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REVIEW

Cardiac remodelling in the era of the recommended four pillars heart failure medical therapy

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Abstract

Cardiac remodelling is a key determinant of worse cardiovascular outcome in patients with heart failure (HF) and reduced ejection fraction (HFrEF). It affects both the left ventricle (LV) structure and function as well as the left atrium (LA) and the right ventricle (RV). Guideline recommended medical therapy for HF, including angiotensin-converting enzyme inhibitors/angiotensin receptors II blockers/angiotensin receptor blocker-neprilysin inhibitors (ACE-I/ARB/ARNI), beta-blockers, mineralocorticoid receptor antagonists (MRA) and sodium-glucose transport protein 2 inhibitors (SGLT2i), have shown to improve morbidity and mortality in patients with HFrEF. By targeting multiple pathophysiological pathways, foundational HF therapies are supposed to drive their beneficial clinical effects by a direct myocardial effect. Simultaneous initiation of guideline directed medical therapy (GDMT) through a synergistic effect promotes a 'reverse remodelling', leading to a full or partial recovered structure and function by enhancing systemic neurohumoral regulation and energy metabolism, reducing cardiomyocyte apoptosis, lowering oxidative stress and inflammation and adverse extracellular matrix deposition. The aim of this review is to describe how these classes of drugs can drive reverse remodelling in the LV, LA and RV and improve prognosis in patients with HFrEF.

Keywords Cardiac remodelling; Heart failure; Medical therapy

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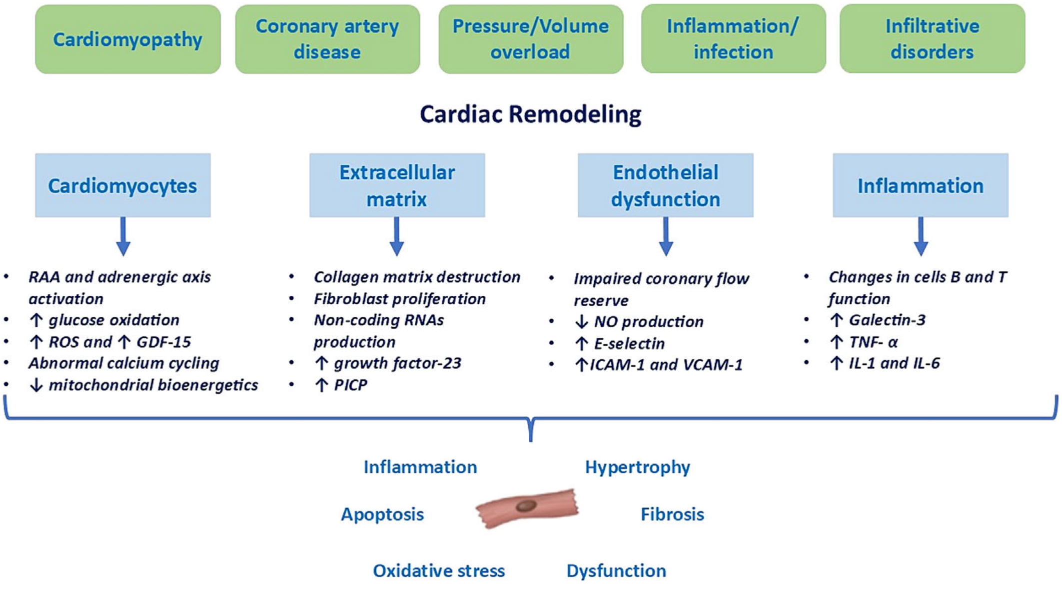
Introduction

Advances in pharmacological therapies have brought a significant breakthrough in the clinical management of patients with heart failure (HF) and reduced ejection fraction (HFrEF).[1–3] The pathophysiology underlying the clinical benefit of guidelines directed medical therapy (GDMT) partly relies upon its positive effects on cardiac structure and function. Cardiac remodelling is a determinant of the clinical process of HF and results in molecular and cellular changes, associated to changes in size, shape and function of the heart.[4–7] It affects both the left ventricle (LV) structure and function as well as the left atrium (LA) and the right ventricle (RV).[8] Angiotensin-converting enzyme inhibitors (ACE-I)/angiotensin receptors II blockers (ARB)/angiotensin receptor blocker-neprilysin inhibitor (ARNI), together with beta-blockers (BB), mineralocorticoid receptor antagonists (MRA) and sodium-glucose inhibitors (SGLT2i) are the key guideline-recommended therapeutic approaches to reduce morbidity and mortality in HFrEF.[9–12] Alone or combined, these therapies improve clinical symptoms, reduce unplanned hospitalizations and prolong survival. There is also evidence that the beneficial clinical effects may be driven by efficacy in cardiac reverse remodelling, promoting a partial or full recovery of cardiac structure and function. The aim of this review is to describe how these classes of drugs can drive reverse remodelling and improve prognosis among patients with HFrEF.

Left ventricular remodelling

The term ventricular remodelling refers to alteration in ventricular architecture and chamber configuration, driven on a histological level by a combination of pathologic myocyte hypertrophy and apoptosis, myofibroblast proliferation and interstitial fibrosis.[3] It is related to inherited or acquired cardiomyopathy, pressure/volume overload, ischaemic events, inflammation/infection or infiltrative disorders (*Figure 1*). Pathological LV remodelling is closely linked to activation of renin-angiotensin-aldosterone axis (RAA), proinflammatory cytokines and endothelin, adrenergic nervous system, oxidative stress and abnormal myocyte calcium cycling.[3,13–15] At a cellular level, the processes underlying ventricular remodelling leading to HF development involve the cardiomyocytes, the fibroblasts and the extracellular matrix, the microvascular endothelium and the immune cells.[16] Cardiomyocyte hypertrophy is one of the main compensatory mechanisms in response to external injury or stress. Several signalling pathways are responsible for the hypertrophic response including adrenergic system and RAA activation, increase of reactive oxygen species (ROS) and inflammatory cytokines and grow-factors (i.e., growth differentiation factor-15 (GDF-15) release). Activation of cardiac fibroblasts and myofibroblasts leads to secretion of structural proteins, such as collagen, fibronectin, carboxy-terminal propeptide of procollagen type I (PICP), as well as growth factors, and non-coding RNAs, leading to an intense deposition of collagen fibres and subsequent myocardial fibrosis. The subsequent endothelial dysfunction leads to increased expression of adhesion molecules for leucocyte infiltration [E-selectin, intercellular adhesion molecule 1 (ICAM-1) or vascular cell adhesion molecule 1 (VCAM-1)], impaired coronary flow reserve, reduced nitric oxide (NO) production whose action favours vascular relaxation, cardiac contraction and oxygen consumption. The above-mentioned processes are amplified by immune cell activations, especially macrophages, that secrete a conspicuous array of cytokines (including tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and Galectin-3. Abnormal calcium cycling also has relevant implication on the failing myocardium. A diastolic reduction of calcium lowers its concentration in the sarcoplasmic reticulum, thereby weakening contraction during systole. Also, a loss of function of the Sarco-Endoplasmic Reticulum Calcium ATPase (SERCA2a) pump reduces the calcium content in the myocyte and hence the quantity of this ion that can be released during myocyte activation, causing systolic dysfunction and ventricular tachyarrhythmias.[15,16] Other pathophysiological pathways are related to volume overload. Hypervolemic hyponatremia is associated with elevated levels of plasma vasopressin. Stimulation of vasopressin receptors V1a promotes vasoconstriction in the coronary circulations and increases intracellular calcium levels in cardiac myocytes, leading to myocyte hypertrophy and adverse remodelling.[15]

Figure 1 Cardiac remodelling pathophysiology. Heart failure is due to different causes such as cardiomyopathy, coronary artery disease, pressure/volume overload disorders, inflammatory/infective processes and infiltrative disorders. Pathological processes involving cardiomyocytes, the extracellular matrix, the endothelial function and inflammation are responsible for mechanism of cardiac remodelling. GDF-15, growth differentiation factor-15; ICAM, intercellular adhesion molecule 1; IL, interleukin; NO, nitric oxide; PICP, carboxy-terminal propeptide of procollagen type I; RAA, renin-angiotensin-aldosterone axis; ROS, reactive oxygen species; TNF-α, tumour necrosis factor-α; VCAM, vascular cell adhesion molecule 1.



Many studies in the last few decades have shed light on the capability of the heart to reverse the consequences of maladaptive mechanisms (*Table 1*). This process can result from any pharmacological treatment, interventional/surgical procedure or after lifestyle modification. Reverse remodelling is ultimately associated with better clinical outcomes and improved prognosis[51] although the prevalence of reverse remodelling has been variably estimated also because of the different parameters used as diagnostic criteria. Transthoracic echocardiography represents the first-line imaging tool for monitoring cardiac structure and function including chamber size, wall thickness, systolic and diastolic function. Speckle-tracking analysis provides a more advanced assessment of LV deformation that is relatively independent of LV volumes and shape and may precede overt structural remodelling. Although the availability and cost may limit its routine use, cardiac magnetic resonance informs tissue changes over time with specific sequences such as late gadolinium enhancement (LGE), T1-, T2- and extracellular volume (ECV) mapping. From a practical standpoint, imaging measures should be integrated with clinical parameters associated with higher odd of reverse remodelling such as sex, HF aetiology and duration and cardiovascular (CV) risk factors, as well as with circulating levels of several biomarkers (in particular NT-proBNP, high-sensitivity (hs)-troponins, and the soluble suppression of tumourigenesis (sST2) factor) whose trajectory over time allows to follow the remodelling process.[52–54] In the next paragraphs, we will discuss the pharmacological effects of GDMT that have been shown to target the maladaptive processes and to slow ventricular dilatation and dysfunction.[55] (*Figure 2*).

ACE-I, ARB, ARNI and LV remodelling

With the advent of the ACE-I in the 1980s, the first studies testing the role of these drugs in HF were carried out.[56–60] The ACE-I enalapril significantly improved the clinical course of patients with LV dysfunction, preventing progressive LV dilatation and systolic impairment. These effects probably resulted from a reduction in preload and afterload, as highlighted in the SOLVD study.[61] Enalapril was related with reduction in LV mass, LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) attenuation and reduction in mitral annular E-wave to-A-wave velocity ratio.[17] Similar results have also been observed for other ACE-I such as captopril; particularly, the administration of captopril after myocardial infarction (MI) in patients with LV disfunction resulted in significant reduction in LVEDV and LVESV, with an increase of left ventricle ejection fraction (LVEF) and stroke volume (SV) index.[18,62] The favourable effect on cardiac remodelling may be explained by a direct wall stress reduction as a result of decrease in the levels of angiotensin II counterbalancing the growth of cardiac myocytes and production of collagen by fibroblasts. The reduction in wall stress and consequent LV filling also explains the improvement of LV filling measures. ARB showed similar effects as compared with ACE-I in terms of LV reverse remodelling. LVEF improvement and LV size reduction were similarly observed with enalapril and valsartan.[19,20] Comparing valsartan to captopril, the VALIANT Echo Study showed that in patients with recent MI and evidence of LV dysfunction and/or HF, treatment with captopril or valsartan resulted in similar changes in cardiac volumes, LVEF and infarct segment length between baseline and 20 months after MI.[63] The observation confirmed previous preliminary animal models where angiotensin receptor blockade was associated with inhibition of LV hypertrophy, ventricular dilatation and collagen deposition compared with placebo.

More recently, a third class of drugs that act on the RAA system has been introduced. ARNI in PARADIGM-HF showed a clinical net superiority compared with enalapril in reducing mortality and morbidity in HFrEF. It has been shown that the switch from RAA-blocker to ARNI improves systolic and diastolic function in HFrEF patients.[64]

In the PROVE-HF trial, treatment with sacubitril-valsartan was associated with an increase of LVEF up to 13% points in a quarter of the population.[21] A meta-analysis conducted to compare the effect of ARNI versus ACE-I or ARB on cardiac reverse remodelling, proved that ARNI is related to significant changes in LVEF (+4.64%), LV diameter and volume, in addition to an increase in functional capacity.[65] Volumetric remodelling was also associated with a reduction in the degree of mitral regurgitation[22,66,67] and improvement in diastolic function (significant drop in E/A ratio and diastolic filling time). The EVALUATE-HF trial similarly showed a reduction in atrial and ventricular volume without an observed effect on load, suggesting an effect on filling pressure perhaps related to increased venous capacitance or natriuresis.[23,24]

This hypothesis is supported by the evidence of neprilysin inhibition whose substrates include atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP), bradykinin, substance P, adrenomedullin and cyclic guanosine monophosphate (cGMP) signalling. These molecules eventually promote reduction in cardiac hypertrophy and attenuation of ventricular remodelling.[68] There is evidence that rapid rise in ANP following initiation of sacubutril/valsartan was significantly associated with later improvements in LVEF and reductions in LA volume.[69]

Initiation of sacubitril/valsartan has also been shown to reduce secondary mitral regurgitation (-0.058 cm^2 in ARNI group vs. -0.018 cm^2 in valsartan group, P = 0.032)[25] and to improve global longitudinal strain (GLS) over time (GLS from 10.2% to 13.9%, $P < 0.001$).[26] GLS improvement was associated with a lower risk of cardiovascular death and hospitalization for HF, and this association was stronger than

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Table 1 Evidence of heart failure medical therapy and left ventricular reverse remodelling

Author	Type of study	Intervention/drug	Follow-up	Outcome
ACE-I, ARB, ARNI				
Greenberg et al.[17]	Randomized, prospective: 301 pts	Enalapril vs. placebo	12 months	Reduction in LV mass (265 ± 82 to 255 ± 82 g, $P < 0.001$), LVEDV (198 to 197 mL, $P = 0{,}025$); not LVEF ($P = 0.612$).
Konstam et al.[18]	Randomized, prospective: 29 pts	Captopril vs. losartan	48 weeks	Reduction in LVEDV index (135 ± 26 to 128 ± 23 mL/m^2 for losartan, $P < 0.05$; 142 ± 25 to 131 ± 20 mL/m^2 for captopril, $P < 0.01$), in LVESV with captopril ($P < 0.01$).
Solomon et al.[19]	Randomized, prospective: 603 pts	Valsartan vs. captopril vs. valsartan + captopril	20 months	Similar reduction in volumes, increase in LVEF ($P < 0.09$).
Lee et al.[20]	Randomized, prospective: 445 pts	Valsartan vs. enalapril	12 months	Reduction in LVEDD (59.4 ± 9.9 to 56.4 ± 8.8 mm, P = NS in valsartan group; 57.8 ± 8.4 to 55.5 ± 8.2 mm, P = NS in enalapril group), increase in LVEF (35.1 ± 8.2% to 42.7 ± 10.5%, P = NS in valsartan group; 34.5 ± 8.7% to 41.9 ± 11.1%, P = NS in enalapril group).
Januzzi et al.[21]	Prospective: 794 pts	Sacubitril/valsartan	12 months	Increase in LVEF from 28.2% to 37.8% (95% CI 8.8% to 9.9%; $P < 0.001$), reduction in LVEDV index from 86.93 to 74.15 mL/m^2 ($P < 0.001$) and LVESV index from 61.68 to 45.46 mL/m^2 ($P < 0.001$).
Wang et al.[22]	Meta-analysis (10 studies): 10 175 pts	Sacubitril/valsartan vs. ACE-I vs. ARB		Reduction in LVEDV by 21.6 mL (95% CI 24.32 to 18.88), increase in LVEF (4.64%, 95% CI 3.93 to 5.35).
Desai et al.[23]	Randomized, prospective: 464 pts	Sacubitril/valsartan vs. enalapril	12 weeks	Reduction in LVEDV index (from 75.1 to 70.3 mL/m^2 vs. from 79.1 to 75.6 mL/m^2, $P = 0.02$).
Januzzi et al.[24]	Prospective single centre: 794 pts	Sacubitril/valsartan R vs. NR	12 months	Increase in LVEF greater in R (regression of MR) vs. NR (+11.0% vs. +7.6%, $P = 0.05$); lower final LVEDV index in R (85.2 vs. 96.9 mL/m^2, $P = 0.02$).
Kang et al.[25]	Prospective: 118 pts	Sacubitril/valsartan vs. valsartan	18 months	Decrease in effective regurgitant office area (−0.058 ± 0.095 with sacubitril/valsartan vs. −0.018 ± 0.105 cm^2 with valsartan, $P = 0.032$), reduction of LVEDV ($P = 0.044$).
Moon et al.[26]	Retrospective: 409 pts	Sacubitril/valsartan	27 months	Increase in LVGLS (from 10.2% to 13.9%, $P < 0.001$).
Shah et al.[27]	Randomized, prospective: 554 pts	Sacubitril/valsartan vs. ramipril	8 months	Less increase in LVEDV ($P = 0.025$), no difference in LVEF ($P = 0.78$).
Carluccio et al.[28]	Prospective: 831 pts	Sacubitril/valsartan vs. ACE-I or ARB	8–12 months	Reduction in LVEDV ($P = 0.0005$), LVESV ($P = 0.0009$), increase in LVEF ($P = 0.002$).
Beta-blocker				
Bristow et al.[29]	Randomized, prospective: 345 pts	Carvedilol vs. placebo	6 months	Increase in LVEF ($P < 0.01$).
Colucci et al.[30]	Randomized, prospective: 366 pts	Carvedilol vs. placebo	12 months	Increase in LVEF (10% vs. 3%, $P < 0.001$).
No authors listed[31]	Randomized, prospective: 415 pts	Carvedilol vs. placebo	12 months	Increase in LVEF (+5.3%, $P < 0.0001$), decrease in LVEDD (−1.7 mm, $P = 0.06$).
Remme et al.[32]	Randomized, prospective: 582 pts	Carvedilol vs. enalapril vs. carvedilol + enalapril	18 months	Reduction in LVESV index with combinated therapy compared with enalapril (−5.4 mL/m^2, $P = 0.0015$); reduction in LVESV index with carvedilol (−2.8 mL/m^2, $P = 0.018$).
Cohn et al.[33]	Randomized, prospective: 131 pts	Carvedilol vs. placebo	6 months	Increase in LVEF (+9% vs. +2%, $P = 0.004$).

(*Continues*)

Table 1 (continued)

Author	Type of study	Intervention/drug	Follow-up	Outcome
Genth-Zotz[34]	Randomized, prospective: 56 pts	Metoprolol vs. placebo	6 months	Reduction in LVEDV (259.1 ± 140.1 mL vs. 189.7 ± 59.1 mL), increase in LVEF (26.6 ± 6.3% vs. 32.8 ± 9.6%).
Hall et al.[35]	Prospective: 26 pts	Metoprolol vs. standard therapy	18 months	Increase in LVEF (24 ± 7% to 41 ± 13%, $P = 0.0002$), reduction in LV mass (333 ± 85 to 275 ± 53 g, $P = 0.011$).
Metra et al.[36]	Prospecitve: 150 pts	Metoprolol vs. carvedilol	15 months	Increase in LVEF more with carvedilol than with metoprolol (+10.9% vs. +7.2%, $P = 0.038$).
Doughty et al.[37]	Randomized, prospective: 123 pts	Carvedilol vs. placebo	12 months	Reduction in LVEDV index (−14 mL/m^2, $P = 0.0015$), LVESV index (−15 mL/m^2, $P = 0.0001$), increase in LVEF (+5.8%, $P = 0.0015$).
Lechat et al.[38]	Randomized, prospective: 557 pts	Bisoprolol vs. placebo	5 months	Increase in LVFS (+0.04 ± 0.06% vs. −0.001 ± 0.05%, $P < 0.001$).
MRA				
Chan et al.[39]	Randomized, prospective: 51 pts	Spironolactone + candesartan vs. placebo + candesartan	12 months	Increase in LVEF (35 ± 3% vs. 26 ± 2%, $P < 0.01$), reduction in LVEDV index (121 ± 16 mL/m^2 vs. 155 ± 14 mL/m^2, $P = 0.001$), LVESV index (88 ± 17 mL/m^2 vs. 120 ± 15 mL/m^2, $P < 0.0005$), LV mass index (81 ± 6 g/m^2 vs. 93 ± 6 g/m^2, $P = 0.002$).
Vizzardi et al.[40]	Randomized, prospective: 168 pts	Spironolactone vs. placebo	6 months	Increase in LVEF (from 35.2 ± 0.7% to 39.1 ± 3.5%, $P < 0.001$), reduction in LVEDV, LVESV.
Cicoira et al.[41]	Randomized, prospective: 106 pts	Spironolactone vs. placebo	12 months	Reduction in LVESV (from 188 ± 94 to 171 ± 97 mL vs. from 173 ± 71 to 168 ± 79 mL, $P = 0.03$), LVEDV (from 275 ± 104 to 251 ± 105 mL vs. from 257 ± 80 to 253 ± 89 mL, $P = 0.06$), increase in LVEF (from 33 ± 7% to 36 ± 9% vs. from 34 ± 7% to 34 ± 9%, $P = 0.02$).
Cittadini et al.[42]	Randomized, prospective: 87 rats	Canrenone vs. ramipril vs. canrenone + ramipril vs. placebo	4 weeks	Reduction in LVEDD (from 8.9 ± 0.2 to 10.1 ± 0.2 mm with placebo vs. from 8.8 ± 0.1 to 8.8 ± 0.4 mm with canrenone vs. from 9.0 ± 0.3 to 8.6 ± 0.5 mm with canrenone + ramipril vs. from 9.0 ± 0.2 to 9.6 ± 0.1 mm with ramipril, $P < 0.001$); increase in LVEF (from 25 ± 3% to 20 ± 2% with placebo vs. from 26 ± 2% to 26 ± 3%with canrenone vs. from 25 ± 3% to 29 ± 3% with canrenone + ramipril vs. 25 ± 4% to 23 ± 2% with ramipril).
Boccanelli et al.[43]	Randomized, prospective: 188 pts	Canrenone vs. placebo	12 months	Increase in LVEF (from 40% to 45% vs. from 40% to 43%, $P = 0.004$); similarly reduction in LVEDV (−18%) in both arms.
SGLT2i				
Soga et al.[44]	Prospective: 58 pts	Dapagliflozin	6 months	Increase in LVEF (from 62.3% to 63.6%, $P = 0.011$), reduction in LV mass index (from 75.0 to 67.0 g/m^2, $P < 0.001$).
Lee et al.[45]	Randomized, prospective: 105 pts	Empagliflozin vs. placebo	36 weeks	Reduction in LVEDV index by 8.2 mL/m^2 (95% CI −13.7 to −2.6 mL/m^2, $P = 0.0042$), LVESV index by 6.0 mL/m^2

(*Continues*)

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Table 1 (continued)

Author	Type of study	Intervention/drug	Follow-up	Outcome
				(95% CI −10.8 to −1.2 mL/m^2, P = 0.015), no difference in LVEF (P = 0.75).
Verma et al.[46]	Randomized, prospective: 97 pts	Empagliflozin vs. placebo	6 months	Reduction in LV mass (2.6 vs. 0.01 g/m^2, P = 0.01), not in LVEF (P = 0.08).
Santos-Gallego et al.[47]	Randomized, prospective: 84 pts	Empagliflozin vs. placebo	6 months	Reduction in LVEDV (−25.1 ± 26.0 mL vs. −1.5 ± 25.4 mL, P < 0.001), LVESV (−26.6 ± 20.5 mL vs. −0.5 ± 21.9 mL, P < 0.001), LV mass (−17.8 ± 31.9 g vs. 4.1 ± 13.4 g, P < 0.001).
Omar et al.[48]	Randomized, prospective: 190 pts	Empagliflozin vs. placebo	12 weeks	Reduction in LVESV index (−4.3 mL/m^2; P = 0.04), LVEDV index (−5.5 mL/m^2; P = 0.03), LV mass index (−9.0 g/m^2, P = 0.03), with no change in LVEF (+1.2%, P = 0.32).
Pascual-Figal et al.[49]	Prospective: 162 pts	Dapagliflozin	6 months	Reduction in LV mass index (P < 0.001), LVEDV and LVESV (P < 0.001), increase in LVEF (P = 0.04).
Singh et al.[50]	Randomized, prospective: 56 pts	Dapagliflozin vs. placebo	12 months	No significant changes in LVESV (P = 0.594), LVEDV (P = 0.495), LV mass index (P = 0.440), LVEF (P = 0.732).

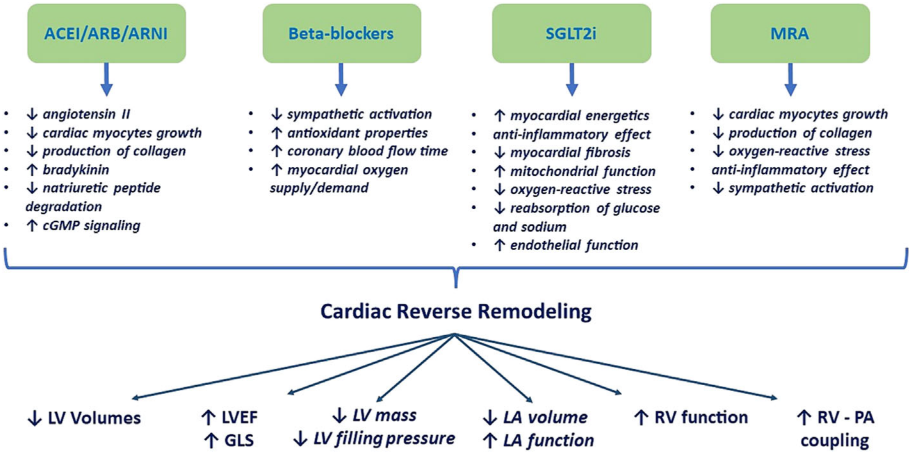
ACE-I/ARB/ARNI, angiotensin-converting enzyme inhibitors/angiotensin receptors II blockers/angiotensin receptor blocker-neprilysin inhibitor; CI, confidence interval; LV, left ventricle; LVEDD, left ventricle end diastolic diameter; LVEDV, left ventricle end diastolic volume; LVEF, left ventricle ejection fraction; LVESD, left ventricle end systolic diameter; LVESV, left ventricle end systolic volume; LVFS, left ventricle fractional shortening; LVGLS, left ventricle global longitudinal strain; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonists; NR, non-responder; NS, not significant; pts, patients; R, responder; RCTs, randomized controlled trials; SGLT2i, sodium-glucose inhibitors.

that of change in other conventional echocardiographic parameters.[27] Similar favourable effects on reverse remodelling have been observed following an acute MI. The PARADISE-MI Echo Study recently demonstrated that patients randomized to ARNI instead of ramipril had less increase in LVEDV and greater decline in LV mass index, decrease in E/e' ratio and decrease in tricuspid regurgitation peak velocity, without significant changes in LVEF.[27] Taken together, these findings highlights the beneficial role of drugs acting on RAA system in promoting LV reverse remodelling. From this perspective, LV reverse remodelling may be used as a marker of treatment response to ACE-I/ARB/ARNI in HFrEF patients[28,70,71] (*Table 1*). The improvement in LVEF secondary to up-titration of this class of drugs, may have potential relevant clinical implication in clinical practice, including the duration of when implantable cardioverter defibrillator (ICD) implantation is indicated or for correction of mitral regurgitation.

Beta-blocker and LV remodelling

Historical clinical trials have proved the benefits of beta-blockers in conjunction with the others recommended medical therapy in the setting of HF.[72–76] Beta-blockers consistently provided clinical benefits and improved LV function over and above those achieved on standard therapy alone.[29–33] Their anti-remodelling effect is due to the blockade of the multiple untoward effects of sympathetic activation on the failing heart and possibly to the antioxidant properties of some agents (i.e., carvedilol),[34,35,77–80] favouring LV mass reduction and increase in LVEF. Due to the favourable chronotropic effect, beta-blockers also increase systolic coronary blood flow time, myocardial oxygen supply/demand and eventually improve diastolic function. Long term therapy with metoprolol resulted in reduction of LV volumes, LV mass and improved LVEF (LVEF from 24% to 41%, P = 0.0002) by 18 months.[35] Comparing metoprolol with carvedilol in HFrEF, carvedilol showed larger increase in LVEF (+10.9% vs. +7.2%, P = 0.038) and LV stroke volume. In addition, carvedilol produced a significant greater decrease in mean pulmonary artery pressure (PAmP) and pulmonary capillary wedge pressure (PCWP), both at rest end during exercise. The effect is thought to be driven by a vasodilatory effect that eventually improves the pulmonary circulation and the coupling with the RV. In contrast, the metoprolol group showed greater increase in maximal exercise capacity, with similar improvement of symptoms and quality of life.[36] Moreover, the use of carvedilol in HFrEF patients with ischaemic or idiopathic heart disease demonstrated a significant increase in LVEF, SV and LV stroke work, along with reduction in mean pulmonary artery pressure and pulmonary capillary wedge pressure, probably due to the LV improvement.[81,82] The combination of carvedilol and ACE-I further decreased LVEDV, LVESV and increases LVEF compared

Figure 2 Four pillars heart failure medical therapy and cardiac reverse remodelling. ACE-I/ARB/ARNI, beta-blockers, MRA and SGLT2i promote cardiac reverse remodelling. The reverse remodelling is explained by different pharmacological effects including antioxidant properties, anti-inflammatory effect, reduction of myocardial fibrosis and sympathetic activation, increase of mitochondrial and endothelial function. These processes eventually lead to reduction of myocardial volumes, mass and filling pressure, increase of LVEF and GLS, improvement of LA and RV structure and function. ACEI/ARB/ARNI, angiotensin-converting enzyme inhibitors/angiotensin receptors II blockers/angiotensin receptor blocker-neprilysin inhibitors; cGMP, cyclic guanosine monophosphate; GLS, global longitudinal strain; LA, left atrial; LV, left ventricle; LVEF, left ventricle ejection fraction; MRA, mineralocorticoid receptor antagonists; PA, pulmonary artery; RV, right ventricle; SGLT2i, sodium-glucose transport protein 2 inhibitors.



with ACE-I alone.[37,83–85] The echocardiographic sub-study of CIBIS I showed that after 5 months of treatment with bisoprolol LV fractional shortening was increased and end-systolic dimensions were significantly reduced.[38] Beta-blockers represent a key foundational therapy in HFrEF patients. Overall, these findings suggest that, beyond the clinical benefits, beta-blockers alone or in combination with ACE-I, have consistent benefits in terms of improvement of LV structure and function (*Table 1*).

MRA and LV remodelling

The addition of mineralocorticoid receptor antagonist to ACE-I or ARB has been shown to have beneficial effect on survival in patients with chronic HF.[86,87] Aldosterone promotes fluid retention, potentiates effects of catecholamines and promotes myocardial fibrosis.[88–94] MRA inhibits myocardial fibrosis, sympathetic activation and parasympathetic inhibition. The evidence is supported by experimental animal studies showing favourable effects of MRA to reduce inflammation and oxidative stress and suppress the progression of cardiac remodelling and fibrosis in rats with induced myocardial injury.[95]

It has been shown that adding spironolactone to angiotensin II receptor blocker improved LVEF, reduced volumes with a significant increase in myocardial systolic velocity and strain in patients with HFrEF.[39,40] Particularly, spironolactone promoted reduction in LVESV (from 188 ± 94 to 171 ± 97 mL, P = 0.03), LVEDV (from 275 ± 104 to 251 ± 105 mL, P = 0.06) and an increase in LVEF (from 33 ± 7% to 36 ± 9%, P = 0.02).

Administration of this drug was also related to amelioration of diastolic function and improvement in exercise capacity.[41] Similarly, canrenone, an active metabolite of spironolactone, has shown important anti-remodelling effects in post infarction LV processes.[42] Canrenone has potential effects on cardiovascular outcomes increasing LVEF and reducing circulating brain natriuretic peptide (BNP).[43] The combination of MRA with ACE-I/ARB potentiated MRA's effect by a complementary prevention of LV fibrosis, cardiac hypertrophy and molecular alterations with an improvement of LVEF and an attenuation of LVEDV[96] (*Table 1*).

SGLT2i and LV remodelling

SGLT2i are the newest class of drugs used for the treatment of HF.[1,2] SGLT2i showed a critical benefit on HF outcomes[97,98] through potential different mechanisms including mild natriuresis, osmotic diuresis,[99] reduction in preload and afterload, inhibition of cardiac sodium-hydrogen exchanger and improved myocardial bioenergetics.[100] SGLT2i seem able to switch myocardial metabolism away from glucose utilization into consumption of fatty acids, ketone bodies and branched-chain amino acids, which enhances myocardial energetics,[101,102] in association with an anti-inflammatory effect, consequently reducing myocardial fibrosis and enhancing endothelial function. Taken together, these mechanisms are thought to be related with the improvement of diastolic and systolic function, eventually favouring the reverse remodelling.[44,103,104] The SUGAR-DM-HF trial showed that empagliflozin reduced LV volumes (−8.2 mL/m^2 for LVEDV,

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P = 0.0042, and −6 mL/m^2 for LVESV, P = 0.015) in HFrEF patients with type 2 diabetes or prediabetes.[45] The addition of empagliflozin to standard therapy in people with type 2 diabetes and coronary artery disease (CAD) was associated with a significant reduction in LV mass (−3.35 g/m^2, P = 0.01), in addition to an important lowering of blood pressure.[46] It has been suggested that SGLT2i may improve mitochondrial function and reduce oxygen-reactive stress that otherwise would favour ventricular hypertrophy and fibrosis in patients with type2 diabetes.[105] Hyperglycaemia contributes to activation of the RAA system, which leads to overproduction of angiotensin II and aldosterone, and to the formation of advanced glycation end products, which cause crosslinking of collagen. The favourable effects on metabolic and glycaemic profile may also explain the improvement in cardiac function.

Even in nondiabetic HFrEF patients empagliflozin was associated with reduction in LV volumes, LV mass and improvement in LVEF (6.0% vs. 3.9%, $P < 0.001$), in addition to improvement of functional capacity and quality of life.[47] To support the concept that SGLT2i improves cardiac metabolism in these patients, animal studies showed that treatment of non-diabetic pigs with ischaemic HF with empagliflozin reduces cardiac remodelling by switching myocardial substrate utilization from glucose towards oxidation of free fatty acids, ketone bodies, and branched-chain amino acids eventually resulting in a 30% increased cardiac production of ATP. The Empire HF trial confirmed the favourable effect of empagliflozin on LV volumes, without promoting a significant improvement in ejection fraction.[48] The DAPA-MODA trial showed an overall improvement in LV size and function. After 180 days of initiation of dapagliflozin, LV geometry improved with significant reductions in LV mass, LVEDV and LVESV.[49] On the opposite, the REFORM trial did not show any improvement in cardiac structure and function following the initiation of dapagliflozin, but this was probably due to a small sample size which resulted in limited power to detect a difference between treatments.[106] CANA-HF study highlighted that treatment with canagliflozin, but not sitagliptin, was associated with a significant improvement in LVEF.[50] There is also evidence that SGLT2i may exert cardioprotective vessel-regenerative effects by shifting circulating vascular progenitor cell towards M2 polarization. Empagliflozin has been shown to improve coronary microvascular function and increase cardiac output in mice, as evidenced by the increase in coronary blood flow by ultrasound imaging.

In a recent meta-analysis on LV remodelling response to SGLT2i in HF, this class of drug showed a consistent reduc-

Table 2 Evidence of heart failure medical therapy and left atrial reverse remodelling

Author	Type of study	Intervention/drug	Follow-up	LA outcome
ACE-I, ARB, ARNI				
Greenberg et al.[17]	Randomized, prospective: 301 pts	Enalapril vs. placebo	12 months	Reduction in LA diameter ($P = 0.08$).
Desai et al.[23]	Randomized, prospective: 464 pts	Sacubitril/valsartan vs. enalapril	12 weeks	Reduction in LAV index (from 30.4 to 28.2 mL/m^2 in sacubitril/valsartan group vs. from 29.8 to 30.5 mL/m^2 in enalapril group).
Milliez et al.[114]	Randomized, prospective: 180 rats	Lisinopril vs. spironolactone vs. atenolol vs. combinations	4 months	Reduction in LA diameter, lowest value with tri-therapy (P = NS).
MRA				
Cicoira et al.[41]	Randomized, prospective: 106 pts	Spironolactone vs. placebo	12 months	Reduction in LA end systolic volume (from 102 to 89 mL vs. from 99 to 95 mL, P = NS).
Boccanelli et al.[43]	Randomized, prospective: 188 pts	Canrenone vs. placebo	12 months	Reduction in LA diameter (from 4.24 ± 0.76 mm to 4.07 ± 0.77 mm vs. from 4.12 ± 0.59 mm to 4.13 ± 0.67 mm, $P = 0.02$).
Mak et al.[115]	Randomized, prospective: 44 pts	Eplerenone vs. control	12 months	Reduction in LAV index (from 50 ± 17 to 52 ± 19 mL/m^2 vs. from 45 ± 12 to 53 ± 23 mL/m^2).
SGLT2i				
Soga et al.[44]	Prospective: 58 pts	Dapagliflozin	6 months	Reduction in LAV index (from 31 to 26 mL/m^2, $P = 0.001$).
Lee et al.[45]	Randomized, prospective: 105 pts	Empagliflozin vs. placebo	36 weeks	Reduction in LA volume ($P = 0.26$).
Omar et al.[48]	Randomized, prospective: 190 pts	Empagliflozin vs. placebo	12 weeks	Reduction in LAV index (−2.5, 95% CI −4.8 to −0.1 mL/m^2, $P = 0.04$).
Pascual-Figal et al.[49]	Prospective: 162 pts	Dapagliflozin	6 months	Reduction in LAV index (−6.6%, 95% CI −11.1 to −1.8 mL/m^2, $P = 0.008$).
Singh et al.[106]	Randomized, prospective: 56 pts	Dapagliflozin vs. placebo	12 months	Non-significant change in LA volume (−2.6 mL, $P = 0.464$).

ACE-I/ARB/ARNI, angiotensin-converting enzyme inhibitors/angiotensin receptors II blockers/angiotensin receptor blocker-neprilysin inhibitor; CI, confidence interval; FAS, fractional area shortening; LA, left atrial; LAV, left atrial volume; MRA, mineralocorticoid receptor antagonists; NS, not significant; pts, patients; SGLT2i, sodium-glucose inhibitors.

tion of LV volumes, LV mass and an LVEF increase.[107] SGLT2i might play an important role in promoting favourable reverse cardiac remodelling and improving LV systolic function in HF patients. Reversed cardiac remodelling may partially explain the favourable clinical effects of SGLT2i on HF (*Table 1*).

Left atrial remodelling

The LA is a thin-walled dynamic chamber playing a physiological role in global cardiac performance, contributing to LV filling and cardiac output, maintaining a dynamic interaction with the LV.[108] In response to different stressors and disease mechanisms, as the development of atrial fibrillation (AF), LA can undergo a remodelling process resulting in its dilatation and functional impairment.[109–111] Atrial stretch activates pro-inflammatory cytokines and favours the deposition of collagen fibres and other factors such as insulin-like growth factor binding protein-7 (IGFBP-7). Elevated serum levels of IGFBP-7 are associated with left atrial stiffness and diastolic dysfunction. Taken together the ultrastructural changes on atrial anatomy lead to dilatation and increased stiffness. Echocardiography can detect these changes through volumes assessment and function evaluation by speckle-tracking analysis.[112] Impaired atrial structure and function independently predict cardiovascular morbidity and mortality in different patient populations.[111] The reverse remodelling occurs after the removal of external stressors leading to a reduction in LA volume and/or a restoration of specific functional parameters.

Recent data suggest that therapeutic intervention can attenuate the process of LA remodelling and potentially promotes LA reverse remodelling, by improving specific functional parameters, with an amelioration in clinical symptoms and outcome[113] (*Table 2*). LA reverse remodelling can be eventually considered an active player of the so-called ‘complete left-sided reverse remodeling’,[116] with evidence of beneficial effects mostly driven by RAA system inhibition and SGLT2i. (*Figure 1*).

ACE-I, ARB, ARNI and LA remodelling

Drugs acting on RAA system play a key role not only in LV remodelling but also in LA reverse remodelling. Among HFrEF patients enrolled in the BIOSTAT-CHF, LA reverse remodelling was associated with ACE-I/ARB up-titration and identified patients at a lower risk of clinical events. Hence, changes in LA dimension may represent a useful marker of response to treatment and may improve risk stratification in HF patients.[117] The VALIANT Echocardiography study[19] that enrolled patients with LV dysfunction, HF or both following MI, showed that early LA remodelling was a predictor of cardiovascular morbidity and mortality. LA remodelling was significantly related to favourable changes in LV dimensions over 20 months.[118] Along with the effect on HF outcomes, ACE-I as enalapril attenuate atrial fibrosis and reduce associated risk of AF.[114,119–122] From a pathophysiological point of view, the RAA system has a role in arrhythmogenic atrial structural remodelling in chronic HF.

Along with the effectiveness of ACE-I/ARB, also ARNI have been shown to promote LA reverse remodelling by reducing LA volume and improving LA function by strain assessment.[21] The PROVE-HF study showed a reduction in LA volume (LAV) (from 30.4 to 28.2 mL/m^2 in sacubitril/valsartan group vs. from 29.8 to 30.5 mL/m^2 in enalapril group) index in HFrEF patients treated with ARNI.[21] Similar results have been confirmed in the EVALUATE-HF trial, with a significant reduction in LAV and E/e′ ratio, albeit without significant changes in LVEF, in patients randomized to ARNI compared with enalapril.[22] Among patients with de novo HF, LA reverse remodelling promoted by ARNI, was more evident following early introduction during hospitalization. On the contrary, in the acute setting after acute myocardial infarction, the PARADISE-MI Echocardiographic sub-study showed that patients randomized to ARNI did not show a significant change in LAV at 8 months.[27] The trial design with an active comparator and the low prevalence of atrial enlargement at baseline may be one explanation for these results.

The number of studies on atrial reverse remodelling among HFrEF population is still limited and further studies are needed to better clarify the role of modern comprehensive up-titration of HF medical therapy on LA structure and function.

MRA and LA remodelling

MRA has been shown to positively affect not only LV but also LA structure and function.[41,115] EMPHASIS-HF trial showed that eplerenone significantly reduced new onset atrial fibrillation (2.7% in eplerenone group vs. 4.5% in placebo group, $P = 0.034$),[123] probably due to beneficial effect on LA structure and function. In AREA IN-CHF study, canrenone reduced LA size and circulating BNP, in addition to increasing LVEF, with potential effects on clinical outcome.[96] However, few data are available among HFrEF patients, and more clinical data are needed.

SGLT2i and LA remodelling

As has been shown for LV, SGLT2i also represents a promising drug class for LA reverse remodelling. Dapagliflozin administration in stable out-setting patients with chronic HF and optimized therapy results in global reverse remodelling of cardiac structure, including reduction in LA volumes and improvement in N-terminal pro-b type natriuretic peptide (NT-proBNP) concentrations.[49] Similar results have also been observed for empagliflozin in the Empire HF, where treatment with empagliflozin was related with significant reduction in left atrial and ventricle volumes [LAV index −2.5, 95% confidence interval (CI) −4.8 to −0.1 mL/m^2, $P = 0.04$].[48] Less clear results were found in SUGAR-DM-HF,[45] where empagliflozin favoured reverse remodelling, without reaching statistical significance in reducing LAV. The LA plays an active role in HFrEF pathophysiology and appears as a promising target to evaluate the efficacy of HF drugs. Although trials have demonstrated conflicting results, additional efforts are needed to clarify whether the assessment of LA reverse remodelling can be considered an independent entity and can provide prognostic information in patients undergoing up-titration of guideline directed medical therapy[111] (*Table 2*).

Right ventricular remodelling

RV dysfunction is a key predictor of poor prognosis in patients with HF.[124–126] As for the LV remodelling, pathophysiological processes that initiate or promote RV failure include myocyte hypertrophy, fibrosis, ischaemia, neurohormonal activation and inflammation.[127,128] Neurohormonal activation ultimately becomes maladaptive with reduction of beta1-adrenergic receptor density, depletion of tissue adrenergic effectors and failure of the cardiac myocytes.[129]

With the increase of the oxygen demand and the overproduction of fibrosis, the RV loses its function and there is a progression of excitation-contraction uncoupling.[130] Longitudinal change of RV function following introduction of HF medical therapy is yet less explored and only few studies are available. Nevertheless, the optimization of HF medical therapy may act similarly for the RV as for LV structure and function (*Table 3*).

ACE-I, ARB, ARNI and RV remodelling

Although there is robust evidence on the role ACE-I, ARB or ARNI to promote LV reverse remodelling, less is known about the efficacy of these medications on RV function. In the ELITE ventricular function sub-study, both losartan and captopril were associated with trends towards increased RVEF and decreased RV volumes, reaching significance for RV end-systolic volume index during losartan treatment.[61] In the Dauna Heart Failure Registry, over 12-months ARNI therapy was

Table 3 Evidence of heart failure medical therapy and right ventricular reverse remodelling

Author	Type of study	Intervention/drug	Follow-up	LV outcome
ACE-I, ARB, ARNI				
Konstam et al.[61]	Randomized, prospective: 29 pts	Captopril vs. losartan	48 weeks	Increase in RVEF ($P < 0.01$) and reduction in RVESV index ($P < 0.05$) in losartan group, similar NS trends in captopril group.
Correale et al.[131]	Prospective: 60 pts	Sacubitril/valsartan	12 months	Reduction in PAsP (from 34.7 ± 12.5 mmHg to 31.0 ± 12.8 mmHg, $P < 0.05$), increase in TAPSE (from 17.8 ± 3.9 mm to 16.5 ± 4.0 mm, $P < 0.001$), reduction in RV area ($P < 0.05$).
Clements et al.[132]	Prospective: rats	Sacubitril/valsartan vs. valsartan	6 weeks	Reduction in RV pressure (46 ± 5 mmHg vs. 62 ± 4 mmHg) and RV hypertrophy (0.46 ± 0.06 mm vs. 0.74 ± 0.06 mm).
Mantegazza et al.[133]	Prospective: 51 pts	Sacubitril/valsartan	6 months	In non-ischaemic pts: increase in 3D-RVEF (48.4 ± 6.5% vs. 44.3 ± 7.5%; $P < 0.05$), 3D-RVEDV index (63 ± 27 vs. 71 ± 30 mL/m^2; $P < 0.05$). In ischaemic pts: increase in 3D-RVEDV index (57 ± 11 vs. 63 ± 14 mL/m^2; $P < 0.05$).
Beta-blocker				
Galves et al.[134]	Prospective: 40 pts	Beta-blocker	3 months	Reduction in RV diameter (from 30 ± 4 to 27 ± 5 mm, $P = 0.03$), increase in TAPSE (from 16.5 ± 4 to 19 ± 4 mm, $P = 0.0006$).
De Man et al.[135]	Prospective - rats	Beta-blocker	3 weeks	Increase in RV contractility and filling pressure (both $P < 0.01$).
Tatli et al.[136]	Randomized, prospective: 74 pts	Carvedilol vs. placebo	4 months	Increase in RVEF (from 28.8 ± 4.2% to 36.3 ± 2.6%, $P = 0.003$).
SGLT2i				
Nassif et al.[137]	Randomized, prospective: 65 pts	Empagliflozin vs. placebo	12 months	Reduction in PAdP) (1.7 mmHg lower (95% CI 0.3 to 3.2; $P = 0.02$).

ACE-I/ARB/ARNI, angiotensin-converting enzyme inhibitors/angiotensin receptors II blockers/angiotensin receptor blocker-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonists; SGLT2i, sodium-glucose inhibitors; pts, patients; RV, right ventricle; RVEF, right ventricle ejection fraction; 3D-RVEF, three-dimensional right ventricular ejection fraction; RVESV, right ventricle end systolic volume; RVEDV, right ventricle end diastolic volume; 3D-RVEDV, three-dimensional right ventricular end diastolic volume; PAsP, pulmonary artery systolic pressure; PAdP, pulmonary artery diastolic pressure; TAPSE, tricuspid annular plane systolic excursion; NS, not significant.

associated with significant improvement of RV parameters (reduction in pulmonary artery systolic pressure (PAsP) from 34.7 ± 12.5 mmHg to 31.0 ± 12.8 mmHg, $P < 0.05$; increase in tricuspid annular plane systolic excursion (TAPSE) from 16.5 ± 4.0 mm to17.8 ± 3.9 mm, $P < 0.001$).[131] In preclinical studies on rats with pulmonary hypertension, ARNI reduced RV systolic pressure, RV hypertrophy and dilatation.[138] These effects may be secondary to pulmonary vascular changes, including reduced pulmonary vascular remodelling, as demonstrated by a reduction of the pulmonary vascular wall thickness.[132] Given the key pathophysiological role of RV dysfunction in HF,[133] more clinical data are needed to assess the role of ACE-I, ARB or ARNI on RV structural and functional remodelling (*Table 3*).

Beta-blockers and RV remodelling

As shown for the LV, beta-blockers have a positive role also on RV structure and function. It has been shown that after 3 months from optimization of beta-blocker therapy, RV size decreased from 30 to 27 mm, while RV systolic function significantly improved based on TAPSE (19 vs. 16 mm, $P = 0.0006$).[134] In rats with induced pulmonary hypertension, bisoprolol delayed the time to right HF. RV afterload was unaffected; however, bisoprolol treatment increased RV contractility and filling. Bisoprolol restored RV beta-adrenergic receptor signalling and histology revealed significantly less RV fibrosis and myocardial inflammation.[135]

Carvedilol was associated with an increase in the RVEF (from 28.8 ± 4.2% to 36.3 ± 2.6%, $P = 0.003$) and decrease of RV volumes. Reduced PCWP could translate into decreased of RV afterload and improvement in RV systolic function.[136] A recent trial took into consideration bucindolol, identifying that the effect of this drug on mortality in HFrEF patients was modified by baseline RVEF. The use of bucindolol reduced all-cause mortality risk if RVEF was 35% or greater (HR 0.70), but not in those with an RVEF of less than 35% (HR 1.02). If these hypothesis-generating findings could be replicated using approved beta-blockers, RVEF may help to risk stratify HFrEF patients for optimization of beta-blocker therapy.[139]

SGLT2i and RV remodelling

Data on the action of SGLT2i on RV structure and function are still poor. In the EMBRACE-HF trial, empagliflozin produced rapid reduction in PA pressures (pulmonary artery diastolic pressure (PAdP) −1.7 mmHg, 95% CI 0.3 to 3.2, $P = 0.02$) measured with CardioMEMS PA pressure sensor), and this appeared to be independent of loop diuretic management.[137] These data must be considered as a starting point to investigate the role of SGLT2i on the right heart (*Table 3*).

Future perspectives

Additional research is required to explore new therapeutic options and improve the possibility of reverse remodelling with GDMT. Novel antidiabetic drugs and metabolic interventions showed promising results in improving cardiovascular outcomes. Yet their role in promoting reverse remodelling needs to be explored. Myosin activators, that is, omecamtiv mecarbil, have shown potentiality to increase contractility in HFrEF and represents a promising option.[140] Other strategies are still in the experimental phase. Proteasome inhibition is a future option for certain genetic cardiomyopathies as well as gene editing to correct specific genetic variants and potentially prevent cardiomyopathy.[141] Early anti-inflammatory treatments to prevent scar development after an ischaemic event and the modulation of cell proliferation and the regulation of calcium cycling by improving contractility and increasing mitochondrial ATP production represent other promising preclinical research targets.[142,143]

Conclusions

Optimization of background HF medical therapy represents a key goal in the management of HF patients. The four classes of HF drugs ACE-I/ARB/ARNI, beta-blockers, MRA and SGLT2i have all been demonstrated to have positive effects on cardiac reverse remodelling. The promotion of myocardial recovery may explain the positive effects on CV outcomes. Yet most of the data derives from studies assessing the effect of each single drug alone. More clinical data are needed to better understand the phenomena of reverse remodelling in patients undergoing combined up-titration HF medical therapy, to improve patient selection, and provide new insights on mechanistic pathways for research and treatment development.

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Conflict of interest

The authors have no conflicts of interest.

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