



The role of cardiac magnetic resonance in identifying appropriate candidates for cardiac resynchronization therapy — a systematic review of the literature

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Abstract

Despite the strict indications for cardiac resynchronization therapy (CRT) implantation, a significant proportion of patients will fail to adequately respond to the treatment. This systematic review aims to present the existing evidence about the role of cardiac magnetic resonance (CMR) in identifying patients who are likely to respond better to the CRT. A systematic search in the MedLine database and Cochrane Library from their inception to August 2021 was performed, without any limitations, by two independent investigators. We considered eligible observational studies or randomized clinical trials (RCTs) that enrolled patients > 18 years old with heart failure (HF) of ischaemic or non-ischaemic aetiology and provided data about the association of baseline CMR variables with clinical or echocardiographic response to CRT for at least 3 months. This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement). Following our search strategy, 47 studies were finally included in our review. CMR appears to have an additive role in identifying the subgroup of patients who will respond better to CRT. Specifically, the presence and the extent of myocardial scar were associated with increased non-response rates, while those with no scar respond better. Furthermore, existing data show that scar location can be associated with CRT response rates. CMR-derived markers of mechanical desynchrony can also be used as predictors of CRT response. CMR data can be used to optimize the position of the left ventricular lead during the CRT implantation procedure. Specifically, positioning the left ventricular lead in a branch of the coronary sinus that feeds an area with transmural scar was associated with poorer response to CRT. CMR can be used as a non-invasive optimization tool to identify patients who are more likely to achieve better clinical and echocardiographic response following CRT implantation.

Keywords Cardiac resynchronization therapy · Cardiac magnetic resonance · Late gadolinium enhancement · Myocardial fibrosis · CRT response

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Introduction

According to current guidelines, cardiac resynchronization therapy (CRT) is recommended in patients with advanced heart failure (HF), impaired left ventricular ejection fraction (LVEF), and a wide QRS complex [1, 2]. However, a significant proportion of CRT patients will fail to respond to the treatment with the rates of success varying according to the definition of the response criteria [3]. Specifically, the CRT response rates can range from 32 to 91% [4]. The identification of baseline characteristics that are associated with a higher probability of CRT response is therefore of great importance.

Cardiac magnetic resonance (CMR) is an imaging modality that can provide valuable clinical data, and therefore its use has been expanded in the current clinical practice [5]. In the field of HF, CMR can provide the “gold standard” method for measurements of biventricular ejection fraction; characterize myocardial tissue and mainly identify presence, location, and burden of myocardial fibrosis; assess myocardial viability; and thus help diagnose specific cardiomyopathies [6]. Furthermore, the presence and degree of myocardial scar on CMR has been associated with an adverse prognosis, including arrhythmias in conditions like aortic stenosis [7] and dilated cardiomyopathy [8, 9]. It is therefore possible that the presence and extent of myocardial scar can adversely affect the benefit following CRT and indeed the use of CMR in the pre-procedural evaluation of CRT candidates in combination with other diagnostic tools is able to identify patients unlikely to respond to CRT [10]. This systematic review aims to present the existing evidence about the role of CMR in identifying patients who are likely to respond to the CRT.

Myocardial tissue characterization

CMR is the only radiation-free modality that enables accurate assessment of myocardial tissue characterization. Various methods exist for this as well as different commercial packages. However, the mainstay of tissue characterization relies on the administration of the paramagnetic agent gadolinium and imaging the myocardium some 10–20 min after the administration. This delayed (or late) phase of imaging after the administration of gadolinium, often referred to as “late gadolinium enhancement, LGE” enables to identify scarred (or dead) myocardium from alive myocardium (Fig. 1). The white areas following gadolinium administration represent muscle that has died, often referred to as replacement (or focal) fibrosis, and there has been extensive validation of the CMR findings with histology. This type of fibrosis/scar is irreversible and forms the mainstay of assessment for viability by CMR. The black areas represent healthy myocardium. This also allows the location of the scar to be identified, with subendocardial or transmural scar relating to myocardial infarction and ischaemic cardiomyopathy. Midwall or subepicardial scar in the context of cardiomyopathy would relate to the non-ischaemic cardiomyopathy. Non-ischaemic cardiomyopathy is an umbrella term, capturing a plethora of conditions, which include cardiomyopathy secondary to dilated cardiomyopathy, myocarditis, cancer (either cancer itself or chemotherapy-related), hypertension, and infiltrative and autoimmune processes. When it comes to the quantification of the scar, there are both visual and semi-automatic/artificial-intelligence-guided methods. A simple, but well-recognized and valuable method, is to simply use the 16 AHA segment model and for each segment allocate 0 if there is no scar, 1 if there

Fig. 1 Imaging in the late phase following gadolinium administration of the mid ventricular level. The white part of the myocardium in the septal and anteroseptal areas, indicated by the yellow arrows, corresponds to hyperenhancement of the myocardium, and effectively dead muscle. This was as a result of a left anterior descending artery myocardial infarction. The remaining myocardium which is black in colour is healthy



is subendocardial non-transmural scar, and 2 if there is transmural scar. This will therefore give a total score of 32, or each of the 16 segments representing 6% of the myocardium. More recent methods such as those provided by Circle CVI (Calgary, Canada) or MASS (Leiden, Netherlands) allow the operator to select a region of interest of normal (or abnormal) myocardium and the software will then automatically select and quantify the total scar for each ventricular slice. The software will then add the scar in all the slices giving an overall percentage both as mass and as a percentage. The quantification relies either on the full width half maximum method using regions defined above 50% of maximal signal intensity of the enhanced area, or the standard deviations method, where LGE can be quantified using a threshold above 2–7 standard deviations above a remote reference region [11].

More recently, different CMR sequences based on T1 mapping, have been histologically validated [12] to show diffuse (or interstitial) fibrosis, effectively a “finer” form of fibrosis that might not be irreversible. This relies on expansion of the extracellular matrix, which is one of the initial hallmarks of pathology and, if the underlying aetiology is left untreated, is thought that it will result to myocardial scar. The two most common forms of measuring this diffuse fibrosis are native T1 mapping (which does not require administration of gadolinium) and extracellular volume fraction (ECV), which relies on measuring myocardial and blood T1 values before and after the administration of gadolinium. Both LGE and T1 mapping are therefore methods that provide myocardial tissue characterization and will be reviewed in this paper.

Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement) [13].

Search strategy

Two independent investigators performed a systematic search in the MedLine database and Cochrane Library from inception to August 2021 without any limitations. In addition, we manually searched the reference lists of the relevant review and research studies. The following algorithm was used to retrieve all relevant studies: “(cardiac magnetic resonance) AND (cardiac resynchronization therapy OR CRT)”. We first screened the titles and abstracts of each study, and when a study was judged as relevant, we reviewed through the full text. Disagreements were resolved by a third investigator.

Eligibility criteria

We considered eligible observational studies or randomized clinical trials (RCTs) that enrolled patients > 18 years old with HF of ischaemic or non-ischaemic aetiology and provided data about the association of baseline CMR variables with clinical or echocardiographic response to CRT for at least 3 months. We excluded studies that provided data about acute CRT response only, studies that did not offer a definition of CRT response, and studies written in a different language than English.

Data collection process

The following data were extracted for each included study: publication data (first author, year of publication), patient characteristics (number of patients in each group (responders/nonresponders), mean age, gender, type of cardiomyopathy, left ventricular ejection fraction, LBBB, sinus rhythm), and the crude data of the reported outcomes. Two independent investigators performed the data extraction.

Results

Search results

Our search strategy in electronic databases returned 489 possible relevant studies. Of them, 19 studies were excluded as duplicate records, and 373 studies were excluded at the title/abstract level while 50 studies were excluded at the full-text level. As a result, 47 studies were finally included in the review (Fig. 2, Table 1).

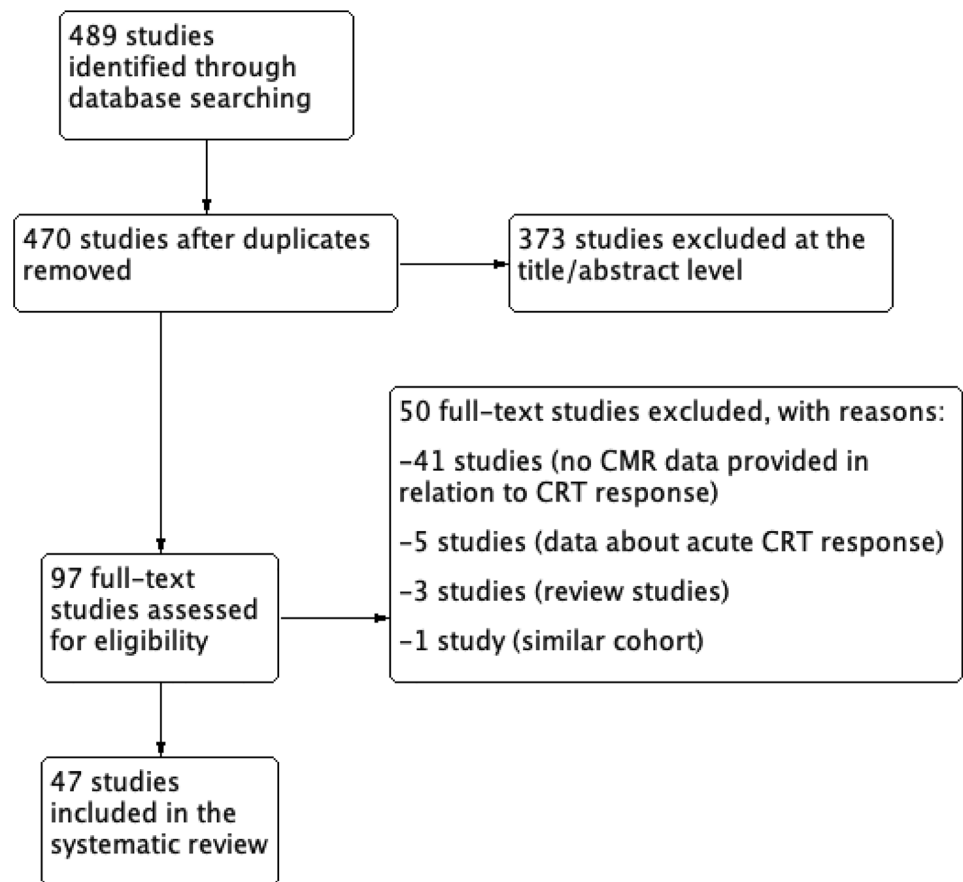
Association of CMR indices with CRT response

Impact of the myocardial scar on CRT response

The association of myocardial scar with CRT response has been studied in several studies. Both the presence of scar and scar extent/scar burden have been associated with increased non-response rates [14–16]. Also, the location of LV scar has been associated with CRT response [17, 18].

In the setting of ischaemic cardiomyopathy, a scar size $\geq 33\%$, a transmural $\geq 51\%$, and pacing over a posterolateral scar have been associated with a suboptimal response to CRT [19]. By CMR imaging in the DCM group, the percentage of regional scar segments and percentage of regional scar score in the left ventricular inferior wall were significantly higher in the nonresponders than in the responders [20]. However, no statistical difference was found in the ICM, mainly because of the small sample size [20]. Midwall fibrosis seems to have

Fig. 2 Flowchart of the search strategy



a different impact on outcomes depending on the cause of cardiomyopathy. Specifically, it has been found that left ventricular reverse remodeling was observed in DCM without midwall hyperenhancement and in ICM but not in DCM with midwall hyperenhancement [21]. The same study showed that there were no differences between groups regarding the clinical response [21].

Focal scar burden detected by LGE CMR has been associated with a poor echocardiographic response to CRT, while diffuse interstitial fibrosis assessment by T1 mapping was not associated with CRT response [22]. A high scar tissue burden is more pronounced in nonresponders [23]. Specifically, in an observational study, scar burden as indicated by the total scar burden score and the number of transmurally infarcted segments was significantly higher in nonresponders [24]. Additionally, another study including ischaemic and non-ischaemic patients, defined scar burden on a 5-point scale, whereby 0 had no scar, and each incremental point corresponded to a group of 25% of transmural, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, 4 = 76–100%. It was found that all patients with high scar burden score of > 1.2 failed to respond to CRT [24].

In a prospective, multicentre study, the septal scar was found to be a significant predictor of reverse remodeling

defined as at least 15% reduction in LVESV indexed to body surface area at 6 months follow-up. In comparison, any scar in the septum showed a sensitivity of 81% for non-response to CRT [25]. In the same study, the combined assessment of septal viability and lateral wall to septal work difference performed better in predicting CRT response than work difference alone [25]. In a small cohort study of both ischaemic and non-ischaemic patients, both global and lateral wall scar burden were significantly associated with reverse remodeling [26]. Specifically, a cutoff value of 36.5% for global LV scar burden showed a sensitivity of 81.8% and specificity of 68.4% for predicting non-response. In comparison, a cutoff for lateral wall scar burden 40.5% of the whole lateral wall had a sensitivity of 72.7% and specificity of 68.4% [26]. Similarly, another study showed that patients with a transmural posterolateral scar had low clinical response rates [17, 18]. A significant positive correlation was found between myocardial scar mass and the evolution of LVESV at 12-month follow-up [27]. On the other hand, in a small observational study, the absence of scar in the posterolateral area (in the region of LV lead placement) was associated with CRT response only in univariate analysis but not in the multivariate analysis [28]. Interestingly, LV dyssynchrony remained the most critical determinant of response to CRT, even in the presence of posterolateral scar.

Table 1 Baseline characteristics and main findings of the included studies

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders CRT response including deaths definition	Outcomes
Aalen JM ¹	2020 [73]	Prospective multi-center study	200	67	71	70	6	172	N/A	164	LGE – scar size quantified semi-automatically in Segment software v2.0 R5270 from a stack of short-axis slices using a 17 segment model	135	65	Decrease of $\geq 15\%$ in LVESV Septal scar predicted CRT response
Ahmed W ²	2016 [74]	Prospective single center study	30	58 \pm 7	80	21	6	6	N/A	N/A	LGE—MR WorkSpace eXplore release workstation	19	11	Decrease of $\geq 15\%$ in LVESV Scar burden, number of scar segments, and lateral wall scar burden were significantly associated with CRT response
Aimo A ³	2021 [75]	Prospective single center study	39	N/A	N/A	N/A	3	39	N/A	N/A	LGE—segmented T1-weighted gradient-echo inversion-recovery pulse sequence—MASS 6.1., Medis, Leiden, Netherlands	25	14	Improvement of ≥ 1 NYHA class; Decrease of $\geq 10\%$ in LVESV Patients with a wide pattern of systolic phase of v/t curve responded more often to CRT
Alpedruma F ⁴	2011 [76]	Retrospective single center study	56	64 \pm 9	76	29	12	N/A	52	46	LGE – inversion recovery gradient echo sequence –quantification using a 16-seg- ment model based on the “full width at half maximum” technique—MRI- MASS, Medis, Leiden, the Netherlands	27	29	Improvement of 5% Preserved RVEF and myocardial scar burden were associated with CRT response
Andre C ⁵	2018 [77]	Prospective single center study	61	61	72	25	6	61	27	61	LGE—seventeen-segment binary qualitative analysis; percentage of LGE in the entire myocardium for quantitative analysis—CVI42 software, Circle Cardiovascular imaging Inc	49	12	No all-cause mortality; No hospitalizations for MACE; Decrease of $\geq 15\%$ in LVESV Presence of LGE and higher percentage of LGE were adversely associated with CRT response. LGE $\geq 14\%$ was associated with no CRT response in multivariate analysis
Auger DA ⁶	2017 [78]	Prospective single center study	50	64 \pm 8	70	26	6	N/A	24	N/A	LGE	N/A	N/A	Decrease of $\geq 15\%$ in LVESV TOS/QRS, TOS, scar at LVLP, and CURE-SVD were significantly associated with LVRR

Table 1 (continued)

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders CRT response including deaths	Outcomes
Bertini M ⁷	2016 [79]	Prospective single center study	50	67.3 ± 9.7	74	23	6	27	29 ± 6	N/A	LGE – (area with delayed enhancement > 75% of the myocardial wall) – fast-gradient-echo inversion-recovery – software Segment CMR (Medviso, Lund, Sweden)	39	11	Decrease of ≥ 15% in LVESV Cardiac imaging using STE and CMR imaging as a guide for CRT implantation increased the response rate
Bilchick KC ⁸	2009 [80]	Prospective single center study	20	58 ± 10	65	8	6	N/A	23	N/A	Delayed enhancement magnetic resonance imaging (DEMRI) – inversion recovery fast gradient-echo pulse sequence – signal intensity at least two standard deviations or more relative to a remote region of interest	N/A	N/A	Improvement of ≥ 2 MR-MT assessment of circumferential mechanical dyssynchrony predicted improvement in NYHA class after CRT. The addition of scar imaging by DEMRI further improved NYHA class
Bilchick KC ⁹	2014 [81]	Prospective single center study	75	65.9 (57.8–74.3)	74.7	N/A	6	67	23.2 (15–28.4)	N/A	LGE – signal intensity at least 2 standard deviations above the mean signal intensity in remote area – Matlab (v7.14, The Mathworks, Natick, MA)	40	35	Decrease of ≥ 15% in LVESV CURE, delayed circumferential contraction onset at LVL P, absent LVL P scar, and time from QRS onset to LVL P electrogram were associated with echocardiographic response to CRT
Bilchick KC ¹⁰	2020 [82]	Prospective single center study	100	64.2 ± 13.4	71	59	6	65	23 (17.5–28.5)	N/A	LGE – signal intensity of at least 5 SDs above the mean in remote areas	55	45	Decrease of ≥ 15% in LVESV CURE-SVD with DENSE strain imaging was significantly correlated with CRT response
Bleeker GB ¹¹	2006 [83]	Prospective single center study	40	67 ± 10	87.5	40	6	40	23 ± 7	34	LGE – inversion-recovery gradient echocardiographic sequence – inversion time was determined with a Look-Locker sequence	23	17 (1 death)	Improvement of ≥ 1 NYHA class; Improvement of ≥ 25% in 6MWD Patients with a transmural posterolateral scar showed a low response rate to CRT. Patients without posterolateral scar tissue and severe baseline dyssynchrony showed an excellent response rate compared to patients with a posterolateral scar and/or absent left ventricular dyssynchrony

Table 1 (continued)

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders including deaths	Outcomes
Chalil S ¹²	2007 [84]	Prospective single center study	62 (29 non-posterolateral scar and 33 posterolateral scar)	67.3 ± 9.6	81	62	24 ± 7	62	22.4 ± 11.3	58	LGE—MASS analysis software (Medis, Leiden, the Netherlands)—segmented inversion-recovery technique – Transmurality was assessed on contrast enhanced images using a 17-segment model	83% (non-posterolateral scar); 47% (transmural posterolateral scar)	17% (non-posterolateral scar); 53% (transmural posterolateral scar)	Improvement of ≥ 1 NYHA class; Improvement of ≥ 25% in 6MWD Presence of a posterolateral scar, imaged using LGE-CMR, was an independent predictor of cardiovascular death or hospitalizations for HF in patients with ICM undergoing CRT
Chalil S ¹³	2007 [85]	Prospective single center study	45	67 ± 10.4	84	45	18	45	22.1 ± 11.1	N/A	LGE – segmented inversion-recovery technique—quantification by planimetry of hyperenhanced tissue on LGE-CMR images—MASS analysis software (Medis, Leiden, The Netherlands)	29	16	Survived for 1 year with no hospitalizations for HF; Improvement of ≥ 1 NYHA class; Improvement of ≥ 25% in 6MWD In patients with ICM, scar size of 33%, transmural of 51%, and pacing over a posterolateral scar were associated with a suboptimal response to CRT
Chen Z ¹⁴	2016 [86]	Prospective single center study	48	66 ± 12	83	27	6	22	24 ± 8	N/A	Inversion-recovery gradient-echo Sequence—modified Look-Locker inversion recovery sequence Focal fibrosis: LGE – quantified by using the two-standard deviation method Diffuse fibrosis: T1 relaxation maps – extracellular volume index	27	21	Decrease of ≥ 15% in LVESV CRT responders had a significantly reduced focal scar burden compared to non-responders Diffuse fibrosis assessment with T1 native and T1 contrast was not statistically different between responders and non-responders
Cochet H ¹⁵	2013 [87]	Prospective single center study	60	59 ± 11	73.3	26	6	N/A	28 ± 4.5	N/A	Delayed enhanced images were used to quantify myocardial scar extent, and to assess the presence of scar – scar was automatically segmented using a threshold at 50% maximal signal intensity—QMass analytical software (Medis, Leiden, The Netherlands)	42	18	Decrease of ≥ 15% in LVESV MRI-defined intra-left ventricular dyssynchrony and myocardial scar extent were independent predictors of CRT response The presence of scar at pacing site was associated with CRT non-response Mechanical delay at pacing site did not influence the CRT response rate

Table 1 (continued)

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders including deaths	Outcomes
D'Andrea A ¹⁶	2009 [88]	Prospective single center study	45	58.3 ± 8.3	53.3	45	6	N/A	29.2 ± 5.1	N/A	LGE – Segmented gradient-echo inversion-recovery turbo FLASH sequence—MRase SYNGO 2002B	30	15	Decrease of ≥ 15% in LVESV Patients not responding to CRT had significantly higher scar burden than responders
Duckett SG ¹⁷	2012 [89]	Retrospective single center study	50	62.8 ± 14	45	24	6	50	25.1 ± 8.2	44	Delayed enhancement CMR—conventional inversion recovery techniques	46 (40 had improved NYHA)	4	Improvement of ≥ 1 NYHA class; Increase of ≥ 10% in quality-of-life chronic responses to CRT
Fernandez-Armenta J ¹⁸	2012 [90]	Prospective single center study	78	64 ± 11	65	41	6	49	22	N/A	Scar tissue was defined as areas with signal intensity at least two SD above the normal myocardium—segmented gradient echo sequence with inversion – recovery – TCTK, Tissue Characterization Tool Kit) based on MATLAB (The MathWorks, Natick, MA, USA)	41	34	Decrease of ≥ 15% in LVESV The percentage of responders was lower among patients with identifiable areas of delayed enhancement on CMR. Scar mass and scar as the percentage of left ventricular myocardium were not significantly different between responders and non-responders
Gathier WA ¹⁹	2020 [91]	Retrospective single center study	30	69.9 ± 5.8	80	30	N/A	23	24.8 ± 7	N/A	Delayed enhancement CMR—Medviso, Lund, Sweden—MATLAB and Statistics Toolbox (The MathWorks, Inc., Natick, MA, USA)	N/A	N/A	Decrease in LVESV LVRR following CRT implantation was affected not only by the presence of myocardial scar but also by the total left ventricular scar burden. Pacing in scar-free segments led to a greater grade of reverse remodeling
Harb SC ²⁰	2019 [92]	Retrospective single center study	84	62 ± 12	63	43	3.7 years	42	24 ± 9	N/A	Delayed hyperenhancement—Scar was defined using a threshold of > 2 SD compared with user-defined viable myocardium for ICM and > 6 SD for NICM—(cvi42; Circle Cardiovascular Imaging, Calgary, Alberta, Canada)	30	37 (10 deaths)	Improvement of ≥ 10% in LVEF Higher levels of scar were associated with non-response to CRT. Incorporating scar quantification to QRS duration and the presence of LBBB had an incremental value in predicting response to CRT. An increase in scar burden was associated with worse outcomes at every location

Table 1 (continued)

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders including deaths	Outcomes
Hartlage GR ²¹	2015 [93]	Prospective single center study	33	61 ± 13	18	7	6	N/A	28	N/A	LGE CMR using a phase-sensitive inversion recovery sequence—Significant scar was defined as enhancement in > 15% of LV myocardium	18	15	Decrease of ≥ 15% A U-shaped wall motion pattern compared to a homogeneous (type I) wall motion pattern and a concordant left ventricular lead predicted CRT response
Jackson T ²²	2014 [94]	Prospective single center study	37	66 ± 11.7	31	14	6	37	22	N/A	n/a	25	12	Decrease of ≥ 15% A U-shaped contraction pattern strongly predicted reverse remodeling and super-response to CRT
Jansen AHM ²³	2007 [95]	Prospective single center study	43	69 ± 8	100	30	3	43	22 ± 7	43	Gadolinium enhanced MRI—three-dimensional segmented inversion-recovery technique	33 clinical responders and 41 echocardiographic responders	10 clinical responders	Clinical response was assessed by improvements in NYHA class or 6MWD
Kawakubo M ²⁴	2013 [96]	Retrospective single center study	73	57 ± 15	41	23	N/A	N/A	38 ± 19	N/A	LGE—LGE positive was considered as the hyperenhanced area involved in more than 50% of the wall thickness	8	6	Improvements in NYHA class or 6MWD
Kim B ²⁵	2008 [97]	Prospective single center study	19	67 ± 8	12	9	3	N/A	26 ± 10 at baseline and 37 ± 14 at 3-month follow-up	N/A	N/A	10	9	Decrease of ≥ 15% in LVESV
Kockova R ²⁶	2017 [98]	Prospective single center study	44	64 ± 12	31	17	47	40	28 ± 7	40	LGE—Segment software (Medviso, Sweden)	74% CRT responders	10/38	Improvement of ≥ 1 NYHA class; Decrease of > 10% in LVESD; Decrease of ≥ 30% in BNP

Table 1 (continued)

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders CRT response including deaths	Outcomes
Leyva F ²⁷	2011 [99]	Prospective single center study	559	70.4 ± 10.7	78	367	666 days (median) or 3323 days (maximum)	N/A	23.5 ± 10.1	N/A	LGE—segmented inversion-recovery technique in identical short-axis slices	385/553 clinical responders	168/553 clinical responders	<p>LYRR was less pronounced in the CMR-guided and pacing scar group than in the non-CMR-guided group. In the CMR-guided and non-pacing scar group, a scar burden of < 10% was not associated with a better LYRR or clinical response compared with a scar burden of ≥ 10%. CMR-guided and non-pacing scar group had the best clinical response, compared with the CMR-guided and pacing scar group and the non-CMR-guided group</p>
Leyva F ²⁸	2012 [100]	Prospective single center study	258	63.6, 9.58 in DCM + MWHE; 66.7, 13.0 in DCM- MWHE; 88.2 in ICM	60 in DCM + MWHE; 62 in DCM- MWHE; 88.2 in ICM	161	2.84 years (median)	N/A	16, 6.06 in DCM + MWHE; 23.9, 9.7 in DCM- MWHE; 23.9, 10.9 in ICM	N/A	LGE—segmented inversion-recovery technique	65.0% in DCM + MWHE; 80.5% in DCM-MWHE; 68.2% in ICM (clinical response)	35.0% (n DCM + MWHE) in DCM without hospitalizations for HF for one year; Improvement of ≥ 1 NYHA class; Improvement of ≥ 25% in 6MWD	<p>LYRR was observed in DCM without MWHE and in ICM but not in DCM with MWHE. There were no differences in the rate of clinical response between groups</p>
Manca P ²⁹	2020 [101]	Retrospective single center study	72	64 ± 10	69	34	38 ± 12	69	26 ± 5	65	LGE	44	28	<p>Right ventricular dysfunction evaluated by CMR was significantly associated with non-response to CRT. Late enhancement presence, lateral wall fibrosis and the percentage of left ventricular fibrosis were not associated with CRT response</p>

Table 1 (continued)

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders including deaths	Outcomes
Marsan NA ³⁰	2009 [102]	Prospective single center study	35	63 ± 11	74	20	6	N/A	24 ± 8	N/A	LGE – inversion recovery gradient echo sequence –hyperenhanced regions were defined using a threshold at SSD above the mean signal intensity—QMass (Medis)	21	14	Decrease of ≥ 15% in LVESV Scar presence, total scar extent, transmural scar and match of LVLP were associated with non-response to CRT. Non-transmural scar was not associated with CRT response. Scar location was not associated with CRT response. Standard deviation of 16 segment time-to-peak radial thickness was significantly larger in responders compared with non-responders
Nakao R ³¹	2019 [103]	Retrospective single center study	25	59.2 ± 16	96	0	38.4, 25.5 (median); 30 (long-term follow-up)	10	16.2 in CMR	N/A	N/A	12	13	Decrease of ≥ 15% in LVESV; Summed maximum vortex flow predicted CRT response in DC. On the other hand, circumferential temporal delay and longitudinal temporal delay were not associated with CRT response
Petryka J ³²	2012 [104]	Prospective single center study	52	60.3 ± 13	84.6	26	6	N/A	23.9 ± 6.6	N/A	LGE—images were obtained with a single-shot inversion recovery TrueFisp sequence—(MASS 6.2.1, Medis, Leiden, The Netherlands)	26	26	No hospitalizations for HF; Improvement of circumferential strain variance was lower and uniformity of radial strain was higher in non-responders than in responders. Transmurality of LGE predicted non-response to CRT in ischemic HF. Regional vector of strain variance and uniformity of radial strain was lower in non-responders than in responders
Shetty AK ³³	2013 [105]	Prospective single center study	20	66 ± 12	85	10	6	17	23 ± 7	15	LGE—segments with 50% transmural LGE were considered non-viable—ITK-SNAP software	15 clinical responders and 12 echocardiographic responders	5 clinical non-responders and 8 echocardiographic nonresponders	Decrease of ≥ 15% in LVESV The chronic response was significantly better in patients paced in a CMR-target segment

Table 1 (continued)

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders CRT response including deaths definition	Outcomes
Sidhu BS ³⁴	2021 [106]	Prospective single center study	252	70.6 ± 10.8	72.6	127	6	139	31.9 ± 10.1	N/A	LGE	82% had an improved clinical composite score and 57% had a decrease of ≥ 15% in LVESV	18% did not have an improved clinical composite score and 43% mortality, no hospitalizations for HF, improvement of ≥ 15% in LVESV NYHA class in global assessment, and a decrease of ≥ 15% in LVESV	The presence of subendocardial scar on CMR predicted CRT clinical non-response but was not associated with echocardiographic response. Pacing outside of scar vs. pacing within scar did not result in a significant improvement in clinical composite score or decrease in LVESV
Sohal M ³⁵	2013 [107]	Prospective single center study	52	64.8 ± 13.1	88	25	6	N/A	24.3 ± 8.7	N/A	Delayed enhancement—conventional inversion recovery techniques	27	25	Decrease of ≥ 15% in LVESV; Improvement in NYHA class; Improvement in 6MWD; Improvement in Minnesota Living with Heart Failure Questionnaire score Patients with presence of block with a cine-CMR identified U-shaped contraction pattern had significantly greater rates of reverse remodeling compared to patients with a homogeneous contraction pattern from septum to lateral wall
Sohal M ³⁵	2014	Prospective single center study	44 in phase one and 50 in phase two	63.3 ± 14.1 in phase one and 68.6 ± 12.2 in phase two	44 in phase one and 50 in phase two	21 in phase one and 19 in phase two	6	31 in phase one and 28 in phase two	25 ± 9 in phase one and 22 ± 9 in phase two	N/A	LGE—multi-slice IR gradient echo sequence imaging—using conventional inversion recovery techniques—Circle Cardio-vascular Imaging Inc, Calgary, Canada	21/44 echocardiographic responders in phase one and 35/50 in phase two; 36/44 echocardiographic and clinical responders in phase one and 42/50 in phase two	23/44 echocardiographic non-responders in phase one and 15/50 in phase two; improvement of ≥ 10% in 6MWD; improvement of ≥ 1 NYHA class; improvement of ≥ 20% in quality-of-life score	A systolic dyssynchrony index derived from volume-change predicted reverse remodeling following CRT, while a 16-segment systolic dyssynchrony index of regional strain did not
Sohal M ³⁶	2014 [108]	Prospective single center study	52	64.8 ± 13.1	88	25	6	52	24.3 ± 8.7	N/A	LGE—conventional inversion recovery techniques at end-systole—QMass; Medis Medical Imaging Systems, The Netherlands	27	25	Decrease of ≥ 15% in LVESV Septal flash predicted increased response to CRT. Septal flash with no scar was a highly specific predictor of CRT response

Table 1 (continued)

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders CRT response including deaths	Outcomes
Stankovic ¹⁷	2014 [109]	Prospective single center study	58	63 ± 10	78	27	41 ± 13	N/A	26 ± 6	N/A	LGE—electrocardiogram-triggered segmented gradient echo technique	39	19	Decrease of ≥ 10% in LVESV Scar burden was significantly higher in non-responders than responders, as indicated by the total scar burden score and by the number of transmurally infarcted segments. All patients with a total scar burden score of > 1.2 failed to respond to CRT
Storkås, HS ³⁸	2020 [110]	Prospective multi-center study	68	69 ± 8	55	68	8	68	27 ± 7 at baseline; 27 ± 8 responders; 28 ± 7 non-responders	N/A	LGE—Cardiac gated recovery prepared gradient echo pulse sequence—ReportCard software (General Electric, Waukesha WI 4.2)	44	24	Decrease of ≥ 15% in LVESV A high scar tissue burden was more pronounced in non-responders to CRT
Taylor AJ ³⁹	2010 [111]	Prospective single center study	38	59.1 ± 1.9	83	15	497 ± 55 days	N/A	23.7 ± 1.3	N/A	LGE—inversion-recovery gradient echo technique—signal intensity greater than two SD above that within a reference region of a remote non-infarcted myocardium within the same slice	21	17	Improved clinical composite score consisting of no all-cause mortality, hospitalizations for HF, improvement in NYHA class in patient global assessment Combined CMR scar and dyssynchrony imaging identified patients who had a clinical response to CRT
Taylor RJ ⁴⁰	2016 [112]	Retrospective single center study	89	66.8 ± 10.8	75	50	4.4 years	N/A	23.1 ± 9.9	N/A	LGE—segmented inversion recovery technique—Circle Cardiovascular Imaging Inc., Calgary, Canada	41	48	Survival for 1 year after implantation; No hospitalizations with LVRR. LVLIP over a segment with scar for HF; Improvement of ≥ 1 NYHA class; Improvement of ≥ 25% in 6MWD; Decrease of ≥ 15% in LVESV No scar in the paced segment was significantly associated with LVRR. LVLIP over a segment with scar was a strong predictor of cardiac mortality or hospitalizations for HF

Table 1 (continued)

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders including deaths	Outcomes
Nguyễn UC ⁴¹	2018 [113]	Prospective single center study	33	65 ± 12	82	16	6	12	24 ± 8	N/A	Delayed enhancement quantified using the 2-SD method—Osirix (Pixmeo, Geneva)	19	14	Decrease of ≥ 15% in LVESV Pre-T1 and extracellular volume were poor predictors for CRT response, while Scar2SD and Gray2SD, markers of focal scar core, were substantially better at predicting CRT response. By combining QRSarea and CMR focal scar assessment, CRT response prediction improved beyond that by either echocardiography or scar parameters alone
Warriner DR ⁴²	2018 [114]	Prospective single center study	50	69.3 ± 11.2	78	23	6	46	N/A	N/A	N/A	25	23	Decrease of ≥ 15% in LVESV (thicker walls in the lateral and basal regions) in the pre-implant left ventricular shape, was an independent predictor of response to CRT
White JA ⁴³	2006 [115]	Prospective single center study	23	64.9 ± 11.7	65	12	3	19	27 ± 10.6 in WMS and 22 ± 9.7 in CMR	N/A	LGE—segmented inversion-recovery pulse sequence—2SD method—Osirix, version 1.7.1, 2005	13	10	Improvement in LVEF; Improvement in 6MWD; Improvement of ≥ 1 NYHA class; Decrease of ≥ 10 in Minnesota Living with Heart Failure score A total scar burden of 15% or a percent septal scar of 40% accurately identified patients with a clinical response to CRT
Yokokawa M ⁴⁴	2009 [116]	Prospective single center study	24	66 ± 8	75	7	6	N/A	28 ± 12 in CMR	N/A	Inversion-recovery gradient echocardiographic sequence Scar: DE was observed in > 1 slice and the intensity of the DE region was > 6 SD above the mean intensity of a remote myocardial region	13	10	Increase of ≥ 5% in LVEF; Decrease of ≥ 15% in LVESV; Both; Improvement of ≥ 1 NYHA class; No hospitalizations for HF By CMR imaging in the DCM group, the percentage of regional scar segments and percentage of regional scar score in the left ventricular inferior wall were significantly higher in CRT non-responders than in responders

Table 1 (continued)

First author	Year	Design	N	Age (years)	Males (%)	ICM	Follow-up (months)	LBBB	LVEF (%)	SR	Method for scar evaluation	Responders	Non-Responders including deaths	Outcomes
Zweerink A ⁴⁵	2018 [117]	Prospective multi-center study	27	65 ± 9	58	7	12	21	27 ± 9 in CMR	N/A	N/A	17	10	Decrease of ≥ 15% in LVESV Measures of dyssynchrony (SD-TT _{LV}) and discoordination (ISF _{LV}) were strongly related to CRT response when using MT. ESSsep was consistently correlated with LVESV change for all techniques
Zweerink A ⁴⁶	2021 [118]	Prospective multi-center study	57	65 ± 10	53	13	12	45	28 ± 10 in CMR	N/A	LGE imaging—infarct size was measured using the full width at half maximum method—QMassMR version 7.6, Medis, Leiden, The Netherlands	43	14	Decrease of ≥ 15% in LVESV Segment length in cine strain analysis could be used for the prediction of CRT response. ESSsep was strongly correlated with reverse remodeling after CRT
Linhart M ⁴⁷	2020 [119]	Prospective multi-center study	218	64.9 ± 10.7	73	79	45	N/A	25.5 ± 6.6	N/A	LGE—segmented two-dimensional (2D) inversion-recovery gradient-echo sequence	127	91	Decrease of ≥ 15% in LVESV at 12-month follow-up The presence of myocardial scar was significantly less prevalent in patients with CRT response as compared to non-response. A significant positive correlation was found between myocardial scar mass and the evolution of LVESV at 12-month follow-up

6MWD: 6-min walking distance; BNP: B-type natriuretic peptide; CM: cardiomyopathy; CMR: cardiac magnetic resonance; CRT: cardiac resynchronization therapy; CURE: circumferential uniformity ratio estimate; CURE-SVD: circumferential uniformity ratio estimate computed with singular value decomposition; DCM: dilated cardiomyopathy; DENSE: displacement encoding with stimulated echoes; DEMRI: delayed gadolinium-enhanced magnetic resonance imaging; EP: electrophysiology; ESSsep: end-systolic septal strain; HF: heart failure; ICM: ischemic cardiomyopathy; LBBB: left bundle branch block; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume; LVP: left ventricular lead position; LVRR: left ventricular reverse remodeling; MACE: major adverse cardiovascular event; MRI: magnetic resonance imaging; MR-MT: magnetic resonance-myocardial tagging; MT: myocardial tagging; MWHE: midwall hyperenhancement; NYHA: New York Heart Association; RVEF: right ventricular ejection fraction; STE: speckle tracking echocardiography; TOS: time to the onset of circumferential shortening; WMS: wall motion scoring

LGE $\geq 14\%$ is associated with non-response, defined as no death or hospitalization for a major cardiovascular event, and a significant decrease in left ventricular end-systolic volume of 15% or more in a study with mixed ischaemic and non-ischaemic patients [29]. The percent of LGE was higher, regional vector of circumferential strain variance was lower, and uniformity of radial strain was higher in nonresponders vs. responders [30]. The same study showed that transmural LGE was an important predictor of lack of response to CRT in ischaemic HF [30]. In a prospective database of patients, it was found that the presence of subendocardial scar on CMR predicted CRT clinical non-response but was not associated with echocardiographic response [10]. Another study which aimed to investigate the role of the delayed enhancement MRI in predicting CRT response showed that a total scar of 15% or septal scar of 40% accurately identified patients with clinical response to CRT [31]. Similarly, in another observational study, the percentage of responders tended to be lower among patients with identifiable areas of delayed enhancement on CMR while scar mass and scar as a percentage of LV myocardium were not significantly different between responders and nonresponders [32].

Scar quantification can have an incremental value in the prediction of CRT response. In this setting, incorporating scar quantification to QRS duration and presence of LBBB was found to improve the prediction of CRT response [33]. The same study also found that an increase in scar burden was associated with worse outcomes in any location [33]. Native T1 mapping and extracellular volume have also been associated with poor response, while Scar2SD and Gray2SD markers of focal scar core were substantially better at predicting CRT response [34]. By combining QRS area and CMR focal scar assessment, CRT response prediction improves beyond that by either vectorcardiography or scar parameters alone [34].

The impact of scar in the left ventricular pacing site on CRT response

Scar in the left ventricular pacing site has been associated with adverse outcomes following CRT implantation [15]. Interestingly, the chronic response has been found to be significantly better in patients paced in a CMR target segment [35]. Pacing in the scar-free segments was found to lead to a greater reverse remodeling [16]. CMR-guided lead placement has been associated with significantly better clinical response rates compared to electrophysiological-guided placement in patients with more advanced HF [36]. However, in another study, left ventricular reverse remodeling was less pronounced in the CMR-guided and pacing scar group than in the non-CMR-guided group [37]. In the CMR-guided and non-pacing scar group, a scar burden of $< 10\%$ was not associated with a better LV reverse remodeling or clinical response compared with a scar burden of $\geq 10\%$ [37].

Scar presence, total scar extent, transmural scar, and positioning the left ventricular lead in a branch of the coronary sinus that corresponds to an area with transmural scar were associated with non-response to CRT. Interestingly, the non-transmural scar was not associated with CRT response [38]. Another study showed that the presence of septal scar was associated with a poor acute and chronic response to CRT in ischaemic cardiomyopathy patients. At the same time, this finding may be related to the inability to achieve a right ventricular septal lead placement [39]. Beyond the impact on CRT response, a myocardial scar in the region of the left ventricular pacing lead has been associated with worse long-term survival in ischaemic heart failure patients treated with CRT [40]. A left ventricular lead position over a segment with scar emerged has also been found to be a strong predictor of cardiac mortality and cardiac mortality or HF hospitalizations [41].

On the other hand, results of another prospective study showed that pacing outside of scar compared to pacing within scar did not result in a significant improvement in clinical composite score or reduction in left ventricular end-systolic volume [10]. However, it should be noted that most patients in this study had a subendocardial scar.

A multimodality cardiac imaging using speckle tracking echocardiography and CMR imaging to guide CRT implantation was found to increase the response rates [42]. These findings highlight the potential use of CMR in guiding the LV lead placement during CRT implantation procedure.

Other variables

Combined CMR scar and dyssynchrony imaging prior to CRT identified those patients who subsequently had a clinical response to CRT [43]. A systolic dyssynchrony index derived from volume change can predict reverse remodeling following CRT while a 16-segment systolic dyssynchrony index of regional strain did not [44]. Measures of dyssynchrony ($SD-TTP_{LV}$) and discoordination (ISF_{LV}) were strongly related to CRT response when using myocardial tagging [45]. The end-systolic septal strain parameter showed a consistent high correlation with LVESV change for all techniques [45]. Magnetic resonance myocardial tagging (MR-MT) assessment of circumferential mechanical dyssynchrony was found to achieve an excellent predictive value for clinical response following CRT. At the same time, its accuracy could be further improved by combining MR-MT with scar imaging by delayed enhancement magnetic response imaging [46]. Circumferential uniformity ratio estimate, delayed circumferential contraction onset at left ventricular lead position, absent left ventricular lead position scar, and time from QRS onset to left ventricular lead position electrogram have been associated with echocardiographic response [47]. Recently, circumferential uniformity ratio estimated with singular value decomposition with Displacement

Encoding with Stimulated Echoes strain imaging was significantly correlated with echocardiographic CRT response [48]. Septal flash predicted increased response to CRT while the presence of septal flash with no scar was a highly specific predictor of CRT response [49]. The left ventricular dyssynchrony and interventricular dyssynchrony were significantly longer in responders, while it was found that the use of the optimal cutoff of left ventricular dyssynchrony ≥ 65 ms can differentiate CRT responders from nonresponders with a sensitivity and a specificity of 100% [50].

On the other hand, internal stretch fraction, defined as the ratio of stretch to shortening during ejection, has been found to differ significantly between responders and nonresponders [46] significantly. The findings of this study show that discoordination rather than dyssynchrony can predict the reserve contractile capacity recruited by CRT [51]. An observational study showed that LV shape might play a role in selecting CRT patients [52]. Specifically, it was revealed that nonresponders had a relatively shorter septal wall and longer lateral wall, while in responders, thicker walls in the lateral and basal regions were revealed compared with nonresponders [52]. Time to the onset of circumferential shortening (TOS)/QRS, scar at the LV pacing site, and circumferential uniformity ratio estimate calculated using singular value decomposition have been found to be significantly associated with the change in LVESV 6 months after CRT [53]. Furthermore, the regional vector of strain variance and uniformity of radial strain was found to be lower in nonresponders than responders [30]. In patients with non-ischaemic cardiomyopathy, a wide pattern of systolic left ventricular volume/time curves measured using CMR was significantly associated with CRT response compared to patients with a narrow pattern [54]. Summed maximum vortex flow can predict CRT response in DCM, while circumferential temporal delay and longitudinal temporal delay were not associated with CRT response [55]. Furthermore, a standard deviation of 16-segment time-to-peak radial thickness was significantly larger in responders compared with nonresponders [38]. Segment length in cine strain analysis can be used for the prediction of CRT response [56]. Specifically, of all parameters, the end-systolic septal strain showed the strongest correlation with reverse remodeling after CRT [56]. In patients with strict LBBB and with an indication of CRT implantation, a “U-shaped” contraction pattern was found to be strongly predictive for reverse remodeling and super-response [57]. Additionally, a “U-shaped” wall motion pattern compared to a homogenous (type I) wall motion pattern and a concordant LV lead can predict CRT response [44, 58]. These findings may help to improve patient selection by evaluating wall motion pattern and targeting LV lead placement.

The right ventricular function may have a significant role in predicting response following CRT implantation.

Specifically, right ventricular dysfunction evaluated by CMR has been significantly associated with non-response to CRT. At the same time, the same study showed that late enhancement presence, lateral wall fibrosis, and the percentage of LV fibrosis were not associated with CRT response [59]. Likewise, another small retrospective study confirmed these results showing that except myocardial scar burden, CMR-derived right ventricular dysfunction was an independent predictor of non-response and adverse outcomes in patients on CRT [60].

Discussion

This systematic review shows the additive role of CMR in the selection of potential CRT candidates and the CMR role in guiding the left ventricular lead placement away from areas of transmural scar, for achieving a better outcome. Furthermore, we confirm that for individuals with high burden of myocardial scar there is less likelihood of having a good response. CRT is mainly recommended in patients with HF and LVEF $\leq 35\%$ in sinus rhythm who have a QRS duration ≥ 130 ms and remain symptomatic despite optimal medical therapy. Additionally, CRT may be considered in patients with HF and LVEF $\leq 35\%$ in AF who have a QRS duration ≥ 130 ms and remain in New York Heart Association (NYHA) class III or IV despite optimal medical therapy, provided biventricular capture can be ensured or the patient is expected to return to sinus rhythm [61]. Occasionally, CRT may be used as an upgrade from a conventional pacemaker or an ICD in patients with HF_rEF who develop worsening HF attributable to a high rate of right ventricular pacing [61]. Although it has been shown that CRT improves cardiac function, symptoms, and quality of life, as well as it reduces morbidity and mortality in appropriately selected patients with HF_rEF, not all patients who have an indication for CRT according to current guidelines respond favourably to this therapeutic modality [61]. Therefore, novel imaging techniques such as CMR that can assess additional factors to LVEF including myocardial scar, cardiac dyssynchrony, and site of latest activation of the LV are increasingly being studied as utilities for the better selection of patients appropriate for CRT, as well as for optimal lead placement [61]. While identification of areas of myocardial scar can guide the branch positioning of the left ventricular lead in the coronary sinus, it should also be appreciated that complex venous anatomy might prevent pacing the optimal scar-free area [62].

It is already known that the type of cardiomyopathy is a significant predictor of CRT response. Most of the included studies in this review consisted mainly of a mixed population. However, six studies [14, 16–19, 23] included ischaemic cardiomyopathy patients and one study [55] included only dilated cardiomyopathy patients. In ischaemic

cardiomyopathy patients, a posterolateral scar imaged using LGE-CMR was an independent predictor of cardiovascular death or hospitalizations for HF [18]. Furthermore, scar size of 33%, transmural of 51%, and pacing over a posterolateral scar were associated with a suboptimal response to CRT in ischaemic cardiomyopathy patients [17, 19]. Scar burden has also been associated with higher non-response rates in the setting of ischaemic HF [14, 23]. Additionally, LV reverse remodeling following CRT implantation was affected by the total left ventricular scar burden [16]. In the setting of dilated cardiomyopathy, summed maximum vortex flow has been found to predict CRT response [55].

According to our systematic literature review, both the presence and burden of scar as identified by CMR, as well as scar in certain locations, may be useful markers of non-response to CRT. Focal scar burden identified by LGE in CMR, numerically represented by the total scar burden score and/or the number of transmurally infarcted segments, has been shown to be a good marker of poor CRT response. Furthermore, the presence of either any septal scar or increased lateral wall scar burden was associated with less induction of reverse ventricular remodeling, while reports regarding scar in the posterolateral area are mixed, and LV dyssynchrony seems to remain the most important determinant of response to CRT, even in the presence of posterolateral scar. Of note, the combined assessment of septal viability and lateral wall to septal work difference has been reported to be a better marker of CRT response than work difference alone, and regional vector of circumferential strain variance was lower, and uniformity of radial strain was higher in nonresponders. By combining scar quantification and QRS duration in the setting of LBBB, or QRS area and CMR focal scar assessment, CRT response prediction significantly improved. Even further, the available evidence summarized in this review suggests that CMR may have an ancillary role in guiding the LV lead placement during CRT implantation procedure. Indeed, pacing in the scar-free segments has been shown to induce reverse remodeling to a greater extent, and CMR-guided lead placement has been associated with a better chronic response and higher BNP response rates. Additionally, pacing over a transmural scar has been associated with non-response to CRT, and pacing over a myocardial scar in the region of the left ventricle has been associated with worse long-term survival in ischaemic heart failure patients treated with CRT, and may portend a worse prognosis with regard to cardiac mortality and/or HF hospitalizations. However, CMR-guided lead placement has not been found to be superior to electrophysiologically guided procedures in some studies, and therefore further research is needed before reaching definitive conclusions. Finally, other CMR modalities such as dyssynchrony and strain imaging, as well as discoordination measures may also have an additive role on CRT candidate selection.

Except for chronic CRT response outcome, acute response following CRT implantation is another outcome of interest. CMR-identified scar had been found to predict acute CRT response adversely [63]. Specifically, septum-to-lateral wall myocardial work ratio at baseline is significantly related to acute response to CRT defined as acute left ventricular pump function improvement [64]. Furthermore, it has been found that pacing within scar on electroanatomic mapping and CMR (both epicardial and endocardial positions) resulted in failure to capture and a poor acute hemodynamic response [65]. Interestingly, patients with a postero-lateral scar as identified on CMR can be benefited from a multi-site left ventricular pacing as it can increase acute response by 16% compared to single-site pacing [65].

Beyond the role of CMR in predicting CRT response, it can be used to predict clinically important outcomes during follow-up. Specifically, the presence and size of myocardial scar have been associated with malignant arrhythmic events irrespective of CRT response [27]. Additionally, the presence of myocardial scar has been associated with all-cause mortality [27], while myocardial dyssynchrony assessed by CMR-tissue synchronization index was an independent predictor of mortality and morbidity after CRT [66]. An index derived by a combination of dyssynchrony, posterolateral scar location, and creatinine has been significantly associated with cardiovascular mortality [67].

As already discussed, pacing in the scar-free segments has led to a greater reverse remodeling and better long-term survival [16, 40]. Overlaying the CMR and CT dataset onto live fluoroscopy during left ventricular lead placement is a feasible technique that may lead to a greater reverse remodeling during follow-up [68]. A double-blind, randomized controlled trial showed the clinical benefit of multimodality imaging-guided left ventricular lead placement in CRT [69]. Specifically, it was found that imaging-guided LV lead placement using cardiac computed tomography venography, 99mTechnetium myocardial perfusion imaging, and speckle-tracking echocardiography radial strain reduced the number of clinical nonresponders [69]. However, a recent randomized study failed to demonstrate the benefit of the evaluation of delayed activation on echocardiography combined with anatomic information from computed tomography (coronary sinus tributary anatomy) and CMR (large scar preventing lead placement) in terms of clinical, echocardiographic response or in a significant reduction of death or heart failure hospitalization [70].

Several echocardiographic and clinical definitions of CRT response have been used to assess the efficacy of CRT [71]. CMR has also been used to evaluate CRT response, providing very high-quality data on the right/left ventricular function and strain/synchrony before and after CRT [72].

This systematic literature review has several potential limitations. Firstly, our results were derived from

observational studies, which are subject to selection biases and have a limited ability to determine causality. In addition, populations were heterogeneous between the studies which prevented reaching definitive conclusions. Furthermore, as all the studies included patients who fulfilled the clinical guideline criteria for a CRT, we were unable to review non-traditional criteria such as pacing-induced cardiomyopathy. Finally, the included studies provided dissimilar CMR data and how the scar was quantified and therefore a quantitative synthesis was not feasible.

Conclusions

The clinical significance of CMR is to identify scar regions that should be avoided during the coronary sinus LV lead implantation. Furthermore, CMR can be used as an optimization tool for identifying those patients with extensive myocardial scar who might achieve a sub-optimal clinical and echocardiographic response following CRT implantation. However, further research is needed to elucidate the role of CMR in predicting important outcomes in CRT patients.

Declarations

Conflict of interest The authors declare no competing interests.

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