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REVIEW ARTICLE

Mechanisms of myocardial reverse remodelling and its clinical significance: A scientific statement of the ESC Working Group on Myocardial Function

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Cardiovascular disease (CVD) is the leading cause of morbimortality in Europe and worldwide. CVD imposes a heterogeneous spectrum of cardiac remodelling, depending on the insult nature, that is, pressure or volume overload, ischaemia, arrhythmias, infection, pathogenic gene variant, or cardiotoxicity. Moreover, the progression of CVD-induced remodelling is influenced by sex, age, genetic background and comorbidities, impacting patients' outcomes and prognosis. Cardiac reverse remodelling (RR) is defined as any normative improvement in cardiac geometry and function, driven by therapeutic interventions and rarely occurring spontaneously. While RR is the outcome desired for most CVD treatments, they often only slow/halt its progression or modify risk factors, calling for novel and more timely RR approaches. Interventions triggering RR depend on the myocardial insult and include drugs (renin–angiotensin–aldosterone system inhibitors, beta-blockers, diuretics and sodium–glucose cotransporter 2 inhibitors), devices (cardiac resynchronization therapy, ventricular assist devices), surgeries (valve replacement, coronary artery bypass graft), or physiological

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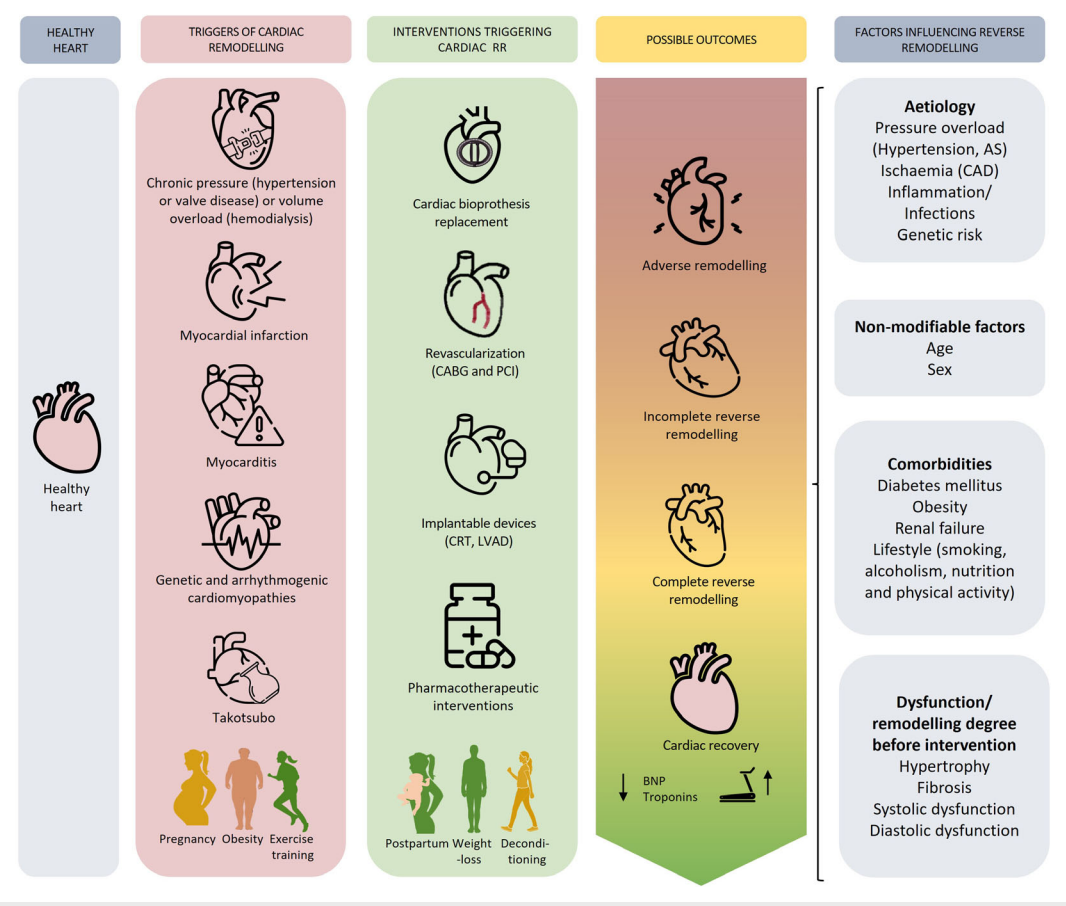
responses (deconditioning, postpartum). Subsequently, cardiac RR is inferred from the degree of normalization of left ventricular mass, ejection fraction and end-diastolic/end-systolic volumes, whose extent often correlates with patients' prognosis. However, strategies aimed at achieving sustained cardiac improvement, predictive models assessing the extent of RR, or even clinical endpoints that allow for distinguishing complete from incomplete RR or adverse remodelling objectively, remain limited and controversial. This scientific statement aims to define RR, clarify its underlying (patho)physiologic mechanisms and address (non)pharmacological options and promising strategies to promote RR, focusing on the left heart. We highlight the predictors of the extent of RR and review the prognostic significance/impact of incomplete RR/adverse remodelling. Lastly, we present an overview of RR animal models and potential future strategies under pre-clinical evaluation.

Graphical Abstract



Pathologic and physiologic cardiac remodelling triggers, interventions that can result in different outcomes and factors influencing its trajectory (aetiology, non-modifiable factors, comorbidities and pre-interventional myocardial state). The cardiac response to different interventions can span from adverse remodelling (worsening of the cardiac morphofunctional condition), incomplete reverse remodelling (RR) (partial structural and functional improvement of the heart), complete RR (characterized by total structural and functional improvement) and cardiac recovery (when an additional improvement of relevant clinical endpoints, such as no further hospital readmission and improved quality of life, is met). AS, aortic valve stenosis; BNP, B-type natriuretic peptide; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device; PCI, percutaneous coronary intervention. Some graphical elements were collected from Flaticon.com.

Keywords Adverse remodelling • Heart failure • Myocardial remodelling • Physiologic remodelling • Reverse remodelling

Introduction

Over 12 million new cases of cardiovascular disease (CVD) are reported every year, leading to a prevalence of 113 million patients in Europe and neighbouring countries.[1] Cardiac diseases lead to remodelling, a combination of geometric and functional alterations imposed by pathophysiologic stimuli (ischaemia, haemodynamic load, neurohumoral activation and others).[2,3] Considering the limited regenerative capacity of this organ, these alterations may compromise the clinical outcome of these patients and lead to heart failure (HF). Cardiac remodelling is a multicellular process involving different myocardial cell types and the extracellular matrix (ECM), encompassing molecular to organ-level adaptations. As the heart remodels, important cellular changes (e.g. hypertrophy, excitation–contraction coupling, inflammation, cell-survival signalling and mitochondrial disturbances) and ECM modifications (e.g. fibrosis) impact remodelling progress and severity.[2]

The term 'reverse remodelling' (RR) is defined as a process where the heart undergoes structural and functional changes that lead to an improvement or restoration to a more normal state. RR can result from any pharmacological treatment,[4] interventional/surgical procedures (e.g. ventricular assist devices, revascularization, resynchronization, or valve surgery),[5] or after certain physiologic events or lifestyle modification, such as partum, significant weight loss, or alcohol abstinence.[6]

An intriguing aspect of RR is the broad spectrum of ventricular responses to interventions. While some patients show sustained cardiac improvement, others exhibit incomplete RR (limited functional and structural recovery), or experience further deterioration of cardiac function, termed adverse remodelling (AR). The factors influencing RR outcomes and prognosis are diverse, including hypertension, coronary artery disease (CAD), obesity, diabetes mellitus (DM), age, sex, genetic risk, lifestyle factors (such as smoking, excessive alcohol and substance use, nutrition, and sedentary behaviour), as well as the degree of systolic and/or diastolic dysfunction, hypertrophy, and fibrosis prior to intervention.[7,8] In clinical practice, changes in ejection fraction (EF), left ventricular (LV) end-diastolic/end-systolic volumes, mass, and sphericity index often serve as surrogates for remodelling or RR.[6,9–11] 'Myocardial recovery' represents the desirable outcome of RR, characterized by sustained, favourable clinical response associated with lower long-term morbimortality, normalization of cardiac biomarkers, increased exercise tolerance[5] and reduced risk of future HF[7] (*Graphical Abstract*).

This scientific statement aims to (i) harmonize the definition of RR and its underlying mechanisms, (ii) discuss RR pharmacological options, (iii) pinpoint predictors of the extent of RR or AR, (iv) highlight the prognostic significance/impact of incomplete/adverse remodelling in the broader clinical outcome, and (v) review animal models of RR and potential new therapeutic options in the pre-clinical stage.

Interventions that trigger reverse remodelling

Current knowledge on the extent of cardiac (reverse) remodelling primarily relies on imaging techniques, notably echocardiography and cardiac magnetic resonance (CMR). These methods gauge cardiac chamber dimensions, LV mass (LVM), and functional parameters such as LVEF and myocardial strain. CMR offers superior accuracy, reproducibility, spatiotemporal resolution, and tissue characterization compared to echocardiography. For instance, T1 mapping assesses interstitial fibrosis through quantifying extracellular volume fraction, while contrast-enhanced CMR with late gadolinium enhancement (LGE) measures focal fibrosis (scarred myocardium).[12–14] Crucially, cardiac imaging parameters may predict RR/AR post-intervention/surgery, either alone or combined with other baseline variables such as circulating biomarkers of cardiac stress or myocardial remodelling (reviewed elsewhere[15,16]), thereby enhancing predictive models' accuracy. Subsequent sections will delve into the clinical significance of RR predictors and their evaluation.

Pressure overload relief-induced reverse remodelling

Pressure overload can arise from various sources such as hypertension (primary or secondary), aortic valve stenosis (AS), and to a lesser extent, subvalvular (subaortic) stenosis and coarctation of the aorta.[17] Hypertension and AS stand as the primary causes, with numerous drugs demonstrating efficacy in controlling hypertension (*Table 1*).[18–57] In Europe, AS remains the predominant valve disease necessitating intervention through transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR).[58] Restricted aortic valve opening increases LV afterload, prompting myocardial remodelling characterized by hypertrophy, reactivation of foetal gene programmes, and interstitial fibrosis.[59]

Aortic valve replacement (AVR, encompassing TAVR/SAVR) fosters myocardial RR, including reductions in hypertrophy, normalization of diastolic function, and molecular remodelling.[60] Improvement in diastolic dysfunction hinges on impeding the advancement of interstitial fibrosis (mediated by matrix metalloproteinases [MMPs] overriding the activity of tissue inhibitors of metalloproteinases [TIMPs]), collagen isoform switch (from stiffer type I to more compliant type III), and restoration of active relaxation mechanisms (elevated expression of sarcoplasmic/endoplasmic reticulum calcium ATPase 2A and other calcium handling proteins).[61–63] The extent of post-AVR RR largely depends on the degree of remodelling prior to valve replacement. Complete normalization of LV afterload at the valve and arterial levels is imperative.[64,65] Indeed, uncontrolled hypertension, cardiac amyloidosis, or prosthesis–patient mismatch heighten the risk of incomplete RR/AR.[66,67] Even in cases of similar afterload, hypertensive AS patients exhibit poorer RR, as assessed by valvulo-arterial impedance (a measure of cumulative valvular and arterial overload), underscoring the influence of neurohumoral activation,[67] known to perpetuate AR across the spectrum of CVD.[68,69]

Pre-existing DM independently predicts increased stiffness and hypertrophy 1 year after AVR.[67,70] Diabetic AS patients exhibit inadequate LVM regression, higher cardiomyocyte passive force, and interstitial fibrosis.[71] Additionally, obesity increases the risk of post-AVR LV hypertrophy, potentially due to cardiac steatosis.[72] However, studies on the association between obesity

Table 1 Class I drugs that induce reverse remodelling

Guideline-recommended drugs	Mechanism of action	Pathologic condition/ cardiac insult	Effect on reverse remodelling	Refs.
AT_1 blocker	RAAS inhibition (angiotensin II receptor antagonism; blood pressure reduction)	HFrEF Hypertension STEMI	↓ Hypertrophy ↓ Fibrosis ↑ Coronary flow reserve	18–23
Angiotensin receptor–neprilysin inhibitor[a]	RAAS inhibition (angiotensin II receptor antagonism; blood pressure reduction) + natriuretic peptide degradation inhibition (neprilysin inhibition) + improving cGMP signalling (neprilysin inhibition)	HFrEF	↓ NT-proBNP ↑ LVEF ↓ Hypertrophy ↓ LVEDVI, LVESVI ↑ Diastolic function (↓ LAVI, ↓ E/e') ↓ NYHA class ↓ Hospitalization ↓ Mortality risk	24–27
Angiotensin-converting enzyme inhibitor	RAAS inhibition (conversion of angiotensin I to angiotensin II is prevented; blood pressure reduction) Bradykinin degradation inhibition (bradykinin preservation enhances vasodilatation)	HFrEF Hypertension STEMI	↓ Hypertrophy ↓ LVESV and LVEDV ↑ Ejection fraction ↓ Hospitalization ↓ Mortality risk	22,23,28–32
Beta-blockers	β-adrenergic receptor inhibition (inotropic/chronotropic effects, blood pressure reduction, depending on selectivity)	HFrEF Hypertension STEMI Ischaemic and non-ischaemic cardiomyopathy Atrial fibrillation (ventricular rate control)	↓ LVM ↓ Hypertrophy ↓ LVEDV and LVESV ↑ Diastolic function ↑ Ejection fraction ↑ Exercise capacity ↑ Diastolic coronary blood flow time ↑ Myocardial oxygen supply/demand ↓ Adverse events ↓ Mortality risk	33–51
Mineralocorticoid receptor antagonists	Aldosterone antagonism at its receptors	HFrEF HFpEF STEMI Hypertension (resistant)	↓ LVMI	52
Sodium–glucose cotransporter 2 inhibitors	Reduction of the reabsorption of filtered glucose (glycaemia control) and sodium + anti-inflammatory, antioxidative effects, endothelial function improvement, modulation of neurohormonal pathways	HFrEF HFpEF	↓ NT-proBNP ↑ LVEF ↑ Diastolic function (↓ E/e') ↓ LVESV, LVEDV ↓ LVM ↓ LAVI ↓ E-wave deceleration time	53–57

AT_1, angiotensin II receptor type 1; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; E/e', ratio of transmitral early filling velocity to early diastolic tissue velocity; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVI, left ventricular end-systolic volume index; LVM, left ventricular mass; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RAAS, renin–angiotensin–aldosterone system; STEMI, ST-elevation myocardial infarction.

[a]May be beneficial in HFpEF patients. Meta-analysis showed that angiotensin receptor–neprilysin inhibitor induced a significant improvement in LVMI and left atrial volume in HFpEF. NT-proBNP was also more reduced when HFpEF patients were treated with LCZ696 than with valsartan.

and post-AVR survival yield conflicting results, with some suggesting better survival for severely obese patients (the 'obesity paradox'),[73] while others indicate protection only for overweight, not obese, patients,[74] and still others refute any protection.[75] Non-revascularized AS patients with moderate CAD show poorer RR 3 years post-AVR, with a slower reduction of LVM and LV dimensions.[76] In addition to the slower regression of LVM, the mechanical performance of subpopulations with both AS and CAD is ∼50% lower than that of individuals with AS alone, as assessed by CMR-tracked intramyocardial circumferential strain.[77] Age and sex have controversial impacts on RR. While one systematic study found no influence of sex on LVM regression,[78] evidence suggests that hypertrophy regression may be faster in women[79] and post-AVR survival lower in older patients.[80]

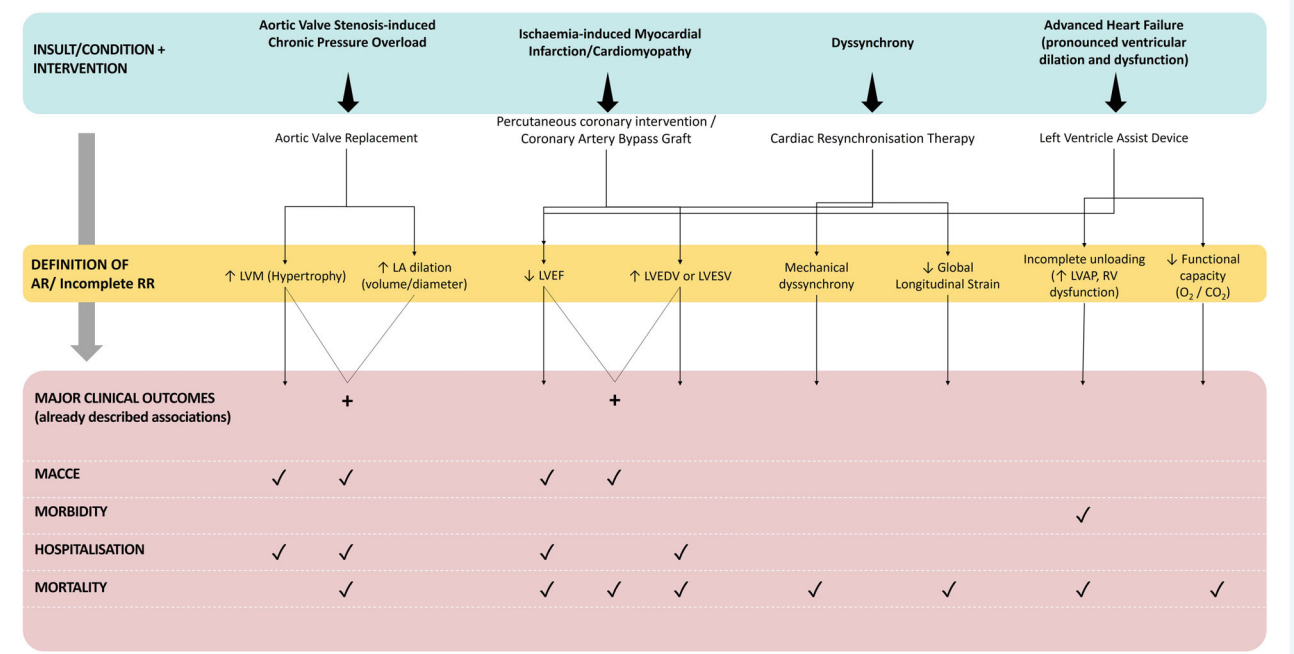


Figure 1 Overview of the main clinical outcomes associated with adverse or incomplete reverse remodelling (RR) as assessed upon main non-pharmacological interventions for the most prevalent cardiac conditions.[9,93–104] AR, adverse remodelling; LA, left atrial; LVAP, left ventricular-atrial pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVM, left ventricular mass; MACCE, major adverse cardiac and cerebrovascular event.

Similar to AS, prolonged exposure to haemodynamic stress from arterial hypertension induces changes in LV shape, size, or function,[81,82] eventually leading to HF.[81,83,84] These modifications are more pronounced when combined with other risk factors, often resulting in additive hypertrophic effects.[85,86] Specific drugs influence long-term RR and prognosis in hypertensive patients, acting at three levels: preventing cardiomyocyte hypertrophy and death, reversing interstitial alterations (inflammation and fibrosis) to reduce stiffness, and promoting coronary angiogenesis to enhance oxygen and nutrient supply[82,87,88] (*Table 1*, see section 'Drugs to promote reverse remodelling'). For example, the antifibrotic effect of beta-blockers in hypertensive patients remains controversial,[33,89] partly due to differences in beta-blocker types,[90] while angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) have established antifibrotic roles.[91,92]

For AS or systemic hypertension, LVM regression serves as the primary endpoint for evaluating RR (*Figure 1*).[9,93–104] Higher baseline LVM consistently predicts independent LVM regression after AVR,[67,105,106] reflecting a greater potential to reverse hypertrophy despite existing comorbidities that are known negative predictors of RR.[67,72,107] In AS, pre-AVR fibrosis and valvulo-arterial impedance correlate with and predict LVM regression.[64,65] Patients with more fibrosis exhibit slower normalization of LV geometry and worse diastolic function,[108] with greater LVM regression observed when fibrosis is lower (no LGE).[109]

Diastolic dysfunction triggers left atrial (LA) remodelling, leading to increased intracavitary pressure, considered an independent predictor of post-AVR systolic dysfunction[110] and worse global peak atrial longitudinal strain 3 months after AVR.[111] Conversely, reduced baseline atrial strain may compromise diastolic function normalization, resulting in higher post-AVR LA pressure.[112] Notably, myocardial strain in any orientation (radial, circumferential, and longitudinal global) predicts LVM regression after AVR.[113] Molecular markers, such as plasma miR-133a, have been shown to predict reversibility of LV hypertrophy.[114]

Early identification of patients with limited post-AVR RR, characterized by marked residual hypertrophy, LA enlargement, and diastolic dysfunction, is crucial due to their poorer outcomes, including hospitalization and death (*Figure 1*). Residual hypertrophy post-AVR is associated with non-fatal HF-related hospitalization, valve reintervention, myocardial infarction (MI), complete atrioventricular block, and LV outflow tract obstruction.[9,93] LV hypertrophy 1 year after surgery, combined with LA dilatation, is linked to major adverse cardiac and cerebrovascular events and increased mortality at 3 years.[94] A larger, long-term study (>9-year follow-up) using the Japan registry J-PROVE-Retro confirmed that patients with increased hypertrophy and LA dilatation 1 year after AVR were more likely to be hospitalized due to HF or at a higher risk of cardiac death.[95]

Volume overload-relief-induced reverse remodelling

In chronic aortic regurgitation, volume overload triggers cardiac remodelling characterized by LV dilatation and eccentric hypertrophy towards a more spherical shape.[115] AVR induces RR after

successful surgery, leading to improved systolic and diastolic performance, New York Heart Association (NYHA) class, and quality of life.[116,117] Despite an early decrease in LVEF post-AVR, significant improvement occurs within 1 year after surgery and persists thereafter, characterized by reductions in LV dimensions and a trend toward LVM regression.[117–119] Preoperative indexed LV end-systolic diameter or volume and LVEF independently predict incomplete RR,[118,119] while restrictive diastolic filling before AVR seems to impair LV RR.[116] Impairment of LV global work index post-surgery is significantly associated with worse LV RR, possibly due to increased myocardial fibrosis.[120] Incomplete RR is associated with more rehospitalizations due to lethal ventricular arrhythmia, HF, or cardiac deaths.[119,121]

In end-stage renal disease (ESRD), cardiac structure is characterized by LV hypertrophy and diastolic dysfunction, which may progress to a dilated phenotype as the disease advances.[122,123] This progression is mainly attributed to uremic toxins alongside haemodynamic factors such as volume increase through fluid retention and high flow related to arteriovenous fistulas and anaemia.[122,124] Uremic toxins are cardio-depressants and can induce dysfunction of the sodium–potassium–ATPase pump.[124]

In young men with ESRD and non-ischaemic dilated cardiomyopathy (DCM) undergoing haemodialysis, optimal fluid volume management through dry weight reduction and sodium and water restriction leads to cardiac RR characterized by progressive improvement of LVEF associated with regression of LV and LA dilatation.[122,125] This RR, also termed reverse uremic cardiomyopathy, is further enhanced as soon as 1 month after kidney transplantation (the most effective form of ESRD treatment[122–124,126]), evidenced by LVM reduction, an important predictor of RR.[123,127] A significant correlation between LVM reduction and global longitudinal strain (GLS) improvement 6 months after kidney transplantation has been reported.[128] History of valvular heart disease, CAD or HF, DM, and haemoglobin changes are predictors of RR after kidney transplantation[129] and are associated with reduced cardiovascular morbidity and mortality in the long term.[126,127]

Post-ischaemic reverse remodelling and cardiac rehabilitation

Myocardial ischaemia can promote cardiac remodelling through various mechanisms. First, chronic coronary syndrome without acute MI (AMI) leads to hibernating myocardium—a region of ischaemic but viable cardiac tissue with chronically depressed contraction.[130] Depending on the number of viable segments, myocardial revascularization can improve regional and global LV function, reverse LV dilatation,[4] lower the incidence of cardiac events,[131] and improve symptoms, LV geometry, and EF. However, trials investigating RR and outcomes after revascularization of ischaemic CAD patients have yielded conflicting results.[132–134]

Second, acute ischaemia in AMI induces myocardial necrosis and stunning,[135] where viable myocardium slowly recovers from ischaemia and is characterized by reversible contractile and biochemical dysfunction.[130,136] Ischaemia–reperfusion injury is a multifaceted pathophysiological process occurring post-AMI. Upon reperfusion, the sudden reintroduction of oxygen triggers a cascade of events, including oxidative stress, inflammation, calcium overload, and mitochondrial dysfunction, leading to transient mechanical dysfunction[130] that usually resolves spontaneously, resulting in global LV function recovery 3 months post-AMI.[137] However, the temporary dysfunction associated with stunning can result in life-threatening post-AMI events. Therefore, in addition to the fastest possible revascularization, various drugs have shown potential to accelerate, recover, or prevent myocardial stunning (*Table 1*).

Third, the substantial loss of viable myocardium after AMI can lead to AR, almost invariably progressing to HF.[4] AR involves cardiomyocyte hypertrophy, replacement (scarring), interstitial fibrosis, and variable degrees of LV dilatation of both infarcted and remote zones, leading to dysfunction and poor prognosis.[11,138] Drugs and devices (e.g. LV assist devices [LVADs]) have been assessed for their efficacy in preventing or reversing AR after MI (*Tables 1* and *2*).[18–57,139–158] Combined therapies of ACEi/ARBs, beta-blockers, mineralocorticoid receptor antagonists, or sodium–glucose cotransporter 2 (SGLT2) inhibitors have demonstrated benefits or are under investigation in clinical trials for restraining LV AR.[4,24,53,139] However, these drugs are non-specific for post-ischaemic RR mechanisms, and their selection may vary depending on the RR stage. Later, scar maturation and contraction pave the way for remodelling, where remote, viable myocardium must adapt to altered loading conditions to maintain cardiac output. Each stage of this process involves different mechanisms contributing to a highly dynamic remodelling. Hence, targeted and phase-specific therapies may be necessary, such as early anti-inflammatory treatments to address wound healing and scar maturation (*Table 3*),[159–198] in addition to standard HF therapies (*Table 1*).

The presence of a transmural ST-elevation MI (STEMI), a large infarct or myocardial-damaged area, higher baseline LV dilatation, microvascular obstruction, intramyocardial haemorrhage, and advanced age are primary predictors of subsequent higher LV systolic volume[199] and AR,[10,200] with limited impact of sex.[138] Myocardial strain analysis is particularly useful for prognosticating post-percutaneous coronary intervention (PCI) RR/AR, offering a more sensitive method for assessing LV function and viability. For instance, in patients with reduced LVEF (≤45%), a basal GLS > −11.3% predicts the absence of LVEF improvement (≥5%) 8 months after PCI (area under the curve [AUC] = 0.73), while a GLS < −12.5% predicts the absence of AR (>15% increase in LV end-systolic volume [LVESV], AUC = 0.83).[201] Incorporating GLS into a baseline model, including LVEF, infarct size, and microvascular obstruction, improves the prediction of AR at 4 months.[202] Additionally, CMR-derived parameters such as infarct size, microvascular obstruction, LVEF, and LV global functional index can predict AR (≥15% increase in LV end-diastolic volume [LVEDV], AUC > 0.70), with LV global functional index remaining a significant independent predictor in multivariable analysis.[203] Molecular markers like serum soluble interleukin (IL)-1 receptor-like 1, plasma galectin-3, and plasma miR-1254 also hold predictive value for 6-month AR in MI patients.[204–206] Identification of RR/AR post-PCI is crucial due to differing outcomes (*Figure 1*). A sub-analysis of the PRESERVATION I trial showed

that STEMI patients with increased LVEF (RR) 1 month after PCI have lower rates of recurrent MI, hospitalization and death 1 year post-intervention.[96] In contrast, STEMI patients showing post-PCI AR (≥20% increase in LVEDV) have higher HF hospitalization.[97]

Furthermore, post-PCI AR combined with LVEF impairment reduces survival and event-free survival rates over a median follow-up of 76 months.[98] In addition, soluble suppression of tumorigenicity 2 (sST2) is a decoy receptor that blocks the IL-33/ST2 system, thereby eliminating cardioprotective effects that include reducing myocardial fibrosis, cardiomyocyte hypertrophy and apoptosis. Indeed, elevated sST2 levels are a strong indicator of AR and predict a lower likelihood of RR and clinical recovery.[207,208] Conversely, in stable ischaemic heart disease patients, invasive therapy needs to be cautiously considered in the setting of angina burden and background medical therapy.[132] Indeed, in patients with stable coronary disease and severe or moderate ischaemia, an initial invasive strategy did not reduce the risk of ischaemic cardiovascular events or death from any cause, compared with a conservative approach.[209] In the ISCHEMIA trial, patients in the invasive-strategy group had more procedural infarctions and fewer non-procedural infarctions during follow-up, while the incidence of death from any cause was similar between groups.[209] However, there was a possible improved benefit from invasive therapy among patients with HF/LV dysfunction, although this evidence does not apply to patients with current/recent acute coronary syndrome or highly symptomatic, left main stenosis, or LVEF <35%.[209] Conversely, the REVIVED-BCIS2 trial failed to show that multivessel PCI improves event-free survival and LVEF among patients with severe ischaemic cardiomyopathy.[132]

Cardiac rehababilitation programmes, centered on exercise training, the fifth pillar of HF management, have demonstrated LV RR, characterized by decreased LV volumes and increased EF in post-AMI patients, halting HF progression.[210–212] Exercise impact varies based on type, duration, and timing.[213] Aerobic training improves diastolic function and Ca^{2+} handling,[213] fostering cardiac mitochondrial biogenesis and metabolic remodelling through AMPK–PGC-1α pathway up-regulation.[214] This supports aerobic glycolysis and fatty acid utilization, reducing lipid deposition and cardiac lactic acid accumulation.[214]

High-intensity training enhances cardiac function by stimulating circulating progenitor stem cells, promoting proliferation and differentiation of resident cardiac stem cells, inducing neoangiogenesis, cardiomyocyte hyperplasia, and reducing myocardial wall stress.[215] However, the efficacy of high-intensity interval training (HIIT) compared to moderate-intensity continuous training remains debatable. While HIIT improves echocardiographic parameters, myocardial work efficiency, and strain measures,[216] the HIIT-EARLY randomized controlled trial observed a long-term worsening of GLS in optimally-treated patients after acute STEMI, with no significant differences in cardiac RR compared to moderate-intensity continuous training.[217] Conversely, moderate-intensity exercise training yields substantial benefits, enhancing exercise capacity without fluctuations in LV end-diastolic diameter (LVEDD), as evidenced in a 3-month programme post-AMI.[218] Similar improvements were noted in cycling training for 2 months in patients with reduced ventricular function post-MI.[219] Although LV volume regression was absent, moderate-intensity treadmill training post-MI after successful primary PCI improved LV systolic function, regional function, and exercise capacity.[220] Additionally, low-intensity training attenuated LVEF decline and significantly decreased N-terminal pro-B-type natriuretic peptide levels in AMI patients undergoing PCI.[221]

High, moderate, and low-intensity aerobic exercises, as documented, show a low risk of cardiovascular events, affirming the safety of these cardiovascular rehabilitation programmes.[222] However, post-cardiac rehabilitation, an enlarged LV cavity and increased percentage of abnormal wall motion in MI patients persist as predictors of unfavourable long-term prognosis linked with LV dilatation.[223]

Immunosuppressive therapy-induced reverse remodelling in myocarditis and inflammatory conditions

Myocardial inflammatory infiltration can lead to acute myocarditis and/or chronic inflammatory cardiomyopathy (CIM), a multifactorial process involving predisposition (e.g. genetic and autoimmune conditions) and various triggering factors, including pathogens or cardiotoxic substances like alcohol or recreational drugs, contributing to tissue inflammation and injury.[224] Pathogens such as viruses may directly infect cardiomyocytes (enteroviruses) or indirectly induce myocardial dysfunction through infection of non-cardiomyocyte cells (e.g. parvovirus B19 infection of endothelial cells).[225] Previous registries indicate that acute myocarditis primarily affects young patients (30–45 years old) and men (60–80%).[226] Acute and severe inflammation results in cardiomyocyte damage (e.g. in giant-cell or lymphocytic myocarditis), diagnosed histologically by the Dallas criteria for myocarditis. These conditions necessitate prompt and potent treatment leading to rapid recovery, but if left untreated, they carry a poor prognosis. CIM, which develops more gradually, may still respond to immunosuppressive therapies with varying outcomes. The Lake Louise criteria have been revised to include imaging (CMR with LGE and T1 and T2 mapping) and endomyocardial biopsy analysis (histology, immunohistochemistry, pathogen detection) to stratify patients and select appropriate candidates for immunosuppressive therapies. However, even gold-standard imaging approaches like CMR have limited sensitivity for early detection before overt dysfunction or morphological remodelling is observed, as in the case of immune checkpoint inhibitor-induced myocarditis, where EF assessed by echocardiography or CMR may be normal, and tissue characterization unremarkable in the early stages.[227] In any case, LVEF improvement is used as a surrogate of the normalization of the inflammatory process upon pharmacological treatment.[228] For instance, virus-negative chronic myocarditis or CIM patients treated with corticoids (prednisone) or other immunosuppressive agents, such as azathioprine, showed a significant improvement of LVEF at long term.[228] Regarding predictors of RR outcomes, an extensive compilation has been described elsewhere,[226] but reduced EF, presence of LGE/oedema, higher NYHA class, type of myocarditis (e.g. giant-cell, lymphocytic, eosinophilic), genetic

predisposition, and signs of myocardial inflammation on histology are generally accepted as independent predictors of AR.

Reverse remodelling in genetic cardiomyopathies

Genetic cardiomyopathies encompass a heterogeneous group of heart muscle diseases and represent a common cause of cardiac dysfunction, HF and sudden cardiac death. While DCM and hypertrophic cardiomyopathy (HCM) are the most prevalent conditions (up to 1:250–1:1000),[229] arrhythmogenic right ventricular, non-dilated left ventricular, and restrictive cardiomyopathies are rare.[230] Targeted therapies for cardiomyopathies are slowly entering the clinic but are mostly in the experimental stage. Most patients receive standard HF treatment, including RR-inducing classical HF drugs, such as beta-blockers (*Table 1*), which induce RR in some patients, while others respond poorly, requiring a pacemaker or an implantable cardioverter-defibrillator. The predictors, impact of comorbidities, age, and sex on RR patterns related to LVAD are detailed in section 'Device-induced reverse remodelling'. The desmoplakin and titin gene truncations are the most common pathogenic variants found associated with arrhythmogenic cardiomyopathy and DCM, respectively.[231] Myocarditis with increased levels of high-sensitivity troponin and arrhythmias but normal LVEF may also occur during the incompletely understood 'hot phase' of desmoplakin cardiomyopathy.[231]

Besides classical HF pharmacotherapy,[232,233] drugs targeting myosin have shown promising results in cardiomyopathies (*Table 3*). Myosin activators, such as omecamtiv mecarbil, have shown potential to increase contractility in DCM, although clinical approval of the compound has not been achieved. Conversely, myosin inhibitors, such as mavacamten, have demonstrated beneficial effects in obstructive HCM.[234] Other strategies are still in the experimental phase. For instance, proteasome inhibition remains an exciting option for certain genetic cardiomyopathies,[235–237] although long-term RR effects and its efficacy in pre-symptomatic mutation carriers remain unproven. Recent reports have uncovered pathomechanisms through gene editing to correct specific genetic variants and thereby prevent/treat cardiomyopathy. CRISPR/Cas9 or antisense oligonucleotides can target cardiac function (HCM-induced by sarcomere gene mutations)[238,239] or mitochondrial metabolism,[229,240] preventing pathological remodelling or promoting RR.

Takotsubo syndrome

Takotsubo cardiomyopathy is an acute and potentially fatal cardiac emergency that presents with sudden and severe LV dysfunction.[241] It predominantly affects middle-aged (50–74 years) women (90%) and is triggered by emotional or physical stress. Its symptoms are indistinguishable from AMI and 1 in 10 will die in hospital. However, patients with Takotsubo cardiomyopathy typically have unobstructed coronary arteries and acute, severe LV dysfunction with 'ballooning' of the ventricular cavity in the absence of any myocardial infarction or scarring. Greater diagnostic recognition has led to a 4–5-fold rising incidence of Takotsubo cardiomyopathy in the last 10 years both in the UK and North America.[242]

After the acute presentation, a natural and spontaneous process of RR begins and invariably the LVEF returns to normal or near-normal.[243] Despite this RR, subclinical cardiac dysfunction and debilitating symptoms like fatigue, breathlessness, and chest pain still persist,[244] and are most likely due to a low-grade chronic inflammation.[245] The persistence of these symptoms triggers recurrent episodes of Takotsubo cardiomyopathy, substantially compromising long-term survival.[246,247] There is still no evidence-based treatment to provide symptomatic or survival benefits for these patients.

Tachycardia-induced cardiomyopathy

Atrial fibrillation, atrial flutter, ectopic atrial tachycardia, atrioventricular tachycardia, atrioventricular nodal tachycardia, ventricular tachycardia and pacemaker-mediated tachycardia have all been linked to cardiomyopathy. Typically, patients with a mean heart rate >100 bpm or atrial fibrillation/ectopic burden exceeding 10% should be considered for diagnosis. Imaging often reveals various degrees of LV dysfunction, with patients commonly exhibiting signs and symptoms of new-onset or acute HF. A diagnosis of tachycardia-induced cardiomyopathy requires restoration of sustained sinus rhythm and subsequent reversibility of LV volumes and EF. Diagnosis is usually confirmed through cardiac imaging, where either echocardiography or CMR or both reveal biventricular dilatation and moderate to severe systolic dysfunction with normal wall thickness and mass, devoid of proportionate MI or fibrosis. Neurohormonal markers such as natriuretic peptides are typically elevated and tend to decrease following tachycardia elimination.[248] Treatment strategies involve optimizing medical therapy for HF (beta-blockers, renin–angiotensin inhibition, diuretics, and SGLT2 inhibitors) to promote RR and eliminate tachycardia. However, there are currently no data regarding the duration of medical HF therapies once restoration of LVEF is achieved.

Device-induced reverse remodelling

Reverse remodelling is also prompted by the utilization of various medical devices, the efficacy of which heavily relies on the stage of disease progression prior to surgery. In this section, we review two primary modalities: cardiac resynchronization therapy (CRT) and LVAD. These modalities are employed in distinct pathological contexts and serve different purposes and mechanisms of action, although they result in similar patterns of RR, as outlined in *Table 2*. CRT is typically employed to achieve RR in patients with less severe HF, often those with HF with reduced EF (HFrEF) and electrocardiogram-based dyssynchrony (e.g. left bundle branch block [LBBB]). In contrast, LVADs are utilized in end-stage HF, usually in patients with significant ventricular dilatation and dysfunction, either as destination therapy, bridge to transplant, or bridge to decision/candidacy. Hence, complete recovery in this scenario is rare,[249] and heart transplantation stands as the final resort.[226]

Table 2 Device-induced reverse remodelling

Pathologic condition/ cardiac insult	Device	Mechanism of action	Reverse remodelling pattern	Refs.
Moderate-to-severe HF Ischaemic and non-ischaemic dilated cardiomyopathy	Cardiac resynchronization therapy	Contraction re-coordination Optimization of atrioventricular delay	↑ Ejection fraction ↓ LV end-systolic and end-diastolic diameters ↓ LVESV and LVEDV ↓ LV mass ↓ LA volume ↓ Mitral regurgitation severity ↓ NYHA class	140–148
Advanced/end-stage HF Ischaemic and non-ischaemic dilated cardiomyopathy	LV assist device	↓ LV load (mechanically) ↓ Neuroendocrine activation (epinephrine, norepinephrine, angiotensin II, and arginine vasopressin levels in plasma) ↓ Myocyte hypertrophy	↑ Ejection fraction ↓ LV end-systolic and end-diastolic diameters ↓ NT-proBNP ↓ Cardiomyocyte hypertrophy ↔ Diastolic amelioration ↓ LAVI ↓ LVESV and LVEDV ↓ Mitral regurgitation severity ↔ Modification of cytoskeletal proteins ↓ Collagen content	149–158

HF, heart failure; LAVI, left atrial volume index; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Cardiac resynchronization therapy-induced reverse remodelling

In CRT, myocardial RR is often assessed by the reduction in LV volume. Maximal RR typically occurs within the first 6 months, although it is influenced by the preoperative myocardial condition. For instance, advanced myocardial AR characterized by LV and/or LA dilatation diminishes the likelihood of a 'super-response' to CRT, defined as a combination of NYHA class reduction with preserved systolic function.[250,251] Additionally, a longer history of HF may hinder post-CRT RR success. Conversely, provided that the myocardial substrate is responsive to electrical stimuli and the global contractile reserve is preserved, a response to CRT is expected, manifesting as improved LVEF and/or a decrease in LVESV.[252] Several factors can predict CRT response, such as a baseline LVEDD ≤71 mm and QRS ≥170 ms, which anticipate a response defined by a 6-month improvement of LVEF ≥5% and NYHA class ≥I (AUC >0.83).[253] In larger studies, female sex, non-ischaemic aetiology, higher baseline LVEF, and longer QRS have all been identified as independent predictors of CRT super-responders, defined by LVEF >50% at follow-up (median of 2.8 years).[254] Conversely, prior episodes of ventricular tachyarrhythmias, HF hospitalization, and non-LBBB intrinsic QRS pattern are considered predictors of incomplete RR.[255] Unlike LVAD-induced RR, age does not seem to be a determining factor for CRT.[256,257]

A limitation in generalizing RR models and predicting outcomes after device implantation is that the extent of RR (fraction of CRT responders and non-responders) depends on the timepoint of RR evaluation. Notably, super-responder patients exhibit a lower rate of major adverse cardiac events, including implantation of cardioverter-defibrillators, HF hospitalization, or cardiac death.[254] Among these, 15% are classified as 'brief responders', experiencing a temporary reduction in LVESV (≥15%) at 6 months but not at 1–2 years of follow-up. Moreover, a reduction in LVESV after CRT correlates with a decreased risk of cardiovascular or all-cause death,[102] and greater reductions correspond to lower mortality rates, as per a retrospective analysis of the PREDICT-CRT.[103] The improvement of GLS, another characteristic of post-CRT RR linked to contractile reserve recruitment, is associated with improved survival, particularly when combined with a ≥15% reduction in LVESV.[104] Achieving an LVEF >35% 1 year after CRT indicates a reduced risk of sudden cardiac death or the need for ventricular fibrillation treatment.[102] Finally, correcting mechanical dyssynchrony 1 year after CRT is also linked to enhanced survival.[103]

Predicting a patient's response to CRT could enhance HF management. Additionally, innovative modalities in CRT may improve outcomes, such as multipoint LV pacing, which demonstrates greater impact on cardiac volume regression and LVEF increase compared to biventricular CRT.[258,259] Furthermore, His-optimized CRT and other methods of conduction system pacing may lead to significant narrowing and often normalization of LBBB, improved LVEF and NYHA class, along with pronounced reduction of LV volumes for up to 12 months after device implantation.[260–262]

Left ventricular assist device-induced reverse remodelling

Only a minority of advanced HF patients achieve sustained cardiac improvement post-LVAD implantation leading to successful explantation, while most exhibit incomplete RR and rely on ongoing LVAD support or heart transplant.[253] Currently, despite LVEF being strongly linked to LVAD flow, the clinical distinction between complete (recovered) and incomplete RR is primarily based on LVEF changes. Nonetheless, various cellular and structural changes have been reported.[155,263] While improved calcium handling has been noted during LVAD-induced RR, regression of cardiomyocyte hypertrophy and ECM turnover has not consistently been reported.[264] Collagen turnover and ECM volume exhibit a slow, biphasic pattern in response to LVAD support.[265] For instance, Klotz *et al.*[266] observed increased type I and III collagen and I/III ratio even 4–6 months post-LVAD implantation, favouring myocardial stiffening.[266] Additionally, decreased MMP-1/TIMP-1 and MMP-1 and MMP-9 levels combined with increased angiotensin I and II suggest ECM preservation post-LVAD therapy.

The implications of post-LVAD RR on patient outcomes are less explored compared to other interventions. Factors like duration or type of LVAD support, age, and HF aetiology (ischaemic or idiopathic cardiomyopathy) all influence the RR process.[150] Patients with shorter mechanical support durations and maximal RR simultaneously have lower HF relapse probabilities, while prolonged mechanical support may lead to cardiac function deterioration.[267–269] The duration of HF history and its aetiology were identified as the main predictors of myocardial recovery.[155] The INTERMACS Cardiac Recovery Score (I-CARS), derived from a study of over 14 000 patients, could predict myocardial recovery (LVAD explantation) based on six independent variables: age <50 years, non-ischaemic aetiology, recent diagnosis (<2 years), absence of implantable cardioverter-defibrillator, creatinine ≤1.2 mg/dl, and LVEDD <6.5 cm, with an excellent performance (AUC = 0.94).[269] Molecular marker-based models, such as a two-cytokine model (interferon-γ and tumour necrosis factor-α), have also been proposed to predict LVAD 'responders' with good accuracy.[270]

Predicting LVAD response may aid in anticipating adverse events and the need for adjunct therapies. Patients with LVEF improvement of ≥40% within 2 years post-implantation had lower incidences of composite endpoints, including HF-driven hospitalization and death.[99] Survival was also superior in LVAD patients with peak oxygen consumption of 12–14 mL/min/kg and minute ventilation/carbon dioxide production slope <35 on cardiopulmonary exercise testing.[100] Moreover, incomplete left heart unloading and right ventricular dysfunction 1 month post-LVAD were associated with worse mid-term outcomes (NYHA class ≥III, HF hospitalization, death).[101]

Postpartum-induced reverse remodelling

The increasing demand of the growing foetus imposes physiological haemodynamic changes on the mother during pregnancy. Preload alterations, along with increased peripheral resistance and myocardial contractility, lead to mild LV hypertrophy to reduce wall stress while maintaining function.[271–275] Recent literature indicates physiological concentric hypertrophy rather than eccentric hypertrophy during gestation.[276,277] This appears to be influenced by oestrogen, resulting in Kv4.3 channel downregulation, increased PI3K/Akt activation, and stretch-responsive kinase c-Src phosphorylation.[278] The latter is also downregulated during hypertrophy induced by AS, leading to increased intracellular calcium and activation of the calcineurin-nuclear factor of activated T-cells (NFAT) pathway.[278] NFAT is silenced during pregnancy, preventing a maladaptive hypertrophic response.[278] Hormonal-induced ECM changes are described during pregnancy and postpartum, including alterations in MMPs/TIMPs[279,280] and a shift in LV expression of collagens I and III in late pregnancy,[279,281] although their mechanisms remain unclear.[281]

Reverse remodelling initiates immediately after delivery, leading to full recovery of women's hearts. RR involves normalization of global and segmental myocardial performance to its pre-pregnancy state, typically occurring around 6 months postpartum.[282–284] Elevated levels of B-type natriuretic peptide and high sensitivity troponin I immediately after delivery have been identified as the best predictors of LA volume and LVM index, respectively, during postpartum RR.[285,286] Cardiovascular risk factors such as arterial hypertension, DM, and overweight interfere with both pregnancy-induced remodelling and postpartum RR, heightening the risk of future CVD and mortality.[284,287–291] In the third trimester, obese pregnant women often display reduced myocardial performance, increased LVM (concentric remodelling), and lower EF, predisposing them to diastolic and systolic dysfunction.[292–294] Similarly, hypertensive pregnant women may experience a five-fold increase in relative wall thickness, without proportional enlargement of LVEDD, leading to concentric remodelling,[276,295,296] which can be exacerbated by environmental, genetic, inflammatory, and placental factors.[296] Despite preserved systolic function, diastolic dysfunction is commonly observed in gestational hypertension, usually manifesting after 20 weeks of gestation and resolving within 42 days after delivery.[291,295,297] During RR, diastolic dysfunction usually resolves within 2 months postpartum.[297] Vasapollo *et al.*[298] identified diastolic dysfunction (increased E/e') and concentric hypertrophy before and after pregnancy as the strongest predictors of incomplete RR and early-to-long-term postpartum complications in women with pre-gestational hypertension. Both diastolic and systolic dysfunction have been observed in women with preeclampsia,[299] whereas normotensive women demonstrated complete RR until 3 months postpartum.[300] Women who develop hypertensive disorders during pregnancy often exhibit incomplete RR postpartum, characterized by subclinical cardiac dysfunction, hypertrophy, reduced LV relaxation, and increased peripheral vascular resistance.[288,290,301–303]

Gestational diabetes may disrupt cardiac remodelling and long-term RR. Pregnant women with gestational diabetes, even with optimal glucose management, exhibit impaired diastolic relaxation, lower LV strain, and increased LVM compared to healthy pregnant women. These changes persist for at least 6 months post-delivery.[304–306] In a 20-year follow-up study (CARDIA), gestational diabetes was significantly linked to impaired diastolic function, reduced longitudinal and circumferential strain, and increased LVM, though the hypertrophic pattern remains

debatable.[304,307] Gestational diabetes is also associated with a higher risk of developing type 2 DM and cardiovascular risk post-delivery.[308–310]

Drugs to promote reverse remodelling

Guideline-recommended drugs

Several guideline-recommended drugs can induce RR in various pathophysiological conditions (*Table 1*).

Pre-clinical/early clinical evidence for novel therapies directed at reverse remodelling

Recent advancements have concentrated on addressing the hallmarks of AR and potentially inducing RR in pre-clinical animal models, as detailed in section 'Lessons learned from animal models of reverse remodelling'. This includes RNA-based, anti-inflammatory, myofilamentary, or mitochondria-targeting drugs, as depicted in *Table 3*.

Lessons from lifestyle changes-induced reverse remodelling

Despite significant differences between pathological and physiological cardiac remodelling, 'human models' such as athletes' LV RR after a deconditioning period, weight loss and alcohol abstinence are valuable for studying specific aspects of RR. They serve as appealing animal-free alternatives.

Deconditioning-induced reverse remodelling

The impact of exercise on the cardiovascular system depends on various factors including frequency, intensity, duration, modality, and conditioning volume.[311] Prolonged, regular, and intensive exercise induces physiological cardiac hypertrophy, enhancing myocardial contractility and stroke volume.[311] Athletes typically experience decreased heart rate and improved diastolic function due to increased filling time and venous return.[312] Endurance and resistance training are associated with eccentric remodelling and concentric hypertrophy.[312,313] Sex influences this remodelling, with female athletes showing greater LV chamber enlargement and males developing higher LV wall thickness and mass.[314] Exercise-induced hypertrophy is characterized by cardiomyocyte growth, reduced fibrosis and apoptosis, improved calcium handling, activation of cardiac stem cells, increased nitric oxide production, angiogenesis, improved endothelial function, and antioxidative protection, preserving heart structure and function.[311,312,315] The insulin-like growth factor-1–PI3K(p110α)–Akt pathway plays a key role in this cardiac remodelling process.[311,315] Exercise training also increases the mitochondrial-to-myofibril volume ratio, promoting a more energy-efficient Frank–Starling mechanism.[312] Maron *et al.*[316] observed decreased LV wall thickness and mass after a deconditioning period in Olympic athletes. Additionally, LVM and wall thickness regressed 4 weeks after marathon completion, with unchanged chamber volumes and function following volume unloading.[317] However, this RR was not evident 8 weeks after the marathon.[317] The delay between the acute blood volume reduction and the Frank–Starling adaptation might be explained by weight gain after deconditioning.[317] Athletes showed decreased LV cavity dimensions and increased chronotropy after a deconditioning period of about 5 years.[318] The duration and level of previous exercise practice also modulate long-term RR, especially if athletes exceed the upper limits of ventricular morphology for physiological cardiac hypertrophy.[312] For instance, former professional cyclists showed slightly larger LVEDV and LVM index than golfers after 38 years of deconditioning, despite similar interventricular septum thickness.[319]

Metabolic unloading and weight loss-induced reverse remodelling

Obesity and DM primarily lead to vascular complications that promote myocardial ischaemia and diabetic cardiomyopathy.[320] This type of cardiomyopathy is more prevalent in women and is characterized by significant structural and functional impairment.[321,322] Diabetic patients exhibit two cardiac phenotypes: concentric LV remodelling with diastolic dysfunction leading to HF with preserved EF, and eccentric LV dilatation with systolic dysfunction leading to HFrEF.[323] Both phenotypes involve interstitial and perivascular fibrosis, cardiomyocyte hypertrophy, and cell loss. Cardiac metabolic dysregulation, including metabolic inflexibility, lipotoxicity, glucotoxicity, impaired mitochondrial respiration, and insulin resistance, plays a critical role in the development of diabetic cardiomyopathy.[324,325]

Rapid weight loss post-bariatric surgery is linked to reduced cardiovascular mortality in both HF and non-HF patients.[326,327] Weight loss leads to a linear regression of LV hypertrophy independent of age, gender, and cardiometabolic risk factors.[328] This reduction in LVM is accompanied by improvements in LV geometry and diastolic function,[329] primarily driven by a decrease in wall thickness rather than changes in end-diastolic volume.[330] However, recent studies suggest incomplete RR after bariatric surgery, with slight decreases in LVEF and worsened diastolic function despite increased LV GLS.[330]

Apart from bariatric surgery, caloric restriction and pharmacological therapies such as SGLT2 inhibitors have shown promise in promoting RR in diabetic HF (*Table 1*), regardless of diabetes status.[4,331] Another emerging target is glucagon-like-peptide-1 receptor agonists (GLP-1RA), which have demonstrated beneficial effects on cardiovascular outcomes, likely through improved lipid profiles, blood pressure, and inflammation biomarkers.[332,333] GLP-1RA actions may prevent adverse post-MI remodelling by targeting inflammation and the ECM independently of glycaemic control.[334] The ongoing SURPASS-CVOT trial aims to further

Table 3 Promising new therapeutic options to achieve myocardial recovery in animal models or phase I clinical trials

Potential novel targets for reverse remodelling and pre-clinical trials	Mechanism of action	Pathologic condition/cardiac insult/animal model	Effect on reverse remodelling	Refs.
Pressure overload conditions				
Treatment with regulatory T cells	Induction of immunosuppressive T-regulatory activity or reduction of proinflammatory T effector lymphocytes.	Mice with aortic banding and angiotensin II-dependent hypertensive mice	↓ Cardiac fibrosis by decreased TGF-β1 activity. ↑ Coronary arteriolar endothelium-dependent relaxation	159–161
Phosphodiesterase 9A inhibitor (PF-9613)	Inhibition of cGMP hydrolysis (mainly that generated by natriuretic peptide signalling, less than that caused by NO signalling, as for PDE5 inhibitors)	Pressure overload (hypertension and/or aortic valve stenosis mimic)	↓ Hypertrophy ↓ LVESD ↑ Fractional shortening	162
Apelin receptor agonist (BMS-986224)	Activation of the apelin receptor pathway (Gαi activation and β-arrestin inhibition, ERK activation)	Renal hypertension-induced cardiac hypertrophy	↑ Stroke volume ↑ Cardiac output ↔ Hypertrophy ↔ Fibrosis	163
Mocetinostat (MGCD0103)	Inhibition of histone deacetylase class I or IV (broad positive transcriptional effect)	Pressure overload (hypertension and/or aortic valve stenosis mimic)	↓ Hypertrophy ↓ Fibrosis	164
MitoTEMPO	Mitochondrial superoxide and peroxyl scavenger (superoxide dismutase mimetic)	Pressure overload + isoproterenol continuous administration (non-ischaemic HF)	↓ Cardiac dilatation ↑ Fractional shortening	165
Nicotinamide	Replenishment of the metabolic cofactor nicotinamide adenine dinucleotide	Cardiometabolic syndrome and HFpEF	↓ Hypertrophy ↓ Passive stiffness ↓ LVEDP ↑ Exercise capacity	166
JQ1 (bromodomain and extra-terminal inhibitor)	Blockage of the transactivation of specific genes	Pressure overload (hypertension and/or aortic valve stenosis mimic) Acute myocardial infarction (without reperfusion)	↓ Hypertrophy ↓ Fibrosis ↑ LVEF	167
Recombinant human bone morphogenic protein 7	Inhibition of TGF-β-mediated endothelial-mesenchymal transition	Mice with aortic banding	↓ Fibrosis ↓ LVEDP ↑ dP/dT_{min} ↔ Hypertrophy	168
Acute myocardial infarction				
Galectin-1	Modulation of cell survival and proliferation, control of inflammation and neovascularization	Acute myocardial infarction	↓ LVESD, LVEDD ↑ Fractional shortening	169
STING inhibitor	Inhibition of STING palmitoylation and multimerization, essential for TANK-binding kinase 1 phosphorylation and subsequent type I interferon gene expression	Acute myocardial infarction	↓ Infarct size ↓ Hypertrophy ↑ LV systolic function (fractional area change)	170
NLRP3 inflammasome inhibitor (16673-34-0)	Inhibition of the cell danger-sensor of intracellular (e.g. bacterial or viral infective agent) or extracellular signals (e.g. ischaemia), ultimately preventing cell death	Acute myocardial infarction Doxorubicin cardiotoxicity	↓ Infarct size (reperfusion only) ↑ LV systolic function (fractional shortening) ↓ Fibrosis (doxorubicin only)	171
MicroRNA-144	Modulation of local inflammation (among others)	Acute myocardial infarction (without reperfusion)	↓ Infarct size ↑ LV systolic function (LVEF, fractional shortening) ↓ LVESV, LVEDV ↑ dP/dT_{max}	172
Ischaemic postconditioning	Mediated mainly through PI3K–PKB/Akt signalling pathway (reducing reactive oxygen species, lipid peroxidation, intracellular and mitochondrial calcium concentrations)	Acute myocardial infarction	↓ Infarct size	173–180

Table 3 (Continued)

Potential novel targets for reverse remodelling and pre-clinical trials	Mechanism of action	Pathologic condition/cardiac insult/animal model	Effect on reverse remodelling	Refs.
Antisense oligonucleotide (GapmeR) for *Wisper*	*Wisper* silencing	Acute myocardial infarction	↓ Hypertrophy ↓ Fibrosis ↓ LVIDd ↑ LV systolic function (LVEF, fractional shortening)	181
Antisense oligonucleotide for miR-132 (antimiR-132, CDR132L)	miR-132 silencing	Acute myocardial infarction Chronic (ischaemic) HF[a]	↓ NT-proBNP ↑ LVEF ↓ LVESVI, LVEDVI ↓ LAVI ↑ dP/dT_{max} ↓ dP/dT_{min} ↓ Hypertrophy ↓ Fibrosis QRS narrowing	182–184
Myocardial infarction and HFrEF				
Neuregulin-1	Activation of the neuregulin-1/ErbB pathway, inducing multiple protective effects (cardiomyocyte proliferation and hypertrophy, enhanced contractility, reduced apoptosis, angiogenesis)	Ischaemic cardiomyopathy HFrEF	↑ LVEF ↓ LVEDV and LVESV	185,186
Sodium/hydrogen exchange inhibitor (EMD-87580)	Prevention of intracellular sodium and calcium accumulation and pH regulation	Myocardial infarction	↔ Infarct size ↓ Hypertrophy ↓ LVEDP ↓ Plasma ANP	187
βARKct peptide (gene transfer by adenovirus)	Inhibition of the membrane translocation-activation of GRK2, normalizing beta-adrenergic receptor signalling	Myocardial infarction	↓ BNP ↓ Hypertrophy ↑ dP/dT_{max} ↓ Fibrosis	188
S100A1 protein (gene transfer by adenovirus)	Regulation of calcium cycling, improving contractility (systolic and diastolic performance) and increase of mitochondrial ATP production	Myocardial infarction and ischaemic HF	↓ Hypertrophy ↑ Ejection fraction ↑ dP/dT_{max} ↓ P/dT_{min} ↓ LVEDP	189
Ataciguat	NO-independent activation of the soluble guanylate cyclase, inducing multiple effects (e.g. vasodilatation)	Chronic myocardial infarction and HFrEF	↓ Hypertrophy ↓ LVEDV and LVESV ↑ Ejection fraction ↑ dP/dT_{max} ↓ dP/dT_{min} ↓ LVEDP ↑ Angiogenesis ↓ Fibrosis	190
Omecamtiv mecarbil	Positive inotropism (myotrope: increases cardiac systolic force by selectively binding to myosin and increasing the number of active cross-bridges)	HFrEF	↑ Stroke volume ↓ HR ↑ Systolic ejection time (while dP/dt remained unchanged) ↓ LVEDV and LVESV	191,192

Table 3 (Continued)

Potential novel targets for reverse remodelling and pre-clinical trials	Mechanism of action	Pathologic condition/cardiac insult/animal model	Effect on reverse remodelling	Refs.
Danicamtiv (MYK-491)	Positive inotropism (myotrope)	HFrEF	↑ Stroke volume ↑ Global longitudinal and circumferential strain ↓ LAVI ↑ LA function index	193
Hypertrophic cardiomyopathy				
Mavacamten (MYK-461)	Negative inotropism (reduces contractility by decreasing the ATPase activity of the cardiac myosin heavy chain)	Hypertrophic cardiomyopathy Obstructive hypertrophic cardiomyopathy	↓ Fractional shortening ↓ Hypertrophy ↓ Fibrosis	194
Aficamten (CK-274)	Negative inotropism (cardiac myosin inhibitor that decreases myosin ATPase activity)	Hypertrophic cardiomyopathy	↓ Fractional shortening ↓ LVIDs ↓ IVRT	195,196
Dilated cardiomyopathy				
Antisense oligonucleotide for titin gene	Exon skipping to correct titin reading frame	Dilated cardiomyopathy	Improvement of sarcomere formation ↑ Contractile performance ↑ LVEF	197
CRISPR/Cas9 gene editing of titin	Correction of a titin truncating mutation restoring wildtype titin levels	Dilated cardiomyopathy[b]	↑ Sarcomere number ↑ Contractile performance	197
Myocarditis				
Interleukin-1β antibody	Interleukin-1β neutralization to prevent inflammation activation	Coxsackievirus B3 myocarditis	↓ Inflammation ↓ Fibrosis	198

ANP, atrial natriuretic peptide; ATP, adenosine triphosphate; BNP, B-type natriuretic peptide; cGMP, cyclic guanosine monophosphate; dP/dT, rate of pressure development; ERK, extracellular signal-regulated kinase; GRK2, G protein-coupled receptor kinase 2; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; IVRT, isovolumic relaxation time; LA, left atrial; LAVI, left atrial volume index; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; LVESVI, left ventricular end-systolic volume index; LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; NLRP3, NACHT, LRR and PYD domains-containing protein 3; NO, nitric oxide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PDE5, phosphodiesterase 5; STING, stimulator of interferon genes; TANK, TRAF family member-associated NF-kappa-B activator; TGF-β1, transforming growth factor-β1.

[a] A phase 2, multicentre, randomized, parallel, 3-arm, placebo-controlled study to assess the efficacy and safety of CDR132L in HFrEF after myocardial infarction is ongoing (HF-REVERT, NCT05350969).

[b] Probably various cardiomyopathies caused by truncated titin.

evaluate GLP-1RA effects on cardiovascular outcomes.[335] Caloric restriction and its pharmacological mimetics have been effective in attenuating remodelling and diastolic dysfunction in animal models of metabolic syndrome, along with reduced fibrosis and oxidative stress.[166,336,337] Initiation of caloric restriction post-MI improves cardiac dysfunction and inotropic reserve in non-diabetic animals.[338]

Overall, these clinical, behavioural, and pharmacological interventions aim to alleviate cardiac overfuelling, which can lead to insulin resistance, metabolic inflexibility, and mitochondrial and contractile dysfunction, ultimately promoting RR.[339]

Alcohol abstinence-induced reverse remodelling

Alcoholic cardiomyopathy, recognized as a distinct clinical entity by the World Health Organization, results from long-term heavy alcohol intake and presents as DCM.[340,341] It is characterized by increased LVM, ventricular dilatation, and wall thinning, resembling LV eccentric remodelling with ventricular dysfunction, in the absence of CAD and nutritional deficiencies.[341–343] Its clinical and histological features resemble those of idiopathic DCM.[341,344] Treatment for alcoholic cardiomyopathy involves pharmacological therapy similar to other non-ischaemic DCMs, with a crucial emphasis on complete or significant reduction of alcohol consumption to prevent further deterioration of cardiac function and HF.[344,345] Notably, abstinence or significant reduction in alcohol intake may lead to cardiac RR within 6 months,[346] resulting in improved LV function, HF symptoms, and prognosis in both short- and long-term outcomes.[344–346]

Lessons learned from animal models of reverse remodelling

Due to challenges in accessing human myocardial tissue during RR, animal models are essential for understanding its mechanisms and predictors. Animal models should mimic both cardiac remodelling induced by a stressor and the RR process post-intervention.[347,348] In theory, every animal with cardiac injury subjected to treatment is a suitable model to study RR. However, when it comes to studying cardiac hypertrophy, fibrosis, angiogenesis, and oxidative stress recovery, surgical models are commonly used, such as aortic banding followed by debanding and left anterior descending (LAD) coronary ligation followed by reperfusion,[347] in small[349,350] and large animals[351,352] (*Figure 2*). Aortic banding simulates chronic

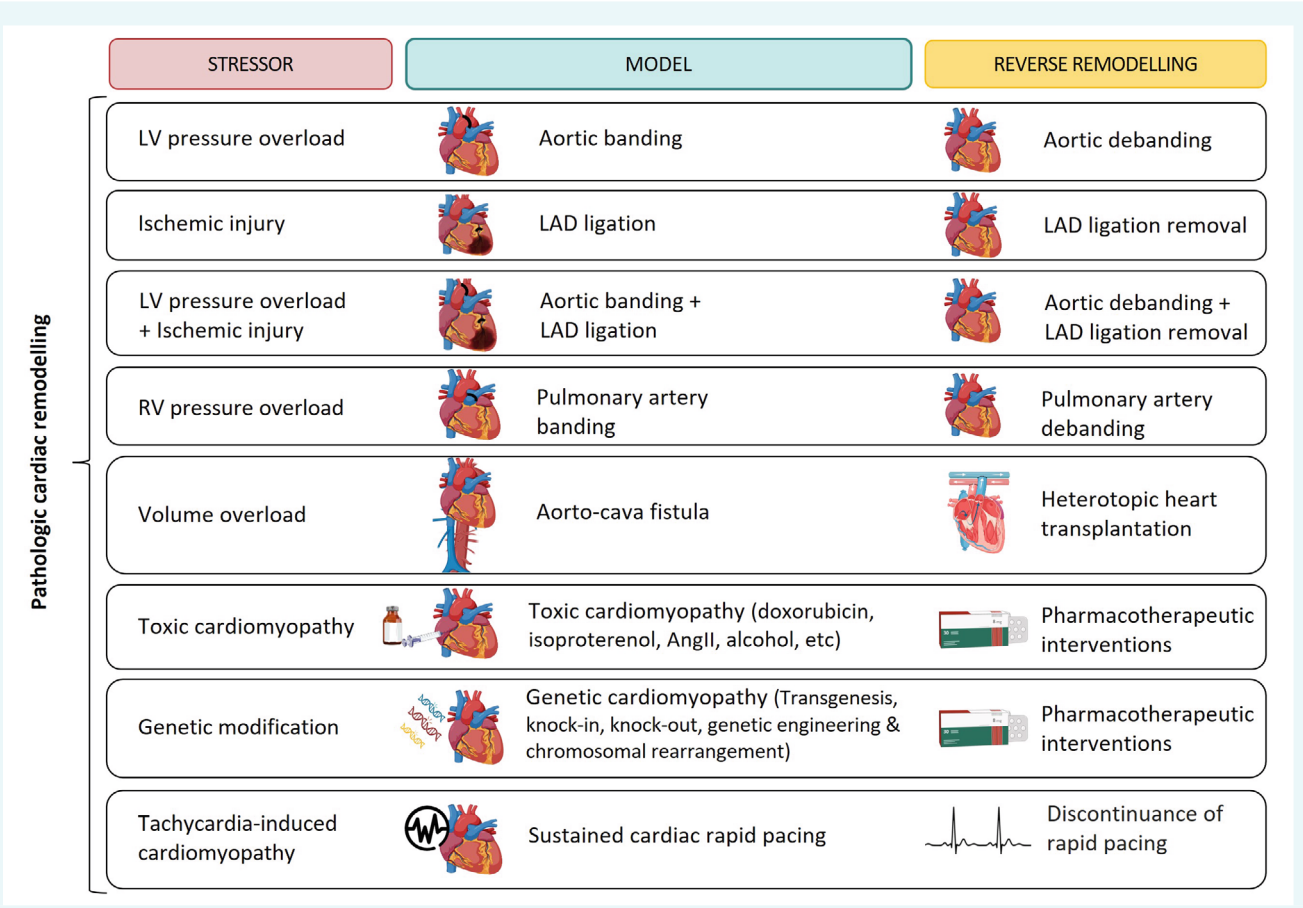


Figure 2 Animal models to achieve cardiac remodelling and reverse remodelling. AngII, angiotensin II; LAD, left anterior descending coronary artery; LV, left ventricular; RV, right ventricular.

pressure overload, and debanding the subsequent relief from this condition, mimicking conditions like AS and hypertension before and after surgical/therapeutic intervention. Heterotopic heart transplantation can also be replicated in aortic banding and other animal models to promote RR. LAD ligation and its removal mimic an ischaemic event followed by myocardial reperfusion.[347] Both models represent human RR processes with high translational potential. Combining these models replicates clinically relevant comorbidities like ischaemic heart disease and arterial pressure overload.[353] To induce cardiomyopathy by tachycardia, a sustained rapid atrial or ventricular pacing can be used. This leads to severe biventricular diastolic and systolic dysfunction, accompanied by profound cardiac chamber dilatation and subsequent spherical remodelling.[354] RR can then be induced by discontinuing chronic rapid pacing, mimicking the effects of controlling chronotropy.[354] In animal models, longitudinal sample collection allows for identifying biomarkers of cardiac disease reversal and utilizing genetic gain-/loss-of-function models.

Replicating comorbidities that impact RR is challenging but can be incorporated into existing models. Aging is linked to cellular senescence, releasing senescence-associated secretory phenotype, contributing to age-associated cardiac diseases, including HF.[69,355] Senescent cardiomyocytes promote cardiac fibroblast activation, leading to pathological cardiac remodelling.[356–358] In experiments with aged animals, aging impaired RR following the cessation of beta-adrenergic-induced cardiomyopathy. Elderly female animals exhibited sustained cardiac hypertrophy, fibrosis, and dysfunction after isoproterenol withdrawal, whereas young females recovered from cardiac remodelling.[357] Further mechanistic studies in aged animals are needed to understand the impact of aging on RR. Studies should also address endothelial-mesenchymal transition in RR, considering its role in perpetuating microvascular dysfunction and pro-inflammatory signalling.[359–361] Moreover, additional research is required to explore new therapeutic options (*Table 3*). In cardiovascular research, simple models like mice pose a significant hurdle to translating experimental data clinically, especially for RR, which involves numerous genetic and environmental factors. Large animal models (e.g. pigs, dogs) more accurately mimic human pathophysiology, including ischaemia followed by reperfusion and relief of aortic banding,[350,351] enhancing translational potential for therapeutic interventions and prognostic stratification.

Conclusion and future perspectives

Globally, CVD remains the leading cause of morbidity and mortality, resulting in diverse cardiac remodelling patterns induced by various insults like pressure overload, ischaemia, or genetic variants. Interventions aim to induce cardiac RR and are influenced by initial cardiac stress and risk factors. Emerging antidiabetic drugs, novel inotropes, and metabolic interventions show promise in improving cardiovascular outcomes. Advanced imaging techniques, particularly CMR, offer valuable insights through radiomics. Integrating classical and innovative molecular biomarkers with CMR data and strain echocardiographic parameters holds potential for predictive models of RR extent. Machine learning approaches enhance RR prediction and will likely soon outperform established guidelines. While traditional factors like LVM, LVEF, volumes, QRS duration, and myocardial scar consistently predict RR, personalized multiscale information, including genetics, metabolism, inflammation, and artificial intelligence, offers a critical avenue for predicting individual therapy responses and assessing RR potential.[362,363]

At the pre-clinical level, animal models play a crucial role in understanding the complex mechanisms of RR and assessing the clinical potential of new targets. These models offer a controlled environment for manipulating variables, allowing detailed exploration of molecular pathways and physiological responses involved in RR. Leveraging these advantages helps validate novel targets and offers insights into the translational potential of emerging therapies for cardiac RR, bridging the gap between pre-clinical and clinical applications. These advancements hold promise for improving RR prediction and determining the optimal timing for both pharmacological and non-pharmacological interventions in patients.

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