Cardiac remodelling – Part 2: Clinical, imaging and laboratory findings. A review from the Study Group on Biomarkers of the Heart Failure Association of the European Society of Cardiology

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In patients with heart failure, the beneficial effects of drug and device therapies counteract to some extent ongoing cardiac damage. According to the net balance between these two factors, cardiac geometry and function may improve (reverse remodelling, RR) and even completely normalize (remission), or *vice versa* progressively deteriorate (adverse remodelling, AR). RR or remission predict a better prognosis, while AR has been associated with worsening clinical status and outcomes. The remodelling process ultimately involves all cardiac chambers, but has been traditionally evaluated in terms of left ventricular volumes and ejection fraction. This is the second part of a review paper by the Study Group on Biomarkers of the Heart Failure Association of the European Society of Cardiology dedicated to ventricular remodelling. This document examines the proposed criteria to diagnose RR and AR, their prevalence and prognostic value, and the variables predicting remodelling in patients managed according to current guidelines. Much attention will be devoted to RR in patients with heart failure with reduced ejection fraction because most studies on cardiac remodelling focused on this setting.
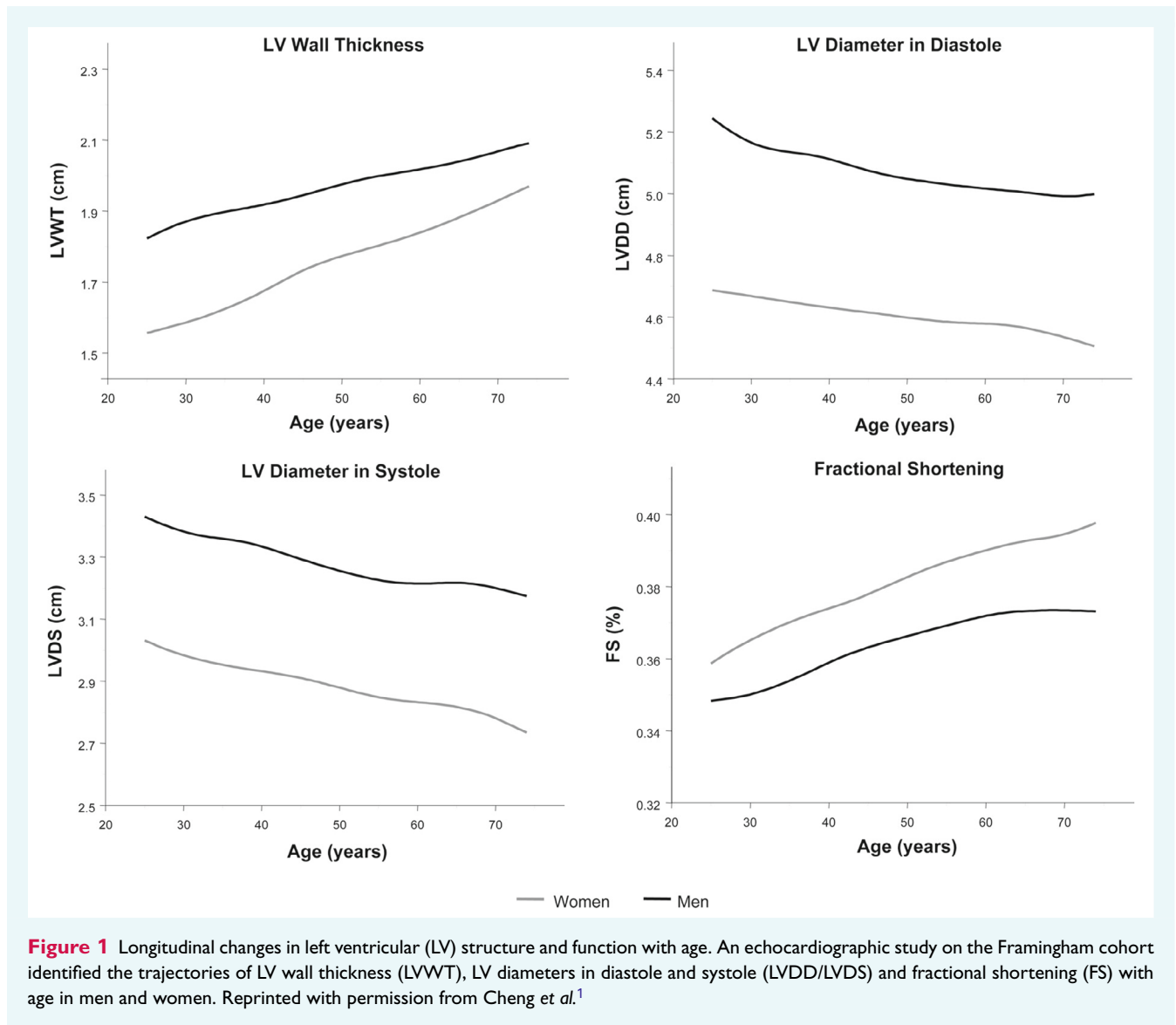
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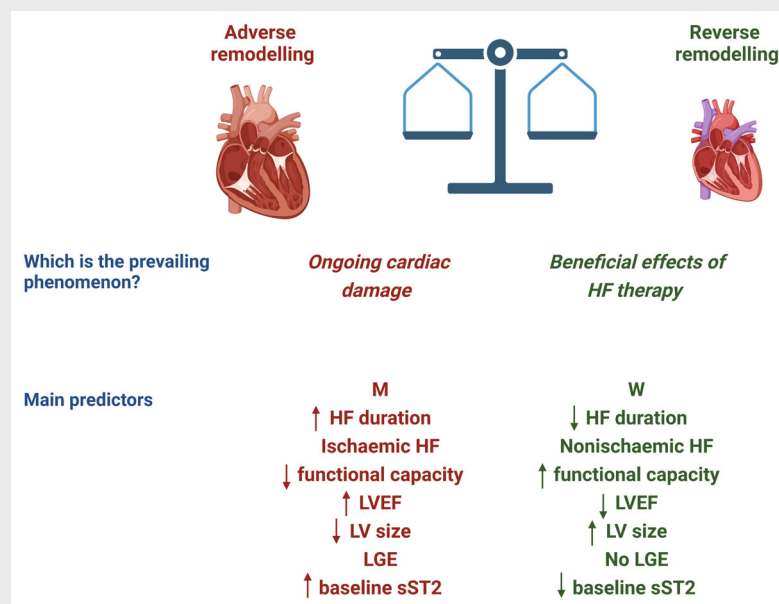
Basic mechanism and main predictors of cardiac remodelling. The net balance between the effects of ongoing cardiac damage and heart failure (HF) therapies will drive cardiac geometry and function towards a further worsening (adverse remodelling) or an improvement (reverse remodelling). The main predictors of adverse versus reverse remodelling are listed; see text for further details. Increased left ventricular (LV) size has been associated with a greater likelihood of reverse remodelling, although very dilated left ventricles are unlikely to undergo reverse remodelling. Lower baseline values of soluble suppression of tumorigenesis-2 (sST2) correspond to <48 ng/ml, which was reported to independently predict reverse remodelling. LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; M, men; W, women.

The shape, size and wall thickness of cardiac chambers change physiologically during the adult life. This evolution is characterized by a progressive increase in left ventricular (LV) wall thickness, decreasing LV dimensions, and increasing fractional shortening with advancing age, and is more prominent in women than men.[1] The notion that LV size and function change over time even in healthy individuals is reflected by the identification of age-specific normal values for echocardiographic (*Figure 1*)[1] and

Figure 1 Longitudinal changes in left ventricular (LV) structure and function with age. An echocardiographic study on the Framingham cohort identified the trajectories of LV wall thickness (LVWT), LV diameters in diastole and systole (LVDD/LVDS) and fractional shortening (FS) with age in men and women. Reprinted with permission from Cheng *et al.*[1]

cardiac magnetic resonance (CMR) measures.[2–4] Furthermore, a physiological cardiac remodelling may occur to meet the increasing metabolic demands related to pregnancy or exercise training. Pregnant women experience significant changes in the cardiovascular system that include increased blood volume and cardiac output, decreased systemic vascular resistance, and physiological cardiac hypertrophy.[5] Endurance athletes tend to have large eccentrically remodelled hearts, with large ventricular volumes, modest wall thickening, and a low relative wall thickness, while power athletes present with concentric remodelling, with thick ventricular walls, relatively small ventricular volumes, and a high relative wall thickness.[6,7] Physiological remodelling is reversed when the cause of increasing cardiovascular demands is no longer present.[5,7] Pathological cardiac remodelling occurs in response to stressors such as myocardial infarction (MI), various causes of cardiomyopathy, or a chronically increased afterload.[8] These stressors have direct and indirect (i.e. mediated by the activation of compensatory

mechanisms such as neurohormonal systems) effects on the heart. These effects persist over time and elicit changes that are initially compensatory, but on the long term may become maladaptive. For example, cardiomyocyte hypertrophy help maintain cardiac output following an MI at the expense of a worsening balance between oxygen supply and demand, which ultimately leads to further disease progression.

Although all chambers undergo dynamic changes over time, the process of cardiac remodelling is usually evaluated in terms of changes in LV volumes and/or ejection fraction, considering just sporadically the contextual changes in LV mass, diastolic function, or left atrial (LA) size. In community-based studies, cardiac remodelling has been associated with worse outcome. For example, in the Cardiovascular Health Study, increased LV mass, assessed at echocardiography, was associated with the development of LV systolic dysfunction (LV ejection fraction [LVEF] <55%).[9] Among Framingham study participants, heart failure (HF)

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risk was influenced by LV hypertrophy pattern, since eccentric and concentric hypertrophy predisposed to HF with reduced (HFrEF) or preserved ejection fraction (HFpEF), respectively.[10] Moreover, LA volumes and function were the best echocardiographic predictors of a composite of atrial fibrillation and congestive HF.[11] The Multi-Ethnic Study of Atherosclerosis (MESA) has pointed out the association between LV dilatation (LV end-diastolic diameter [LVEDD] >52 mm or >95th percentile) and incident HF,[12] and between asymptomatic LV systolic dysfunction and increased all-cause mortality.[13]

In the setting of HF, the process of remodelling has been investigated most extensively in patients with HFrEF, who can follow four trajectories: (i) a progressive worsening in LV volumes and function (adverse remodelling [AR]), when cardiac damage progresses unopposed; (ii) a substantial stability over time, when cardiac protective therapies balance the detrimental effects of ongoing cardiac insults; (iii) a recovery (reverse remodelling [RR]), (iv) or even a normalization (remission).[14] RR or remission usually require a drug or device therapy or correction of mitral regurgitation, although the removal of the underlying cause may even be sufficient (as in some cases of tachycardia-induced cardiomyopathy, alcohol abuse, cardiotoxic drugs, or peripartum cardiomyopathy).[15] AR has been associated with worsening clinical status and outcome, while RR or remission predict a better prognosis, unless HF medications are withdrawn.[16]

This is the second part of a review paper by the Study Group on Biomarkers of the Heart Failure Association of the European Society of Cardiology dedicated to ventricular remodelling. Following the characterization of remodelling at the cellular and subcellular levels in Part 1, this Part 2 examines the proposed criteria to diagnose RR and AR, their prevalence and prognostic value, and the variables predicting remodelling in patients managed according to current guidelines (*Graphical Abstract*). Much attention will be devoted to RR in patients with HFrEF because most studies on cardiac remodelling focused on this setting.

Diagnostic criteria of reverse and adverse remodelling

The definition of RR has not been standardized.[17] A dedicated search for diagnostic criteria of RR identified as many as 25 criteria from 42 studies (online supplementary *Table 1*),[18] some of them quite elaborate and difficulty applicable in everyday clinical practice. All these criteria considered changes in LV diameters or volumes, LVEF or fractional shortening (FS), either alone or in combination, and with the use of arbitrarily defined cut-offs, and just one criterion considered changes in LV mass over time. The most frequently used criterion was LV end-systolic volume (LVESV) reduction ≥15% (12 studies out of 42).[18]

Adverse remodelling was first described as the progression of the left ventricle with large transmural infarctions towards HF.[16] A more progressive deterioration of LV geometry and function can be encountered in patients with HF, although progresses in drug and device therapy are making such deterioration increasingly

rare. Contrary to RR, most studies on AR considered absolute or percent changes in LV volumes or function over time.[19] MI studies proposed heterogeneous criteria such as 5% decrease in LVEF, or 10 ml increase in LV end-diastolic volume (LVEDV) or LVESV over 20 months,[20] and LVEDV increase >20%[21] or ≥15%,[22] LVEF reduction >10% and <50% or a >10% increase in LVEDV to above the normal range.[23] The transition from HFpEF to HF with mildly reduced ejection fraction (HFmrEF) or HFrEF has been evaluated.[24] With this possible exception, we are not aware of HF studies proposing diagnostic criteria for AR (*Table 1*).[19,24–67]

In summary, no standardized definition of RR exists, and definitions of AR in HF have not been proposed so far.

Prevalence and prognostic value of reverse and adverse remodelling

The frequency of RR has been variably estimated from 29% to 60% in cohorts with different characteristics and using heterogeneous criteria for RR.[67] When applying all the RR criteria on a same cohort of HF outpatients with baseline LVEF <50%, as many as 52% of patients had RR when using the criterion 'final LVEF >35%' (although 43% of patients had a baseline LVEF >35%), and just 2% with an elaborate criterion (LVEDD decrease >5 mm to a final LVEDD <55 mm AND FS increase >5% to a final FS >25% AND LV mass decrease >10%). Thirty-one percent of patients were categorized as having RR when using the most common criterion for RR (LVESV reduction ≥15%).[18]

Broadly speaking, RR predicts a better long-term outcome, as indirectly confirmed by a meta-analytic assessment of drug and device trials reporting a proportional relationship between short-term changes in LV parameters and longer-term effects on survival.[68] The strength of the relationship between RR and outcome is also influenced by the definition of RR. In a cohort of 927 outpatients with baseline LVEF <50% undergoing two echocardiograms over 1 year and followed up thereafter, LVESV reduction ≥15% proved less effective in risk reclassification than two LVEF-based criteria: LVEF increase >10 U, and LVEF increase ≥1 category (severe [LVEF ≤30%], moderate [LVEF 31%−40%], mild LV dysfunction [LVEF 41%−55%] and normal LV function [LVEF ≥56%]). Similar results were found in subgroups with more severe systolic dysfunction (LVEF <40% and ≤35%).[18]

The prevalence of AR in HF is surprisingly difficult to estimate from serial imaging studies because of biased indications for repeat imaging tests (e.g. clinical suspicion of worsening or improvement)[67] and because of the lack of diagnostic criteria in HF studies. It is intuitive that a deterioration in LV volumes and function portends a worse outcome, as confirmed by the consistent decline of LVEF shortly before patient death (*Figure 2*).[26]

To summarize, the prevalence of RR has been variably estimated also because of the multitude of diagnostic criteria. The prevalence of AR in HF has not been defined; for this reason, the following sections will consider only RR.

Predictors of reverse remodelling

Clinical findings

Many factors affect the likelihood of RR in patients on guideline-recommended HF therapy. These include patient demographics, HF duration and aetiology, electrocardiographic (ECG) findings, blood pressure values, comorbidities, and exercise capacity (*Table 1*).[67]

Women have often been reported to have a greater propensity to RR. For example, female sex was an independent predictor of RR in a large nationwide registry.[24] Furthermore, female sex independently predicted RR over 1 year in patients with baseline LVEF <50%, which was confirmed in different LVEF ranges, and in patients with either ischaemic or non-ischaemic HF.[25] Sex-related differences in the response to cardiac injury and HF therapies might contribute to these differences.[69] Conversely, patient age did not emerge as a predictor of RR.[27]

In a retrospective study on 304 patients with HFrEF, lower HF duration and non-ischaemic aetiology emerged as independent predictors of recovery.[27] Other studies confirmed that patients with recent-onset HF[24,26] and those with non-ischaemic HF are more prone to RR.[25,26,28,42] RR is also more common in patients with non-genetic or non-familial dilated cardiomyopathy (DCM) than those with genetic or familial DCM (40% vs. 25%; *p* = 0.04).[70] Furthermore, among patients with genetic DCM, those with truncating mutations in the titin gene have a lower likelihood of RR than those with mutations in lamin A/C, sarcomere, or cytoskeleton genes.[71]

The main ECG finding associated with the likelihood of RR outside of cardiac resynchronization therapy (CRT) studies is the absence of left bundle branch block (LBBB).[27,29] Baseline heart rate did not emerge as a predictor even in patients starting beta-blockers.[30] A single study found a higher propensity of RR in patients with atrial fibrillation or flutter.[24] Higher systolic blood pressure at baseline was reported to predict RR in response

Table 1 Main predictors of reverse remodelling in patients with heart failure with reduced ejection fraction

Predictor category	Predictor	Ref.
Clinical variables	Female sex	24,25
	Lower HF duration	24,26,27
	Non-ischaemic aetiology	25,27,28
	Higher systolic BP	29−32
	Hypertension	24,32
	Anaemia	24
	COPD	24
	No diabetes	24,32
	Atrial fibrillation/flutter	24
	NYHA class I−II	24
	Higher peak oxygen consumption, better exercise performance	24,33
Echo/CMR findings	Lower LVEF, greater LV diameters	19,27,28
	Greater contractility on strain imaging	34
	LV dyssynchrony, lower LV volumes, preserved LV contractile reserve, lower degree of MR, lower LA dimensions, preserved right heart geometry and function	35−41
	LGE absence	42−44
	Lower ECV	45,46
	Higher dobutamine LV contractile reserve	47
Biomarkers	Lower sST2	27,48
	Lower Gal-3, emerging biomarkers (miRNAs, mimecan, etc.)	49−52
Therapies	Start of HF therapy	26
	Beta-blocker therapy	27,53−55
	Ivabradine	56
	Omecamtiv mecarbil	57
	SGLT2i (++empagliflozin)	58
	CRT	59
	MR correction	60−62
	TAVR	63
	Myocardial revascularization	64−66

See text for details. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; BP, blood pressure; CMR, cardiac magnetic resonance; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ECV, extracellular volume; Gal-3, galectin-3; HF, heart failure; LA, left atrial; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; miRNA, micro-RNA; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium−glucose cotransporter 2 inhibitor; sST2, soluble suppression of tumorigenesis-2; TAVR, transcatheter aortic valve replacement. Modified with permission from Aimo *et al.*[67]
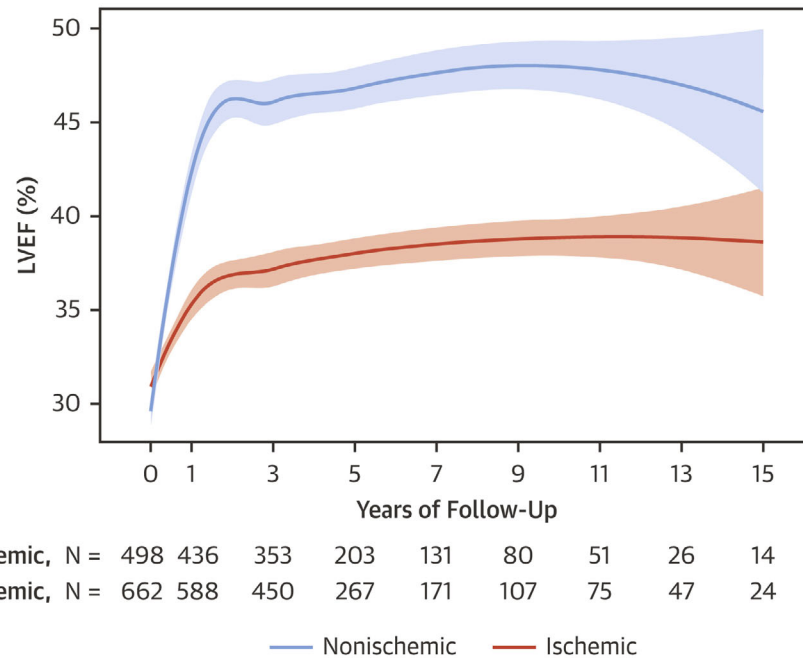
Figure 2 Dynamic trajectories of left ventricular ejection fraction (LVEF) after the start of guideline-directed medical therapy, according to heart failure aetiology. Loess spline curves are reported. Ischaemic versus non-ischaemic aetiology. $p < 0.001$ for LVEF trajectory changes for both groups; $p < 0.001$ for comparison between groups. Shaded regions represent 95% confidence interval. Reprinted with permission from Lupón et al.[26]

to HF therapy.[29−32] Furthermore, hypertension, anaemia, chronic obstructive pulmonary disease, but also absence of diabetes, were associated with a higher likelihood of RR.[24,32]

Functional status at baseline could hypothetically display some relationship with the response to HF therapy and the occurrence of RR. New York Heart Association (NYHA) functional class I−II predicted RR in a nationwide study,[24] but NYHA class did not independently predict RR in a model including HF aetiology and duration and LVEF, among others.[27] Among patients undergoing CRT implantation, those showing an echocardiographic response over 6 months had higher peak oxygen consumption and an overall better exercise performance at baseline than non-responders. CRT responders also showed a significant improvement over time in metrics of exercise capacity, while non-responders had relatively stable results.[33]

In conclusion, the likelihood of RR is higher in women, in patients with a short history of HF, those with non-ischaemic HF, no LBBB (if we do not consider cohorts of patients referred to CRT), hypertension, and better functional capacity.

Imaging

Patients with a larger and more dysfunctional left ventricle at baseline seem to have a greater propensity to RR.[19,27,28] This may simply reflect that RR is usually defined based on relative proportional changes in LV volumes and/or LVEF, and that any change can be achieved more easily when starting from larger LV

volumes and a worse systolic function. This relationship between HF severity and frequency of RR is likely retained until LV function is so severely depressed that cannot recover following the start of therapy.[67]

Transthoracic echocardiography represents the first-line imaging tool for assessment of cardiac chamber size, wall thickness, systolic and diastolic function. It includes two/three-dimensional echocardiography, pulsed and continuous wave Doppler, colour flow Doppler, tissue Doppler imaging, contrast echocardiography and deformation imaging (strain and strain rate); despite its wide availability, its reproducibility is operator-dependent, particularly for volumetric measurements and in patients with a poor acoustic window. Speckle-tracking analysis provide an assessment of LV contractility that is relatively independent of LV volumes and shape. A better preserved LV deformation has been associated with greater propensity to RR,[34,72,73] which supports the notion that a functional reserve of the left ventricle is needed to respond favourably to HF therapies. Patients with greater degrees of LV dyssynchrony are more likely to develop RR following CRT.[35,36] For example, the strain delay index across LV segments correlated with LVESV reduction 6 months after CRT (r = 0.61, $p < 0.001$), as confirmed in patients with either ischaemic or non-ischaemic HF.[37] Even radial dyssynchrony was associated with LVESV reduction after CRT regardless of QRS duration or morphology.[38] Three-dimensional echocardiography and speckle-tracking analysis allow rapid quantification of LV dyssynchrony and may predict RR after CRT.[74] Even in patients who already experienced RR (i.e.
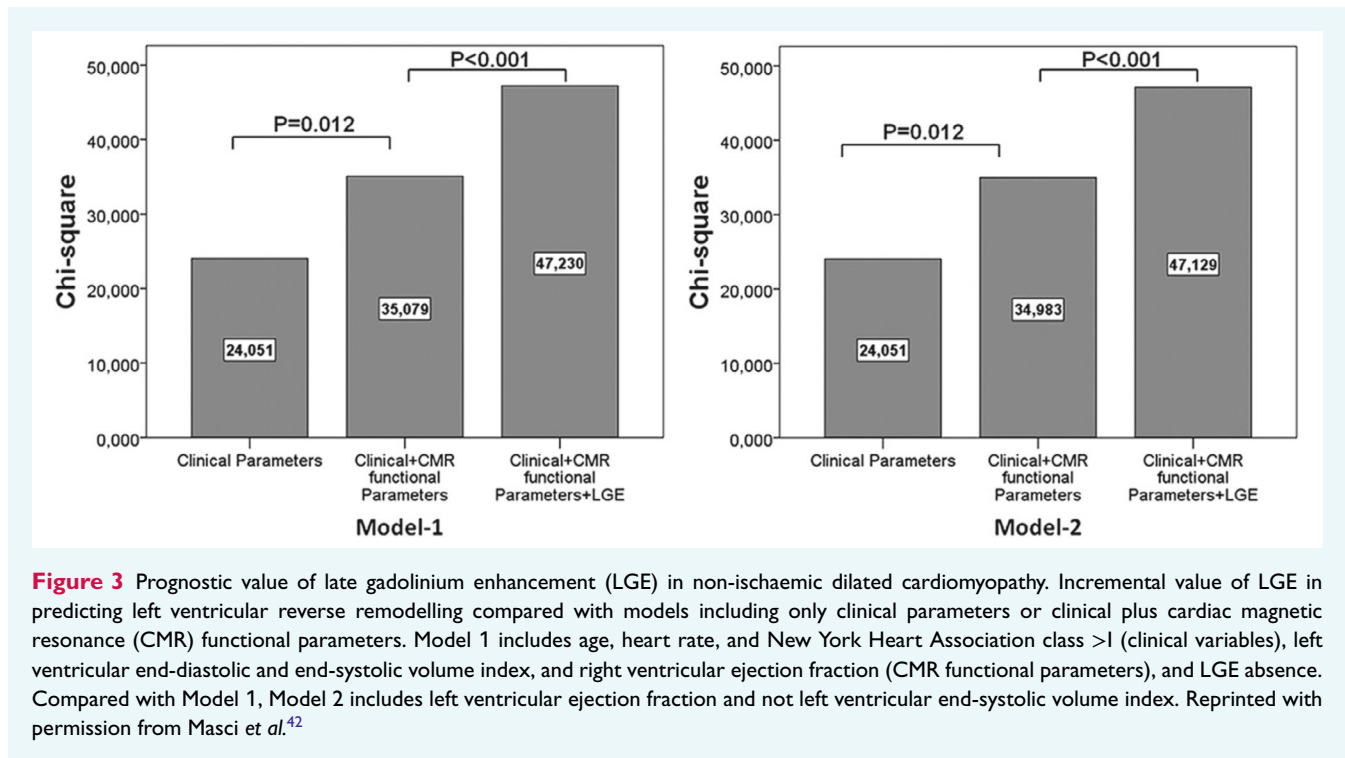
Figure 3 Prognostic value of late gadolinium enhancement (LGE) in non-ischaemic dilated cardiomyopathy. Incremental value of LGE in predicting left ventricular reverse remodelling compared with models including only clinical parameters or clinical plus cardiac magnetic resonance (CMR) functional parameters. Model 1 includes age, heart rate, and New York Heart Association class >I (clinical variables), left ventricular end-diastolic and end-systolic volume index, and right ventricular ejection fraction (CMR functional parameters), and LGE absence. Compared with Model 1, Model 2 includes left ventricular ejection fraction and not left ventricular end-systolic volume index. Reprinted with permission from Masci *et al.*[42]

HF patients with improved ejection fraction), global longitudinal strain at two-dimensional speckle-tracking echocardiography has been demonstrated to predict the occurrence of cardiovascular mortality or HF hospitalization.[75]

Cardiac magnetic resonance presents greater contrast resolution than echocardiography, higher reproducibility and independence from the acoustic window, and informs on tissue changes with specific sequences such as late gadolinium enhancement (LGE),[76] T1-, T2- and extracellular volume (ECV) mapping. CMR has proved able to accurately track the remodelling process in patients with reperfused MI.[77] In the setting of HF, LGE absence or a lower LGE extent are strong predictors of RR.[42–44,78–84] For example, LGE absence predicted RR in patients with non-ischaemic DCM with a high specificity (92%) and positive predictive value (91%),[43] and regardless of the severity of LV dilatation and dysfunction (*Figure 3*).[42,44] In a recent study on 138 patients with recent-onset DCM and an initial LVEF <45%, re-worsening of LVEF was defined as an initial RR (to an intermediate LVEF ≥45%) followed by AR (LVEF decrease >5% to a final value <45% after the initial LVEF recovery). High LGE burden, higher B-type natriuretic peptide (BNP) level, and lower LVEF at the initial LVEF recovery were independent predictors of LVEF re-worsening.[85] Moreover, patients with LVEF re-worsening ($n = 39$, 28%) showed a clinical prognosis (incidence of HF hospitalization and sudden death during a median 6-year follow-up) that was intermediate between those with RR ($n = 83$, 60%) and AR ($n = 16$, 12%).[85]

A lower myocardial T2 and a lower ECV have been demonstrated to predict RR[45,46]; nevertheless, only a lower LVEF and LGE absence remained independent predictors of RR at multivariable analysis.[46] In another small study on 56 DCM patients, only LV contractile reserve at dobutamine stress CMR independently predicted RR, while LGE presence and extent, T1 and ECV did not.[47]

Baseline and follow-up CMR scans allow to track myocardial tissue changes over time. LGE shows little or no increase during follow-up, its increase being associated with AR.[42,44,45] Moreover, native T1, absolute ECV and absolute cellular volume decrease significantly in patients on optimized medical therapy, while T2 and percentage ECV seem to remain stable over time,[45] suggesting a balanced regression of both the cellular and the extracellular compartments during RR, mirroring the regression of LV volumes and mass.

To summarize, strain analysis at echocardiography and tissue characterization at CMR, including LGE, native T1, T2 and ECV mapping, have emerged as imaging predictors of RR, compared with traditional parameters such as LV volumes and ejection fraction.

Circulating biomarkers

Circulating biomarkers related to cardiac remodelling have been described in depth in the first part of the document. Herein, we will focus on their use to predict and monitor the process of remodelling.

B-type natriuretic peptide and N-terminal proBNP (NT-proBNP) are produced in equimolar fashion from the cleavage of the 108-aminoacid precursor proBNP by proprotein convertases such as corin and furin. The biologically active BNP is rapidly degraded by several peptidases, including neprilysin.[86]

Natriuretic peptides are mainly released by ventricular cardiomyocytes in response to myocardial wall stretch due to volume or pressure overload. BNP plays a major role in HF pathophysiology given its diuretic, natriuretic, vasodilator and anti-hypertrophic properties.[86] BNP and NT-proBNP are routinely used for HF management in a large variety of clinical settings, from diagnosis to risk prediction.[87] Changes in natriuretic peptide levels across serial measurements reflect the variations of LV wall stretch over time, which is related with the evolution of LV volumes and systolic function, and then to RR. A pre-specified echocardiographic analysis of the Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial examined the relationship between changes in NT-proBNP and RR in 268 HFrEF patients receiving medical therapy. The reduction in LV volumes and LVEF recovery were proportional to the magnitude of NT-proBNP decrease.[88] The Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF) prospectively enrolled 794 patients with HFrEF starting sacubitril/valsartan. Changes in log-transformed NT-proBNP over 12 months correlated with changes in LVEF (r = −0.381), LVEDV index (r = 0.320), or LVESV index (r = 0.405) (*Figure 4*).[89] In a study on 732 patients with HFrEF and cardiac dyssynchrony randomized to CRT or medical therapy alone, NT-proBNP in the CRT arm decreased dramatically by 3 months (from baseline 1920 ng/L [interquartile range 744−4288] to 1112 ng/L [482−3053]) compared with the control arm (from baseline 1809 ng/L [719−3949] to 1649 ng/L [609−3704]), with sustained reductions to 18 months. NT-proBNP reductions following CRT were associated with significant improvements in LVESV, LVEDV and LVEF.[90]
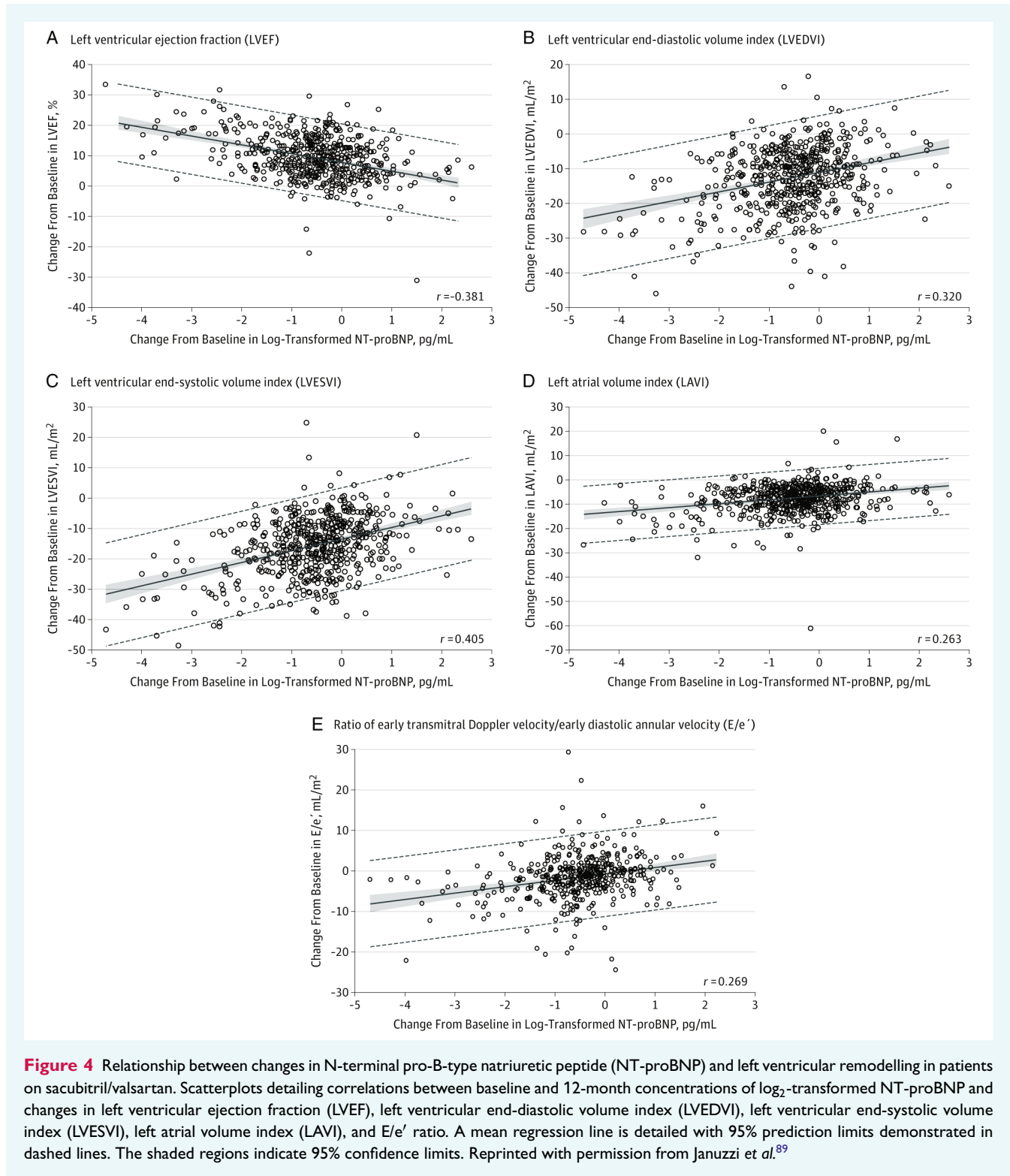
A relatively large fraction of patients with HF have elevated plasma troponin T and I. For example, in the Valsartan Heart Failure Trial (Val-HeFT), only 10% showed measurable troponin T with the conventional, non-high-sensitivity (hs) assays, and this fraction increased to up to 92% when samples were reassessed with a hs method.[91] Circulating levels of troponins, particularly when measured through hs assays, allow accurately quantifying the intensity of ongoing cardiomyocyte damage.[92] This damage may derive from the underlying myocardial insult (for example, a gene mutation) as well as chronic neurohormonal activation and haemodynamic overload.[92,93] The relationship between hs-troponin levels and the severity of cardiac damage may explain the strong prognostic value of hs-troponins in HF patients,[94] and the possible relationship between serial hs-troponin values and cardiac remodelling. Limited information is available regarding the latter point. Patients with hs-troponin I in the lowest tertile (≤29 ng/L) 6 months after an episode of acute HF displayed a more prominent RR over the same time-span.[95] The ProBNP Outpatient Tailored Chronic Heart Failure Therapy (PROTECT) study evaluated 151 patients with HFrEF over 10 months, with visits every 3 months or more often if needed. A longer percent time with hs-troponin I ≤10.9 ng/L (i.e. the median value at baseline) was associated with a decrease in LVEDV index from baseline to follow-up; furthermore, patients with hs-troponin I ≤10.9 ng/L during all visits had the highest frequency of LVEF improvement, and those with all values >10.9 ng/L had the lowest rates of LVEF increase.[96] Conversely, the time spent with hs-troponin T <14 ng/L (i.e. the upper reference limit) did not display an association with RR.[97]

Soluble suppression of tumorigenesis-2 (sST2) is the soluble form of the receptor of interleukin-33 (IL-33). sST2 sequesters IL-33 and blocks its positive anti-hypertrophic and antifibrotic effects.[98] sST2 is released in the heart and extra-cardiac tissues (particularly the lung and vessels) in response to inflammatory and profibrotic stimuli and vascular congestion, and are strong predictors of outcome in patients with HF.[99] sST2 has been studied in several cardiac disorders, particularly MI and HF. sST2 correlates with the clinical severity of HF, LVEF and natriuretic peptide levels.[100,101] In the PROTECT cohort, more time spent with sST2 <35 ng/ml predicted a decrease in LV end-diastolic index (odds ratio [OR] 1.22; 95% confidence interval [CI] 1.04−1.43; $p = 0.01$) after adjusting for relevant baseline variables.[97] Even lower baseline sST2 predicts the future occurrence of RR. Lupón et al.[27] developed a score to predict RR, named ST2-R2 score and including sST2 <48 ng/ml (3 points) together with non-ischaemic aetiology (5 points), absence of LBBB (4 points), HF duration <12 months (2 points), beta-blocker treatment (2 points), and baseline LVEF <24% (1 point). The frequency of RR ranged from 10% in patients scoring 2−5% to 86% in patients scoring 15−17. The score had area under the curve values of 0.79 and 0.73 in the derivation and validation cohorts, respectively.[27] Furthermore, a graded increase in LVEF (from +5.6% to +17.3%; $p < 0.001$), and a progressive reduction in LVESV index (from −6.1% to −32.1%; $p < 0.001$) and in LV end-systolic diameter index (from −1.1% to −18.6%; $p < 0.001$) were observed across ST2-R2 score values.[48] The ST2-R2 score then represents a valuable tool for the prediction of RR, and becomes even more appealing following the demonstration of a relationship between score values and all-cause mortality up to 4 years.[48]

Galectin-3 (Gal-3) is a lectin secreted by macrophages and able to interact with several extracellular matrix proteins.[102] Higher Gal-3 levels were associated with AR after MI[103,104] and in patients with HFrEF.[105,106] Conversely, a longer time spent with Gal-3 ≤20 ng/ml independently predicted a recovery from systolic dysfunction in HFrEF,[49] although Gal-3 seemed to have a lower prognostic value than sST2.[27] High preoperative Gal-3 was also independently associated with the lack of functional recovery after mitral valve repair.[50] Finally, Gal-3 concentrations were not found associated with CRT response in a Cardiac Resynchronization-Heart Failure (CARE-HF) trial sub-study.[107]

Many circulating biomarkers related to myocardial fibrosis and hypertrophy have been reported to predict the evolution of LV volumes and function, such as several micro-RNAs,[108,109] matrix metalloproteinases and their tissue inhibitors,[110] osteoglycin (also known as mimecan, a protein regulating matrix remodelling and bone formation, and associated with myocardial hypertrophy[111]),[51] and orexin (a regulator of sleep/awake balance, blood pressure, heart rate, and sympathetic nerve activity).[112,113] The evidence is too fragmentary to allow any definite

Figure 4 Relationship between changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) and left ventricular remodelling in patients on sacubitril/valsartan. Scatterplots detailing correlations between baseline and 12-month concentrations of $\log_2$-transformed NT-proBNP and changes in left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), left atrial volume index (LAVI), and E/e′ ratio. A mean regression line is detailed with 95% prediction limits demonstrated in dashed lines. The shaded regions indicate 95% confidence limits. Reprinted with permission from Januzzi *et al.*[89]

conclusions about these molecules as remodelling biomarkers. Interestingly, a lower degree of cardiac fibrosis, as assessed by lower procollagen type I C-terminal propeptide (PICP; see Part 1) was found associated with a positive response after CRT implantation.[114]

To summarize, circulating levels of several biomarkers (most notably natriuretic peptides, hs-troponins, and sST2) reflect the severity of ongoing cardiac damage, and therefore allow to follow the remodelling process. The prognostic value of these biomarkers at baseline seems more limited.

Heart failure treatment and reverse remodelling

Drug therapy

Until recently, the pharmacological treatment of HFrEF relied on the combination of beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARB) and possibly mineralocorticoid receptor antagonists (MRA). The historical trials on these therapies focused more on hard endpoints than RR.[115–127] The Survival and Ventricular Enlargement (SAVE) trial provided some evidence that treatment with ACEi was effective in preventing RR after acute MI.[128] After the demonstration of a significant mortality benefit from enalapril in severe congestive HF from the data from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),[129] the Treatment Trial of Studies of Left Ventricular Dysfunction (SOLVD) showed that treatment with enalapril was also associated with a reversible reduction in LVEDV and LVESV and increase in LVEF (assessed by serial radionuclide ventriculograms), compared to placebo, in patients with mild to moderate HF.[130] Even in asymptomatic patients enrolled in the prevention arm of the SOLVD, enalapril administration appeared to slow ventricular dilatation.[131] Such beneficial effects of ACEi on RR were additive to other strategies of neurohormonal antagonism.[132] Furthermore, beta-blockers were found to independently predict RR in patients with asymptomatic LV systolic dysfunction[133] or HFrEF,[27,53–55] starting after at least 1 month of therapy.[53] The prognostic value of drugs for neurohormonal antagonism did not emerge clearly in studies where most patients are on beta-blockers and ACEi/ARB, and many on MRA. For example, in a cohort where 94.4% of patients were on beta-blockers, 94.1% on ACEi/ARB, and 46.1% on MRA, these therapies did not independently predict RR.[27] Nonetheless, an early increase in LVEF following the start of HF therapies was observed in the same cohort (*Figure 2*), supporting the notion that beta-blockers, ACEi/ARB and MRA promote RR.[26] Based on an analysis of the A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) registry, different remodelling patterns could be associated with a different response to therapy in patients with HFrEF. Indeed, up-titration of beta-blockers conferred a mortality benefit to patients with HFrEF and eccentric LV hypertrophy, but not to those with concentric hypertrophy (p for interaction < 0.001), while ACEi/ARB tended to be more effective in patients with concentric hypertrophy. MRA were not specifically analysed.[134] Spironolactone has been evaluated in patients at risk of developing HF (namely individuals with or at high risk of coronary artery disease and with raised natriuretic peptides), and patients with HFpEF. In the first setting, spironolactone treatment for 9 months had no appreciable effects on cardiac geometry or function except for a reduction in LA volume compared with controls.[135] As for HFpEF, 12 to 18 months of therapy with spironolactone was not associated with alterations in cardiac structure or function in a sub-analysis of the Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial.[136]

More recent studies examined the additive benefit of novel drugs such as sacubitril/valsartan or sodium–glucose cotransporter 2 inhibitors (SGLT2i). The non-randomized PROVE-HF study demonstrated a significant 37% reduction in NT-proBNP after initiation of sacubitril/valsartan; reduction in NT-proBNP was strongly associated with reverse cardiac remodelling. For example, from a baseline LVEF of 28%, by 12 months LVEF increased an average of 9.4%; many patients had even more dramatic improvement.[89] In a similar fashion, there were decreases in indexed LV and LA volumes, LV mass index, and improvement in diastolic function as reflected in reduction of E/e' ratio. Results were consistent between those with new-onset HF and/or those not taking an ACEi or ARB at enrolment ($n = 118$ at baseline), or those not achieving the target sacubitril/valsartan dose ($n = 264$).[89] Interestingly, among patients eligible to cardioverter-defibrillator implantation for primary prevention at baseline, 32% improved their ejection fraction to >35% by 6 months and 62% to >35% by 12 months after initiation of sacubitril/valsartan therapy.[137] The randomized Study of Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction (EVALUATE-HF) trial compared sacubitril/valsartan with enalapril, on top of beta-blocker therapy in most patients, and MRA in one quarter of patients. Sacubitril/valsartan proved more effective in reducing LV volumes as well as in relieving diastolic dysfunction and LA dilatation, while it did not cause a greater recovery in LVEF.[138]

A meta-analysis on SGLT2i and RR included 13 trials and a total of 1251 patients. SGLT2i therapy was found to significantly improve LVEF (standardized mean difference [SMD] 0.35, 95% CI 0.04–0.65; $p = 0.03$), LV mass index (SMD -0.27, 95% CI -0.49 to -0.05; $p = 0.02$), LVESV index (SMD -0.35 ml/m^2, 95% CI -0.64 to -0.05; $p = 0.02$), and E-wave deceleration time (SMD -0.37, 95% CI -0.70 to -0.05; $p = 0.02$) in the overall population. The favourable effects of SGLT2i on LV remodelling were particularly evident in patients with HFrEF, with no interaction with glycaemic status. Among the four SGLT2i included, empagliflozin was associated with a greater improvement of LV mass index, LVESV index and LVEDV index (all $p < 0.05$).[58]

Sparse evidence is available on other HF drugs. A sub-analysis of the Systolic Heart Failure Treatment with the I$_f$ Inhibitor Ivabradine Trial (SHIFT) found that ivabradine reverses cardiac remodelling in patients with HF and LV systolic dysfunction (LVEF ≤35%).[56] Even a 20-week treatment with cardiac myosin activator omecamtiv mecarbil improved cardiac systolic function (as assessed through global longitudinal and circumferential strain) on top of optimal medical therapy for HFrEF.[57]

In a meta-analysis of randomized controlled trials, the magnitude of remodelling effects induced by drug or device therapy has been associated with a decreased risk of death on the long term.[68] HF therapy should be continued even after RR has been reached. Indeed, the small Therapy withdrawal in REcovered Dilated cardiomyopathy-Heart Failure (TRED-HF) trial showed that withdrawing HF therapy leads to a rapid reduction in biventricular systolic function and an increase in LV mass in patients recovering from HFrEF.[23]

To summarize, optimal medical therapy (now including sacubitril/valsartan and SGLT2i) promote RR, and therapy should not be withdrawn after recovery.

Interventional procedures and devices

Coronary revascularization, either surgical or percutaneous, has been demonstrated to induce RR in patients with chronic ischaemic cardiomyopathy,[139,140] particularly in the presence of viable myocardium as assessed through dobutamine stress echocardiography, myocardial perfusion nuclear scan or CMR.[64–66] Mitral valve surgical repair[60] and percutaneous mitral valve interventions[61] reduce volume overload to the left ventricle and might potentially lead to RR. Nonetheless, percutaneous mitral valve repair just slowed down the decline of LVEF and the increase in LV volumes even in the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation Trial (COAPT),[141] where the intervention conferred a prognostic benefit,[142] contrary to the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR).[143] An appreciable RR was found only in trials using the CARILLON® device, particularly in the Carillon Mitral Contour System for Reducing Functional Mitral Regurgitation (REDUCE-FMR).[62]

In the general population, RR after surgical aortic valve surgery for either stenosis or regurgitation is predicted by a higher preoperative LVEF and lower LVESV, while patients with severe LV dysfunction usually do not experience RR.[144–146] A variable degree of RR, affecting LV function, size and mass, has been reported also in patients undergoing transcatheter aortic valve replacement (TAVR), following afterload reduction.[147,148] Even patients with low-flow, low-gradient aortic stenosis may experience RR after TAVR,[63] reasonably until the left ventricle has not been irreversibly damaged by the longstanding elevation of LV afterload. The presence of myocardial oedema[149] and the absence of myocardial fibrosis[150] have been shown to predict RR after TAVR, but further larger studies are needed to identify reliable predictors of RR after TAVR.

Patients receiving CRT may experience a substantial recovery of LV volumes and function, occasionally with a 'super-response' (defined as absolute LVEF increase ≥15%), which in turn is associated with better quality of life and survival. Predictors of 'super-response' to CRT include female sex (OR 1.96, 95% CI 1.32−2.90, p = 0.001), absence of prior MI (OR 1.80, 95% CI 1.20−2.71, p = 0.005), presence of LBBB (OR 2.05, 95% CI 1.24−3.40, p = 0.006), QRS duration ≥150 ms (OR 1.79, 95% CI 1.17−2.73, p = 0.007), absence of obesity (OR 1.51, 95% CI 1.03−2.20, p = 0.035), smaller baseline LA volume index (OR 1.47, 95% CI 1.21−1.79, p < 0.001),[59] absence of LGE in the LV pacing region,[151,152] and also myocardial contractile reserve assessed by dobutamine stress echocardiography.[153]

In summary, surgical or percutaneous correction of mitral regurgitation may improve outcomes in selected patients without inducing a significant RR. Several predictors of super-response to CRT have been identified.

Future perspectives

The therapeutic approach to HFrEF (and to a lesser extent to the other forms of HF) is quite standardized,[154] but some choices between alternative drug options, the timing of drug up-titration, follow-up visits and device implantation must be decided on an individual basis according to patient history and the predicted evolution of disease.

Cardiac dysfunction develops following an insult to the heart (such as a MI, a myocarditis, or the effects of a gene mutation), and the detrimental consequences of a sustained activation of compensatory mechanisms (such as the sympathetic and renin−angiotensin−aldosterone systems). Conversely, disease-modifying therapies mitigate cardiac damage. The net effect of these opposing forces will drive cardiac geometry and function towards a further decline (AR), a substantial stability, an improvement (RR), or even a normalization. Many factors influence the individual response to cardiac damage and HF therapies, and multiple clinical, imaging and laboratory findings may help predict functional recovery. The search for reliable predictors has been hampered by the lack of definitions of AR, and the plethora of definitions of RR. There is a clear need for large studies with core lab reading of serial echocardiograms (to limit the intrinsic variability of transthoracic echocardiography) or repeated CMR exams. These studies should lead to standardized definitions of RR and AR, which could be used in clinical practice and as surrogate endpoints in clinical trials. Preference should be given to simple criteria that can be readily employed and hold prognostic value for hard endpoints. The most commonly used definition of RR is percent LVESV decrease ≥15%. Although two LVEF-based criteria (LVEF increase >10 U, and LVEF increase ≥1 category) were more predictive of cardiovascular death,[18] it is reasonable to consider percent LVESV decrease ≥15% as a standardized definition of RR. Proposing a definition of AR is more challenging. Future studies may consider the following three criteria: (1) the change in category from HFpEF to HFmrEF or HFrEF, or from HFmrEF to HFrEF,[24] (2) percent LVEDV increase ≥15% (a criterion proposed in a study on post-MI remodelling,[22] and easy to remember because the change value is the same as in the proposed definition of RR), or (3) percent LVESV decrease ≥15% (simply as the inverse of RR).

As other suggestions for future research, we may envisage a better understanding of cardiac remodelling as a process involving dynamic changes in LV mass, diastolic function, as well as the LA and also right heart chambers. We may also advocate for a more extensive application of serial echocardiography and biomarker measurements in clinical practice, to refine the management strategy according to the evolution of cardiac geometry and function over time and the intensity of ongoing cardiac damage, the latter evaluated based on natriuretic peptides and possibly also hs-troponins.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: none declared.

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