Left ventricular reverse remodelling and its predictors in non-ischaemic cardiomyopathy

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Abstract

Adverse remodelling following an initial insult is the hallmark of heart failure (HF) development and progression. It is manifested as changes in size, shape, and function of the myocardium. While cardiac remodelling may be compensatory in the short term, further neurohumoral activation and haemodynamic overload drive this deleterious process that is associated with impaired prognosis. However, in some patients, the changes may be reversed. Left ventricular reverse remodelling (LVRR) is characterized as a decrease in chamber volume and normalization of shape associated with improvement in both systolic and diastolic function. LVRR might occur spontaneously or more often in response to therapeutic interventions that either remove the initial stressor or alleviate some of the mechanisms that contribute to further deterioration of the failing heart. Although the process of LVRR in patients with new-onset HF may take up to 2 years after initiating treatment, there is a significant portion of patients who do not improve despite optimal therapy, which has serious clinical implications when considering treatment escalation towards more aggressive options. On the contrary, in patients that achieve delayed improvement in cardiac function and architecture, waiting might avoid untimely implantable cardioverter-defibrillator implantation. Therefore, prognostication of successful LVRR based on clinical, imaging, and biomarker predictors is of utmost importance. LVRR has a positive impact on prognosis. However, reverse remodelled hearts continue to have abnormal features. In fact, most of the molecular, cellular, interstitial, and genome expression abnormalities remain and a susceptibility to dysfunction redevelopment under biomechanical stress persists in most patients. Hence, a distinction should be made between reverse remodelling and true myocardial recovery. In this comprehensive review, current evidence on LVRR, its predictors, and implications on prognostication, with a specific focus on HF patients with non-ischaemic cardiomyopathy, as well as on novel drugs, is presented.

Keywords Heart failure; Non-ischaemic cardiomyopathy; Predictors; Reverse remodelling; Left ventricular reverse remodelling; Cardiac remodelling

Introduction

Adverse remodelling following an initial insult is the hallmark of heart failure (HF) development and progression that leads to clinical deterioration, impaired prognosis, and, ultimately, death. It is defined as abnormalities in genome expression, molecular, cellular, and interstitial transformations that are manifested as changes in size, shape, and function of the myocardium. While it has been initially described in patients in whom ventricular dilation after transmural myocardial infarction was observed, similar observations could be made in non-ischaemic cardiomyopathy (NICM) irrespective of aetiology, for example, genetic mutations in hereditary dilated cardiomyopathy (DCM), myocarditis, alcohol or cardiotoxic exposure, and tachycardia induced. In the past two decades, it has been shown that this deleterious process driven by further neurohumoral activation and haemodynamic overload is not irreversible and that it could be reversed. Despite recent advances in HF therapies with a possible effect on cardiac remodelling, many issues remain unresolved. Here, we review the current evidence on left ventricular reverse...
remodelling (LVRR), its predictors, and implications on prognostication in patients with NICM.

Reverse remodelling

The term ‘reverse remodelling’ was first introduced by Kass et al., who observed reductions in end-diastolic volumes (EDV) and increased ejection fraction of the left ventricle (LVEF) in a series of patients with idiopathic DCM following a cardiomyoplasty procedure.4 In general, LVRR can be characterized as a decrease in chamber volume and normalization of shape associated with improvement in both systolic and diastolic function. There is a large heterogeneity in the definition of LVRR (for summary, see Table 2). Many of the studies rely on echocardiography5–8 or cardiac magnetic resonance (CMR),9 and LVRR is most often defined as an increase in LVEF ≥ 10%6,7,9,10 and/or its normalization (≥50%) accompanied by indexed left ventricular diameter reduction > 10%5,9,10 and/or its normalization (≤33 mm/m²).

It is important to note that most changes take place at the microscopic level and manifest as a reversal in increased fibrosis of extracellular matrix, restoration of cellular energetics, and metabolic properties, as well as a shift in gene expression of the myocardium11—changes that are challenging to observe and study in detail (for summary, see Table 2). Limited data are available from tissue samples of patients undergoing left ventricular support device explantation during heart transplant or following sufficient recovery.12–15 In one of the landmark studies of transcriptome analysis, Margulies et al. have shown that while expression of as many as 3000 genes is changed in advanced HF, the expression of only 5% of those genes tends to normalize in association with left ventricular assist device (LVAD) unloading.14 Similar persistent transcriptional abnormalities were observed in 16 paired tissue samples before and after LVAD support (eight of which were from patients with NICM).16 In addition, Yang et al. have shown that long non-coding RNA expression profiles show significant differences in ischaemic and non-ischaemic HF and when compared with mRNA and microRNA profiles, they also show the most apparent shift in response to mechanical unloading.16 All these data suggest that reverse remodelled hearts continue to have abnormal features. Therefore, it is important to distinguish between reverse remodelling and true myocardial recovery. As Mann et al. suggested, the term myocardial recovery represents a successful and complete reversal of HF phenotype that is associated with freedom from future HF events and that could, they speculate, only be achieved in the myocardium that has not yet suffered irreversible damage (Figure 2). This statement is supported by the observation from the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) where the highest rate of myocardial recovery allowing LVAD explantation was observed in patients with myocarditis and post-partum cardiomyopathy18—aetiologies of injury that are classically considered transient in comparison with long-lasting, permanent abnormality seen in genetically mediated cardiomyopathy. In fact, <1.5% of patients with DCM recover enough to undergo LVAD explant.19 Taken together, reverse remodelled hearts continue to show susceptibility for more profound malfunction when undergoing mechanical or biological stress, one that would normally be well tolerated.17

Pharmacological reverse remodelling

Left ventricular reverse remodelling might occur spontaneously or more often in response to therapeutic interventions that either remove the initial stressor or alleviate some of the mechanisms that contribute to further deterioration of the failing heart, such as activation of the renin-angiotensin-aldosterone and adrenergic nervous systems.1 Numerous large placebo-controlled trials of drugs that are the cornerstone of guideline-directed HF therapy20 have demonstrated a positive effect on mortality. A portion of these studies that provide serial measurements of LVEF and diameters indicating the effect of pharmacotherapy on LVRR will be discussed.

| Reference | Number of patients | Time of evaluation (months) | LVRR definition |
|-----------|--------------------|-----------------------------|-----------------|
| Echocardiography |                         |                             |                 |
| Merlo et al.5 | 361 patients with idiopathic DCM | 24                          | LVEF increase ≥ 10% or LVEF ≥ 50% |
| Chung et al.6 | 498 HFrEF patients (267 with NICM) | 6                           | LVEDD decrease ≥ 10% or iLVEDD ≤ 33 mm/m² |
| Wilcox et al.7 | 3994 HFrEF patients (1421 with NICM) | 24                          | LVEESV reduction ≥ 15% |
| Brenyo et al.8 | 612 HFrEF patients (283 with NICM) | 12                          | LVEF increase > 10% |
| Cardiac magnetic resonance |                         |                             |                 |
| Masci et al.9 | 58 patients with idiopathic DCM | 24                          | LVEF increase ≥ 10% or LVEDV decrease ≥ 10% |

DCM, dilated cardiomyopathy; HFrEF, heart failure with reduced ejection fraction; iLVEDD, indexed left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVEESV, left ventricular end-systolic volume; LVRR, left ventricular reverse remodelling; NICM, non-ischaemic cardiomyopathy.
below. In contrast with previous reviews on this topic,\textsuperscript{21–23} we will specifically focus on NICM as well as on novel drugs that have been recently introduced.

**Beta-blockers**

Beta-adrenergic blocking agents are strongly associated with LVRR. In a meta-analysis of 88 randomized control trials (RCTs) including 19 741 patients, which evaluated the effect of 25 drug or device therapies on LVRR, changes in left ventricular volumes and LVEF were apparent the most in groups treated with various beta-blockers (BB).\textsuperscript{24} After 6 months of treatment, metoprolol succinate was associated with an 8.8% increase in LVEF, as Goldstein et al. have shown in a small trial of 61 patients, of whom more than 60% presented with NICM.\textsuperscript{25} Anti-remodelling effects of metoprolol were demonstrated in the CMR substudy of MERIT-HF where significant reductions in indexed left ventricular end-systolic volume (ESV) and EDV were found.\textsuperscript{26} Comparable results with no significant differences between non-ischaemic and ischaemic groups were presented in the RESOLVD pilot II study\textsuperscript{27} and the REVERT trial observed akin findings in 149 asymptomatic patients with only mild systolic dysfunction.\textsuperscript{28} Moreover, the amount of remodelling appeared to be dose dependent.\textsuperscript{28} Studies with other BB have brought similar

| Initial insult       | LVRR induced by       | Molecular and cellular changes                                                             | Structural and functional phenotypes                              |
|----------------------|-----------------------|---------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| Genetic mutation     | Spontaneously         | Reversal of cell hypertrophy\textsuperscript{117,118}                                      | Normalization of chamber geometry                                 |
| Inflammation         | Pharmacotherapy       | Improved contractility\textsuperscript{115}                                               | Increased ejection fraction                                       |
| Cardiotoxicity       | Resynchronization therapy | Changes in collagen content\textsuperscript{13}                                           | Reduced volumes and diameters                                     |
| Abnormal energetics  | Mitral valve repair   | Ca\textsuperscript{2+} metabolism\textsuperscript{115,116}                                 | Leftward shifts in EDPVR                                          |
| Mechanical/biological stress | LVAD                | β-Adrenergic responsiveness\textsuperscript{13,114}                                        | ↓ Functional mitral regurgitation                                 |
|                      |                       | Reduced apoptosis/necrosis\textsuperscript{122}                                             |                                                                   |

EDPVR, end-diastolic pressure–volume ratio; LVAD, left ventricular assist device; LVRR, left ventricular reverse remodelling.

**Figure 1** This figure represents the cycle of cardiac adverse and reverse remodelling. Spontaneous or therapy-driven left ventricular reverse remodelling might lead to complete myocardial recovery, but most often leads to the phenotype of myocardial remission, in which many abnormal characteristics of the myocardium persist. Susceptibility to future heart failure events is illustrated by a dashed grey arrow. [Created with BioRender.com.]
results. A small RCT of 48 highly symptomatic patients with idiopathic DCM compared treatment with carvedilol vs. placebo over 12 months. Carvedilol significantly reduced end-diastolic diameter (EDD) (40 ± 4 to 41 ± 4 mm/m² in placebo arm vs. 38 ± 5 to 36 ± 4 mm/m², \( P = 0.001 \)) as well as end-systolic diameter (ESD) (31 ± 5 to 31 ± 4 mm/m² in placebo arm vs. 30 ± 3 to 28 ± 4 mm/m², \( P = 0.01 \)) of the left ventricle, with observed improvement in LVEF (29 ± 5% to 30 ± 6% in placebo arm vs. 27 ± 8% to 35 ± 6%, \( P = 0.01 \)). These data were confirmed in the PRECISE and MOCHA trials, two large multicentre double-blind, placebo-controlled studies of carvedilol. In addition, observations from the MOCHA trial suggest a dose-dependent effect on LVRR. LVRR is far less clear. The SOLVD trial was a large multicentre, randomized, placebo-controlled RCT of 2569 patients treated either with enalapril or placebo. Both the echocardiography substudy and the radionuclide ventriculography and catheterization substudy showed significant differences in change of left ventricular volumes during serial measurements between active treatment and placebo groups (\( P = 0.025 \) and \( P = 0.008 \) for EDV and \( P = 0.019 \) and \( P = 0.002 \) for ESV, respectively). However, while Konstam et al. observed significant reductions in EDV (140 ± 44 to 127 ± 37 mL/m², \( P = 0.02 \)) and ESV (106 ± 42 to 93 ± 37 mL/m², \( P = 0.01 \)), as well as an increase in LVEF (25 ± 7% to 29.8%, \( P = 0.01 \)) after 1 year study period, no significant change in the aforementioned parameters was seen in the echo substudy. Also, no change in EDV was observed after 12 months of treatment with captopril in a small, single-centre RCT of 50 patients followed up by echocardiography. Finally, when effects of captopril and carvedilol in 57 patients (mainly with ICM) were directly compared, treatment with captopril increased LVEF to a significantly lesser extent (4.74% vs. 1.46%, \( P = 0.01 \)) with no discernible change in ESV. When combined, a further increase in LVEF was achieved. To make these observations more relevant to the NICM population, the MOCHA trial showed a trend towards greater efficacy of carvedilol on left ventricular function in ACE inhibitor-treated HF patients with NICM compared with ICM. These data suggest that ACE inhibition prevents further remodelling (as previously demonstrated in numerous studies following patients after myocardial infarction), although it may not drive the reversal of such a process in developed HF.

Evidence for the anti-remodelling effect of angiotensin II receptor antagonists appears to be more promising. Val-HeFT echocardiographic substudy examined the effect of valsartan vs. placebo in addition to treatment with BB and/or ACE inhibitor in 5010 symptomatic HF patients (of whom more than 40% had NICM) and found out that valsartan lead to a significant decrease in left ventricular EDD (\(-1.2 ± 4 \text{ mm vs. } -0.5 ± 4 \text{ mm/m²}, P = 0.00001\)), which was accompanied by a significant increase in LVEF (4.5 ± 8.9% vs. 3.2 ± 8.6%, \( P = 0.00001 \)). Matsumori et al. investigated 6 month treatment with candesartan in a multi-centre, double-blind RCT of 305 patients (including 166 patients with DCM). There was a significant change in left ventricular ESD (\(-6.2 ± 11.7 \% \text{ vs. } -2.0 ± 12.2\%, P = 0.07 \)) and LVEF (23.8 ± 46.0% vs. 8.4 ± 34.4%) and no difference in left ventricular EDD (\(-2.4 ± 9.2 \% \text{ vs. } -0.8 ± 9.0\%, P = 0.15 \)). However, the study was terminated prematurely and based on the observations that more profound LVRR occurs after a longer time period, it is possible that the effect was not fully expressed at the end of follow-up.

The first study that investigated the anti-remodelling effect of a mineralocorticoid receptor antagonist was conducted by Tsutamoto et al., who showed improvement in left ventricular volumes and function after 4 month treatment with spironolactone in patients with NICM. These results were confirmed in a larger RCT of a mixed HF population, in which serial echocardiographic measurements were available at baseline and 12 months after randomization in 93 patients (\( P < 0.01 \) for both increase of LVEF and reduction in left ventricular volumes). Whether a combination therapy of candesartan and spironolactone over a longer time induces further LVRR was studied by Chan et al. in an RCT of 52

**Renin-angiotensin-aldosterone inhibition**

The role of angiotensin-converting enzyme (ACE) inhibitors in LVRR is far less clear. The SOLVD trial was a large multi-centre, randomized, placebo-controlled RCT of 2569 patients treated either with enalapril or placebo. Both the echocardiography substudy and the radionuclide ventriculography and catheterization substudy showed significant differences in change of left ventricular volumes during serial measurements between active treatment and placebo groups (\( P = 0.025 \) and \( P = 0.008 \) for EDV and \( P = 0.019 \) and \( P = 0.002 \) for ESV, respectively). However, while Konstam et al. observed significant reductions in EDV (140 ± 44 to 127 ± 37 mL/m², \( P = 0.02 \)) and ESV (106 ± 42 to 93 ± 37 mL/m², \( P = 0.01 \)), as well as an increase in LVEF (25 ± 7% to 29.8%, \( P = 0.01 \)) after 1 year study period, no significant change in the aforementioned parameters was seen in the echo substudy. Also, no change in EDV was observed after 12 months of treatment with captopril in a small, single-centre RCT of 50 patients followed up by echocardiography. Finally, when effects of captopril and carvedilol in 57 patients (mainly with ICM) were directly compared, treatment with captopril increased LVEF to a significantly lesser extent (4.74% vs. 1.46%, \( P = 0.01 \)) with no discernible change in ESV. When combined, a further increase in LVEF was achieved. To make these observations more relevant to the NICM population, the MOCHA trial showed a trend towards greater efficacy of carvedilol on left ventricular function in ACE inhibitor-treated HF patients with NICM compared with ICM. These data suggest that ACE inhibition prevents further remodelling (as previously demonstrated in numerous studies following patients after myocardial infarction), although it may not drive the reversal of such a process in developed HF.

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ambulatory HF patients (of whom 21 had NICM) using serial CMR imaging. After a 12 month treatment period, there was a significant decrease in both indexed left ventricular EDV (154.68 ± 14.21 to 121.10 ± 15.76 mL/m² in the combination group vs. 138.03 ± 10.29 to 135.13 ± 10.60 mL/m² in the candesartan-only group, \( P = 0.01 \)) and ESV (120.30 ± 14.74 to 88.14 ± 17.10 mL/m² vs. 101.96 ± 9.42 to 97.51 ± 10.16 mL/m², \( P = 0.01 \)), accompanied by an increase in LVEF (26 ± 2% to 35 ± 3% vs. 28 ± 2% to 31 ± 2, \( P = 0.03 \)). Only one study assessing the effect of eplerenone on ventricular remodelling in chronic HF is available. Udelson et al. conducted a double-blind RCT of 226 patients assigned to either eplerenone or placebo and showed no significant change in function or volumes of the left ventricle.\(^{46} \)

All of these data were encompassed in a meta-analysis of 19 trials including 2053 HF patients, which found a beneficial effect of mineralocorticoid receptor antagonists (spironolactone, eplerenone, or canrenoate) on reduction of left ventricular EDV and ESV as well as on the improvement of LVEF.\(^{47} \)

### Angiotensin receptor-neprilysin inhibitor

The introduction of angiotensin receptor-neprilysin inhibitor sacubitril/valsartan into chronic HF management is one of the most important milestones in the past decade. In the PARADIGM-HF trial, when compared with enalapril, sacubitril/valsartan reduced mortality and risk of HF hospitalizations in patients with guideline-directed optimal medical therapy.\(^{48} \)

Whether this effect is conveyed by LVRR was evaluated in several studies. After sacubitril/valsartan initiation, Martens et al. observed a significant improvement in LVEF (29.6 ± 6% to 34.8 ± 6, \( P < 0.001 \)) as well as a decrease in left ventricular volumes (147 ± 57 to 129 ± 55 mL in ESV, \( P < 0.001 \) and 206 ± 71 to 197 ± 72 mL in EDV, \( P = 0.027 \)) in 125 symptomatic HF patients (of whom 45% presented with NICM) over a median follow-up of 4 months.\(^{49} \)

Similar findings were reported in 654 patients with HF with reduced ejection fraction (HFrEF) and 12 month echocardiographic follow-up. LVEF increased by 5.2% (95% confidence interval [CI], 4.8% to 5.6%, \( P < 0.001 \)) at 6 months to a total increase of 9.4% (95% CI, 8.8% to 9.9%, \( P < 0.001 \)) with a corresponding decrease in indexed left ventricular volumes at 1 year.\(^{50} \)

Furthermore, 25% of patients achieved an absolute increase in LVEF of more than 13%, all being treated by sacubitril–valsartan on top of contemporary guideline-directed therapy.\(^{50} \)

Among the 371 consecutive patients with HF [mean baseline LVEF of 27.8% (22.9–33.1), 67.5% with non-ischaemic origin] treated with sacubitril/valsartan, 60.9% achieved LVRR defined as a composite of an improvement in LVEF to ≥45% or a reduction in ESV by ≥15% from baseline.\(^{51} \)

Only one randomized, double-blind remodelling study comparing sacubitril/valsartan in addition to standard medical therapy of HF is available. In the PRIME study, in which 118 patients with severe HF and chronic functional mitral regurgitation were assigned to sacubitril/valsartan or valsartan alone and followed for 12 months, there was a significant difference in indexed left ventricular EDV change (−11.8 ± 17.3 to −4.8 ± 19.9, \( P = 0.04 \)) in the sacubitril/valsartan group while there was no significant change in LVEF in both groups.\(^{52} \)

These data confirm the beneficial role of angiotensin receptor-neprilysin inhibitor therapy in the LVRR process, and similar to other aforementioned studies,\(^{28,31,44} \) this effect seems to be dose dependent.\(^{49} \)

### Sodium-glucose cotransporter 2 inhibition

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors reduce the risk of HF development in patients with type 2 diabetes,\(^{53} \)

but, more importantly, they diminish the risk of HF hospitalizations and death in HF patients both with and without diabetes.\(^{48,54} \)

The underlying mechanism of action is not fully understood and whether it includes the induction of LVRR is not known. Currently, there is a paucity of evidence regarding this topic. We identified only two trials, both assessing the potential anti-remodelling effect by CMR. The REFORM trial, a small RCT of 56 patients with type 2 diabetes and HF, investigated the effect of 12 month treatment with dapagliflozin on LVRR and observed no significant difference in volumes or function of the left ventricle.\(^{55} \)

A larger RCT studied empagliflozin in 105 patients with HFrEF (of whom 31 were of non-ischaemic origin) and observed significant reductions in indexed left ventricular ESV (80.8 ± 37.2 to 72.9 ± 37.0 mL/m² in the empagliflozin group vs. 76.7 ± 29.3 to 75.2 ± 29.2 mL/m² in the placebo group, \( P = 0.015 \)) as well as in EDV (114.7 ± 37.0 to 105.7 ± 37.6 mL/m² vs. 111.4 ± 29.2 to 110.9 ± 28.3 mL/m², \( P = 0.004 \)), with no significant change in LVEF at 9 months.\(^{56} \)

These data are inconclusive and insufficient both in terms of sample size and the length of follow-up.

### Non-pharmacological reverse remodelling

Left bundle branch block (LBBB) is prevalent in around one-third of patients with DCM.\(^{57} \)

Dyssynchrony affects both systolic and diastolic function and worsens prognosis.\(^{58,59} \)

In a recently published paper, Sze et al. showed an association of LBBB and lower LVRR response in patients with HF receiving guideline-directed optimal medical therapy.\(^{60} \)

Cardiac resynchronization therapy (CRT) improves survival in patients with symptomatic HFrEF and prolonged QRS duration\(^{44,61} \), there is also a sufficient evidence of a positive impact on LVRR. In the CARE-HF trial, at 18 month echocardiographic
follow-up, CRT reduced indexed left ventricular ESV by 26.0 mL/m² (95% CI, –31.5 to –20.4 mL/m², \( P < 0.001 \)) and increased LVEF by 6.9% (95% CI, 5.6% to 8.1%, \( P < 0.001 \)). Even more profound anti-remodelling effect of resynchronization therapy was found in the MADIT-CRT trial, in which serial echocardiographic measurements at baseline and 1 year were available in 1366 symptomatic HF patients (of whom 45.1% had NICM) receiving either CRT plus implantable cardioverter-defibrillator (ICD) or ICD alone.62

There was a significant decrease in left ventricular EDV (52 mL vs. 15 mL, \( P < 0.001 \)) accompanied by an increase in LVEF (11% vs. 3%, \( P < 0.001 \)) in the resynchronization group.62 The LVRR effect of CRT is greater among patients with HF of non-ischaemic origin.44,63,64 Importantly, improvement of secondary mitral regurgitation, which stands as an adverse remodelling phenotype actively contributing to further functional worsening rather than a simple result of left ventricular dilation, as the recent concept of disproportionate vs. disproportionate mitral regurgitation hypothesized.70 Therefore, functional mitral regurgitation could be a rational therapeutic target. Surgical mitral valve repair of severe mitral regurgitation in patients with DCM was associated with LVRR.71 A percutaneous edge-to-edge mitral valve repair using the MitraClip device (Abbott Vascular, Menlo Park, CA, USA) is used as an alternative treatment for patients with advanced HF and high surgical risk. However, the COAPT and MITRA-FR, two large RCTs, showed mixed results in regard to a mortality benefit.72,73 Also, the effect of MitraClip device implantation on LVRR seemed uncertain. While in COAPT a significant decrease in left ventricular EDV (–3.7 ± 5.1 mL vs. 17.1 ± 5.1 mL, \( P = 0.004 \)) 12 months after device implantation was observed,72 no change in volumes at 1 year was observed in MITRA-FR.73 Few remodelling trials investigated HfEF patients with functional mitral regurgitation. One of the first remodelling studies of the MitraClip device in these patients observed a significant decrease in indexed left ventricular EDV (100 mL [interquartile range (IQR), 84–134 mL] to 85 mL [IQR, 86–116 mL], \( P < 0.05 \)) and ESV (64 mL [IQR, 49–93 mL] to 51 mL [IQR, 36–69 mL], \( P < 0.05 \)), accompanied by an increased LVEF (35% [IQR, 31–41%] to 42% [IQR, 36–48%], \( P < 0.05 \)) 6 months after device implant in a cohort of 26 subjects.74 Reductions in left ventricular volumes (219 ± 74 to 193 ± 66 mL, \( P = 0.001 \) and 152 ± 68 to 136 ± 43 mL, \( P = 0.004 \) for EDV and ESV, respectively) were observed 1 year after MitraClip implantation in 58 patients (mean LVEF 31.9 ± 8.4%, 33% with DCM).75 Bristow et al. observed a temporary increase in left ventricular volumes immediately after the procedure followed by a subsequent, significant decrease (95 ± 39 to 100 ± 40 to 82 ± 35 mL in indexed EDV and 60 ± 31 to 65 ± 34 to 52 ± 29 mL in indexed ESV, baseline, 1 month after procedure, and 6 months after procedure, respectively, \( P < 0.001 \) for all values). Interestingly, 40 out of 79 patients who achieved LVRR showed no early increase in left ventricular EDV (1.2 ± 10% vs. 8 ± 15%, \( P < 0.001 \)).61 In a meta-analysis of 16 MitraClip trials (trials including only patients with primary mitral regurgitation were excluded) with 1266 patients and echocardiographic follow-up, MitraClip implantation was associated with significant reductions in EDV (–14.24 mL [95% CI, –22.53 to –5.94 mL], \( P < 0.001 \)) as well as in ESV (–7.67 mL [95% CI, –12.30 to –3.03 mL], \( P = 0.001 \)), accompanied by increased LVEF (2.78% [0.91% to 4.66%], \( P = 0.004 \)).76 Similar to CRT, LVRR following MitraClip is more frequent in patients with non-ischaemic aetiology of mitral regurgitation.77 However, in comparison with the aforementioned therapies, these changes are modest and as many of these studies have shown, only around half of the patients achieved LVRR despite significant mitral regurgitation severity reductions.44,61,74,77 It is yet to be distinguished which of the HF-associated mitral regurgitation...
represent irreversible and therapeutically unmodifiable remodelling phenotype.

Predictors of reverse remodelling

The process of LVRR in patients with DCM and new-onset HF may take up to 2 years after initiating treatment.\(^6\)\(^8\),\(^7\)\(^8\) However, there is a significant portion of patients who do not improve despite optimal therapy, and based on previously published data, LVRR occurs only in about one-third of cases, ranging from 19% to 45%.\(^5\),\(^1\)\(^0\),\(^7\)\(^9\)–\(^8\)\(^1\)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(^)\(n\)
are needed to confirm the importance of its quantification (Figure 2).

The clinically most relevant biomarker in the HF population is N-terminal pro-brain natriuretic peptide (NT-proBNP). Several studies of pharmacological and non-pharmacological LVRR linked responders to therapies with reductions in NT-proBNP levels.\textsuperscript{43,44,50} Januzzi et al. showed in a comparison of NT-proBNP-guided vs. standard of care HF treatment that significant reductions of NT-proBNP in the active treatment arm at 10 months were associated with a greater reduction in indexed left ventricular volumes and improvement of LVEF.\textsuperscript{92} In the echocardiographic substudy of the GUIDE-IT trial, patients achieving NT-proBNP levels \(< 1000\) pg/mL showed a greater increase in LVEF (9.9 ± 8.8% vs. 2.9 ± 7.9%, \(P < 0.001\)) and reductions in indexed left ventricular systolic and diastolic diameters (-24.6 ± 28.8 mL/m\(^2\) vs. -8.9 ± 17.3 mL/m\(^2\), \(P < 0.001\)) and -22.0 ± 31.8 mL/m\(^2\) vs. -8.0 ± 15.9 mL/m\(^2\), \(P = 0.006\), respectively) regardless of treatment strategy (biomarker guided vs. usual care).\textsuperscript{93} The extent of natriuretic peptide level reductions correlated with the amount of LVRR, and among patients achieving NT-proBNP levels \(< 1000\) pg/mL, there was a significantly higher portion of NICM (76.1% vs. 37.5%, \(P < 0.05\)).\textsuperscript{93} Several other biomarkers were investigated. Lupón et al. studied NT-proBNP, high-sensitivity troponin T, galectin-3, and soluble ST2 as possible predictors of LVRR in 304 consecutive HF patients (of whom 43.8% were of non-ischaemic origin) with 12 month echocardiographic follow-up. In a multivariable analysis, soluble ST2 was the only biomarker associated with LVRR; a cut-off value of \(< 48\) ng/mL was then used in ST2-R2 predictive score.

Figure 2 Cardiac magnetic resonance study of the same patient at the time of the diagnosis (A–D) and 14 months after treatment initiation (E–H). Chamber dilation, ventricular remodelling (A and B), and late gadolinium enhancement (arrows) are present (C and D). Despite substantial left ventricular reverse remodelling (E and F), focal fibrosis persists (G and H) and its extent seems to be greater on the follow-up study (H).
which includes soluble ST2, non-ischaemic aetiology, absence of LBBB, HF duration of <12 months, baseline LVEF < 24%, and BB treatment. The score was validated externally proving the prediction of LVRR and its magnitude reasonable. Implementation of these predictors in the routine clinical management (for early treatment escalation in therapy non-responders, for ICD indication postponement, etc.) will require more robust evidence.

**Impact of reverse remodelling on prognosis**

In a meta-analysis of 88 remodelling trials, Kramer et al. have demonstrated the association of the LVRR with lower long-term mortality. As mentioned above, a distinction should be made between reverse remodelling and cardiac recovery. Structural and functional abnormalities, with a susceptibility to dysfunction redevelopment under biomechanical stress, persist in most patients. In a prospective study of 1160 consecutive HF patients followed up for 15 years, Lupón et al. have shown long-term LVEF trajectories under guideline-directed therapy. In patients with NICM, there was a typical inverted U-shape pattern with marked improvement in the first year, which was maintained during the first decade with a subsequent decline thereafter. Interestingly, these dynamics were related to outcomes as patients who died showed less initial improvement and greater declines afterward. Similar temporal trends were seen in 747 patients with DCM from the Heart Muscle Disease registry of Trieste.

Resulting from the fact that there is still not enough understanding of the recovery process, there has been some ambiguity in the clinical classification and nomenclature of patients who achieve LVRR and who form a distinct group within the general HF population—HF with mid-range ejection fraction, HF with improved ejection fraction, and HF with recovered ejection fraction, being just some of the terms used. Recently, an expert panel consensus on clinical management of HF with recovered left ventricular ejection fraction was published and comprehensively differentiates this patient population by documentation of LVEF < 40% at baseline and ≥10% absolute improvement in LVEF with the second measurement of LVEF > 40%. While this paper proves that the topic is eventually being discussed, still, several issues with important implications remain to be studied.

One of the clinical concerns is the timing of the evaluation of the prescribed therapy effect on reverse remodelling. As mentioned above, while the improvement in cardiac function and architecture often occurs relatively fast after treatment optimization, in some patients, the process of LVRR might take longer. The PROLONG study showed that while 65 (41.7%) out of 156 newly diagnosed HFrEF patients achieved adequate LVRR as early as 3 months after initiating treatment, additional 26 (16.6%) patients showed delayed improvement that avoided untimely ICD implantation during 12 month follow-up. Moreover, even the most aggressive up-titration regimen using the whole pharmacotherapy armamentarium takes at least 6 (but more realistically 12) months to fully optimize the guideline-directed treatment. Next, in patients that improve profoundly, there is a paucity of data regarding possible treatment discontinuation. In the TRED-HF, a small RCT with a single-arm crossover design, which examined the effect of withdrawal of HF medication in patients with DCM that achieved LVRR, 40% (20 out of 50) subjects met the primary endpoint of relapse at 6 months, defined by a reduction in LVEF > 10% to <50%, an increase in left ventricular EDV > 10% to higher than a normal range, a two-fold rise in NT-proBNP to >400 pg/mL, or a manifestation of HF symptoms, compared with none of those who continued the treatment (P = 0.0001).

Similar observations were seen in super-responders to CRT 12 months after pacing deactivation, with a significant decline in LVEF (55 ± 3% to 36 ± 12%, P = 0.001) accompanied by a profound dilation of the left ventricle (40 ± 3 to 53 ± 8 mm, P = 0.001 in ESD and 53 ± 3 to 61 ± 6 mm, P = 0.001 in EDD). Based on these results, until more is known about the distinction between substantial LVRR and myocardial recovery phenotypes, treatment de-escalation should not be advised.

Despite many advances in the transcriptional analysis of reverse remodelled hearts, it is not fully understood which of the mechanisms are linked to LVRR, which are directly affected by medical and device therapy and why do genetic, transcriptional, and metabolic profiles of reversely remodelled myocardium differ distinctly from the normal state. Although paired tissue samples of HF patients before and after LVAD implant represent an invaluable opportunity to study the biology of reverse remodelling in vivo, research will always be restricted with the limited availability of human hearts specimens. Several animal models (both small and large) that simulate LVRR in NICM are available. Apart from the ischaemic injury to induce HF, surgical techniques causing volume overload, genetic engineering using gene overexpression or knockout, as well as different pharmacologic agents such as anthracyclines, isoproterenol and tachycardia-mediated HF models have been used to study structural, molecular, and transcriptional components of LVRR. Rodents used as small animal models share a high degree of homology to the human genome, but they often arise from a similar genetic background that does not reflect the genetic variety of the patient population. Because NICM can be caused by different insults (genetic mutations, inflammation, long-standing impaired energetics, etc.), information gained from a specific animal model might not be uncritically translatable to heterogeneous underlying aetiologies of HF. In animal models, stressors that cause HF are often of rapid induction and occur.
in early life, whereas in human, insults are long-lasting, disease progression is usually slow and HF often manifests at a later time. Studies that investigate the potential effect of a new therapy on LVRR in animal models use single-drug regimens while in humans, the effect has to be observed on top of the optimal medical therapy. Despite these limitations, animal models are adjustable, controllable, and free of background confounder factors, thus providing mechanistic insight into the pathogenesis of HF and LVRR. They are incremental in the identification of important, yet currently unaffected, modulating pathways and drivers of further remodelling that could represent a target for future development of HF therapies. Examples of such pathways that might be involved in the process of LVRR include beta-adrenergic, calcium handling, cardiomyocyte hypertrophy, as well as integrin signalling pathways and various microRNAs that regulate gene expression and proteome on the post-translational level. Nevertheless, if we could quantify the extent of initial myocardial injury irrespective of aetiology by obtainable clinical, biochemical, or imaging parameters, earlier implementation of more advanced treatment strategies in patients at risk of rapid deterioration would be possible.

In conclusion, reverse remodelling poses an essential objective and an important marker of successful treatment of patients with NICM. Appropriate timing of LVRR evaluation, identification of reliable predictors of positive and negative outcome, and introduction of novel HF therapies present an unmet challenge.

Conflict of interest

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