result in a low level of evidence for treatment recommendations and highlight the importance of decision-making by the patient's heart team. According to the latest guidelines, surgery is indicated in patients with severe secondary mitral regurgitation undergoing coronary artery bypass graft and LV ejection fraction > 30%[6,7]. When revascularization is not indicated, optimal medical therapy in line with the HF guidelines should be the first step. Furthermore, patients with HF and FMR eligible for cardiac resynchronization therapy (CRT) could benefit from resynchronization in terms of reduction of the degree of FMR[8,9]. Unlike medical therapy, CRT specifically targets myocardial dyssynchrony, which is an important factor of FMR onset. However, in a subset of CRT patients, significant MR persists and may even worsen.

The purpose of this paper is to provide a comprehensive review on predictors of improvement in FMR after CRT.

## ACUTE AND LONG-TERM EFFECTS OF CRT ON FMR IN THE PRESENCE OF DYSSYNCHRONY

FMR results from multiple factors: ventricular remodeling, decreased contractility, impairment of mitral annular function, imbalance between tethering and closing forces, and mechanical dyssynchrony. LV mechanical dyssynchrony could be a potential contributing factor to FMR through several mechanisms. First, LV dilatation due to dyssynchrony leads to displacement of papillary muscles with consequent lack of leaflet coaptation. Second, uncoordinated regional mechanical activation due to dyssynchrony results in distorted mitral valve apparatus geometry[10]. Lastly, LV dyssynchrony generates a positive pressure gradient between the LV and the left atrium, leading to a diastolic FMR during incomplete mitral valve closure[11].

CRT effects may be distinguished as acute or chronic. Acute, short-term FMR reduction occurs suddenly after CRT implantation, while chronic, long-term FMR reduction occurs weeks to months after CRT implantation. Immediately after CRT device implantation, global LV contraction efficiency improves and closing forces increase consequently. Breithardt *et al*[12] first showed that an increase in LV dP/dt after CRT is directly correlated to MR reduction. Indeed an increase in LV dP/dt leads to an increase in transmitral pressure gradients that facilitate mitral valve leaflet coaptation. Furthermore, CRT acutely determines resynchronization of the papillary muscles leading to a shortening of MR duration and later onset of MR. Indeed, Kanzaki *et al*[13] showed that the inter-papillary muscle-activation time delay is the main determining factor related to MR in HF patients with left bundle branch block and that this delay is immediately improved by CRT.

Data from the literature suggest that short-term reduction in FMR after CRT implantation predicts a favorable clinical response, whereas FMR persistence is associated with reduced survival[14]. In addition to the early effect of CRT on FMR, long-term beneficial effects on FMR have been described. They are mainly represented by the increase of the closing forces and the global LV remodeling. Specifically, LV dimensions, shape and function are main determinants of FMR, and CRT attenuates LV remodeling, which therefore improves FMR. These results could be achieved after 3–6 mo of CRT on top of optimized medical treatment and are even more evident during longer follow-up[15].

Large randomized trials have confirmed short and long-term reduction of FMR following CRT implantation, although the magnitude of this reduction is modest (20%–35% using different quantification methods)[16,17]. In 20%–25% of CRT patients, significant MR persists and may even worsen in 10%–15%. Specifically, this concerns patients with grade ≥ 2 FMR who have a significantly worse outcome than other CRT patients. This subset of patients is often found to be CRT non-responders, and the reasons why these patients do not benefit from CRT are still unclear.



## PREDICTORS OF IMPROVEMENT OF FMR AFTER CRT IMPLANTATION

Data from the literature show that reductions in MR occur mainly in patients with response to CRT. However, FMR reduction was also demonstrated in CRT non-responders. Porciani *et al*[18] reported that FMR may improve even in CRT non-responders because of the reversal of LV dyssynchrony. Reversal of LV mechanical dyssynchrony, especially at the papillary muscle level, has been suggested as one of the mechanisms implicated in CRT-induced FMR improvement[19]. Reviewing the literature, several predictors of MR improvement in CRT patients were found and can be distinguished by patient, clinical, imaging and electric-targeting LV lead-related predictors.

## PATIENT-RELATED PREDICTORS

Karaca *et al*[20] analyzed 142 patients who received biventricular pacemaker devices and found that  $\Delta$ QRS (baseline - paced) after CRT [hazard ratio (HR): 1.242, 95% confidence interval (CI): 1.019-1.465,  $P = 0.028$ ] was associated with LV reverse remodeling and reduced FMR at 6 mo. There were also lower rates of death or hospitalization at midterm follow-up. The cut-off  $\Delta$ QRS value to predict FMR response after CRT was 20 ms, with a sensitivity of 72% and a specificity of 85%. Multivariate analysis found that  $\Delta$ QRS was an independent predictor of FMR response at 6 mo. The same authors observed that non-ischemic HF etiology [odds ratio (OR): 3.13, 95%CI: 1.169-8.380,  $P = 0.021$ ] and the baseline presence of left bundle branch block morphology (OR: 2.49, 95%CI: 1.086-5.714,  $P = 0.032$ ) were independent predictors of “reverse mitral remodeling” and predictors of MR amelioration[21]. The abovementioned preoperative features are those that the majority of previous CRT studies found as “classical” predictors of CRT response.

Sadeghian *et al*[22], in a small study of 69 patients, found that independent predictors of early MR improvement (48 h after CRT implantation) were older age and longer baseline QRS duration. Among the MR improvement group, the mean age was  $60 \pm 7$  years (*vs*  $55 \pm 12$  years in the no MR improvement group), and baseline QRS width was  $172 \pm 31$  ms (*vs*  $147 \pm 28$  ms).

Profibrotic biomarkers were also evaluated as potential predictors of FMR reduction. It was found that at the time of CRT device implantation, elevated concentrations of gal-3, a protein (lectin family) upregulated in HF that is involved in fibrogenesis, are associated with a lack of MR amelioration (OR: 0.14, 95%CI: 0.03-0.58,  $P = 0.007$ )[23]. These results are consistent with molecular changes in HF settings where fibroblast proliferation and collagen production have a pivotal role on LV remodeling and consequently in mitral annulus dilatation/dysfunction.

## IMAGING-RELATED PREDICTORS

Sitges *et al*[24] found that baseline mitral valve tenting area, as a remodeling parameter of the mitral valve, was a powerful independent predictor of MR reduction with CRT (OR: 8.05, 95%CI: 1.15-56.60,  $P = 0.03$ ). A cut-off value  $> 3.8$  cm<sup>2</sup> yielded sensitivity of 53% and specificity of 89% to predict the absence of a significant reduction in MR with CRT. Similar results have been reported for predicting the success of restrictive annuloplasty in patients with functional MR who undergo surgery. Indeed, Magne *et al*[25] reported that a tenting area  $> 2.5$  cm<sup>2</sup> was associated with failed mitral valve repair in these patients. Results described by Sitges *et al*[24] were confirmed subsequently by Karaca *et al*[21]. In that study, baseline tenting area was identified as an independent predictor of FMR response at 6 mo (HR: 2.011, 95%CI: 1.268-2.754,  $P = 0.012$ ). Values of tenting area differed significantly in FMR responders compared with non-responders ( $4.68 \pm 1.02$  cm<sup>2</sup> *vs*  $3.22 \pm 0.88$  cm<sup>2</sup>,  $P = 0.002$ ). These data suggest that the more advanced the LV remodeling and the more distorted the LV geometry, the lower the probability of effective treatment for functional MR.

Subsequently, studies were performed with tissue Doppler imaging (TDI) and speckle tracking echocardiography to elucidate the role of myocardial dyssynchrony in the genesis of FMR in HF patients. Sadeghian *et al*[22] showed that septolateral delay by TDI was a significant predictor of MR improvement. In a previous small study with moderate/severe MR patients, Karvounis *et al*[26] showed that inferior papillary muscle time delay ( $R^2 = 0.945$ ,  $P = 0.04$ ) together with an increase in posterior papillary muscle longitudinal negative strain ( $R^2 = 0.727$ ,  $P = 0.01$ ) (both evaluated with TDI) were significant predictors of reduction in MR volume post-CRT implantation.

Naqvi *et al*[27] found that septolateral delay of  $> 60$  ms was a univariate but not a multivariate predictor of MR reduction and demonstrated that the combined presence of delayed longitudinal strain in the mid inferior LV segment along with preserved systolic strain in the basal and mid posterior segments predicted reduction in MR severity post-CRT. The sensitivity and specificity of this composite variable to predict follow-up MR was 88% and 93%, respectively. These aforementioned findings added important information about acute MR reduction post-CRT. Indeed, patients who developed significant MR reduction had discoordination at the mid ventricle level. Therefore, the mid anterolateral segments were the earliest, and the mid inferoposterior segments were the most delayed as well as viable

segments. This suggested delayed posterior papillary muscle compared to anterior papillary muscle contraction resulted in malcoaptation of mitral leaflets and MR. Therefore, CRT in the MR improvement group probably reduced MR by correcting the mid inferoposterior wall delay and by improving function in these viable segments as assessed by strain and strain rate.

Unlike these studies, Goland *et al*[28] evaluated radial instead of longitudinal strain and used a two-dimensional method of strain assessment instead of TDI. It was found on multivariable logistic analysis that time to peak two-dimensional radial strain between inferior and anterior LV segments of  $> 110$  ms (OR: 8.4, 95%CI: 8.4–54.0,  $P = 0.02$ ) and two-dimensional radial strain in the posterior segment of  $> 18\%$  were significant predictors of early post-CRT MR improvement (OR: 7.6, 95%CI: 1.2–72.4,  $P = 0.006$ ). These results confirmed the role of viability and dyssynchrony of the areas adjacent to posterior papillary muscle. Obviously, the presence of non-severe MR predicted MR reduction after CRT as suggested by MR jet area/Left area ratio (OR: 8.1, 95%CI: 1.2–52.4,  $P = 0.02$ ).

Onishi *et al*[29], in a large series, showed that anteroseptal to posterior wall radial strain dyssynchrony  $> 200$  ms (OR: 2.65, 95%CI: 1.11–6.30,  $P = 0.0277$ ) and end systolic dimension index  $< 29$  mm/m<sup>2</sup> (OR: 2.53, 95%CI: 1.03–6.20,  $P = 0.0420$ ) predicted MR improvement at 6 mo after CRT implantation. Therefore, the present study combined the presence of radial dyssynchrony and lack of excessive LV dilatation (simply measured by end-systolic diameter index) with strong amelioration of significant MR. Furthermore, it added another important element: the lack of echocardiographic scar at the papillary muscle insertion site (wall motion score index  $\leq 2.5$ ) that resulted as a significant predictor of MR improvement (OR: 2.59, 95%CI: 1.06–6.30,  $P = 0.0360$ ).

An interesting study was recently conducted by Galand *et al*[30]. It included 54 HF patient candidates for CRT who underwent dual-source computed tomography (CT) scan imaging in order to guide the CRT implantation procedure. Cardiac dual-source computed tomography is an ideal non-invasive imaging modality with very fast features, so patients receive less radiation. It also creates sharper images. This study evaluated the impact of LV wall thickness using dual-source CT in response to CRT and MR improvement. In multivariable analysis, an area  $\geq 25\%$  of LV wall thickness  $< 6$  mm including at least one papillary muscle insertion was the only predictor of no MR improvement at 6 mo (OR: 16.82, 95%CI: 1.72–164.2,  $P = 0.015$ ). The study confirmed the crucial role of papillary muscle insertion site and suggested that normal wall thickness could promote a mitral valve apparatus remodeling after CRT.

## ELECTRIC-TARGETING LV LEAD-RELATED PREDICTORS

Among invasive electric predictors of the response to CRT, a commonly studied measure of electric delay is the QLV interval, which is the time from the onset of the QRS complex on the surface electrocardiogram to the local LV activation at the site of the LV lead[31]. Previous studies demonstrated the predictive value of QLV interval as a measure of LV electric delay for acute hemodynamic changes and clinical outcome with CRT[32]. Recently, Upadhyay *et al*[33] provided an interesting link between a simple electric measurement, such as QLV, and improvement in MR. They demonstrated that greater changes in MR were achieved by targeting the LV lead in regions of longer QLV at implant (multivariate  $\beta$  coefficient = 0.0040,  $P = 0.0072$ ).

Chatterjee *et al*[34] analyzed data from patients enrolled in the SMART-AV study[29] and provided strong evidence of the association between baseline QLV and reduction in MR after CRT. After multivariable adjustment, increasing QLV was an independent predictor of MR reduction at 6 mo as reflected by an increased odds of MR response (OR: 1.13, 95%CI: 1.03–1.25/10 ms increase QLV,  $P = 0.02$ ).

## STUDY LIMITATIONS

This was not a systematic review. Heterogeneity among included studies was widespread. Studies included showed variations in study design, cohort characteristics and response definitions. Another source of heterogeneity is that CRT implantation techniques and indications have evolved over the last 20 years. These limitations are particularly important to consider in future research studies.

## CONCLUSION

Over the past two decades, numerous invasive and non-invasive predictors of the response to CRT have been proposed, and it was shown that reductions in MR occurred mainly in patients with response to CRT (Table 1). However, not all CRT responders are “MR responders,” and FMR reduction was also demonstrated in CRT non-responders, hence the importance of identifying MR improvement predictors after CRT implantation. Among “MR predictors” proposed, the possibility to recognize viability and dyssynchrony by imaging, especially near papillary muscles, is very useful. Also the measurement of

**Table 1 Variables that predict mitral regurgitation improvement or lack of improvement**

Predictor category	Predictors of MR improvement	Ref.	HR	P value
Clinical parameters	ΔQRS (at least 20 ms) after CRT	[20]	1.242	0.028
	Non ischemic HF etiology	[20]	3.13	0.021
	Baseline presence of LBBB morphology	[20]	2.49	0.032
	QRS narrowing after CRT	[21]	NA	0.001
	Older age	[23]	NA	0.001
	Baseline longer QRS duration	[23]	NA	0.001
Echo imaging	Septal-lateral delay by TDI	[23]	NA	0.001
	Baseline tenting area < 3.8 cm <sup>2</sup>	[24]	NA	0.02
	Baseline tenting area	[21]	NA	0.01
	Septal-lateral delay by TDI	[22]	NA	0.001
	Baseline inferior papillary muscle time delay	[26]	NA	0.04
	Increase in posterior papillary muscle longitudinal negative strain	[26]	NA	0.01
	Combined presence of delayed longitudinal strain in the mid inferior LV segment and preserved systolic strain in the basal and mid posterior segments	[27]	NA	0.001
	Time to- peak 2-DRS between inferior and anterior LV segments of > 110 ms	[28]	8.4	0.02
	Preserved radial strain in posterior segments assessed by 2-DRS	[28]	7.6	0.006
	MR jet area/left atrium area ratio < 40%	[28]	8.9	0.02
	Anteroseptal to posterior wall radial strain dyssynchrony > 200 ms	[29]	NA	0.028
	Lack of severe left ventricular dilatation (end-systolic dimension index < 29 mm/m <sup>2</sup> )	[29]	NA	0.042
	Lack of echocardiographic scar at papillary muscle insertion sites	[29]	NA	0.036
Electric-Targeting LV Lead	Degree of delay at the LV lead site	[34]	1.13	0.02
	Predictors of lack of MR improvement			
CT imaging	≥ 25% of LVWT < 6 mm inclusive of at least one papillary muscle insertion using CT	[30]	1.04	0.032
Biomarkers	Higher levels of galectin 3	[23]	0.16	0.01

CRT: Cardiac resynchronization therapy; TDI: Tissue Doppler imaging; 2DRS: 2D radial strain; MR: Mitral regurgitation; LVWT: Left ventricular wall thickness; CT: Computed tomography; LV: Left ventricular; NA: Not available.

LV electric ventricular delay, such as QLV, is simple, does not require echocardiography or surface electrocardiographic measurements and has the potential to be measured automatically by devices that would further simplify lead optimization.

The concept that more advanced LV remodeling remains valid. Therefore, the lower the probability of successful CRT treatment for FMR and other treatment strategies to reduce MR should be evaluated. Long-term results in a larger cohort together with new imaging techniques, such as three-dimensional imaging, are needed to keep track of the developments and the changes in this exciting field.

## FOOTNOTES

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