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REVIEW

Left atrial disease and left atrial reverse remodelling across different stages of heart failure development and progression: a new target for prevention and treatment

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The left atrium is a dynamic chamber with peculiar characteristics. Stressors and disease mechanisms may deeply modify its structure and function, leading to left atrial remodelling and disease. Left atrial disease is a predictor of poor outcomes. It may be a consequence of left ventricular systolic and diastolic dysfunction and neurohormonal and inflammatory activation and/or actively contribute to the progression and clinical course of heart failure through multiple mechanisms such as left ventricular filling and development of atrial fibrillation and subsequent embolic events. There is growing evidence that therapy may improve left atrial function and reverse left atrial remodelling. Whether this translates into changes in patient's prognosis is still unknown.

In this review we report current data about changes in left atrial size and function across different stages of development and progression of heart failure. At each stage, drug therapies, lifestyle interventions and procedures have been associated with improvement in left atrial structure and function, namely a reduction in left atrial volume and/or an improvement in left atrial strain function, a process that can be defined as left atrial reverse remodelling and, in some cases, this has been associated with improvement in clinical outcomes. Further evidence is still needed mainly with respect of the possible role of left atrial reverse remodelling as an independent mechanism affecting the patient's clinical course and as regards better standardization of clinically meaningful changes in left atrial measurements. Summarizing current evidence, this review may be the basis for further studies.

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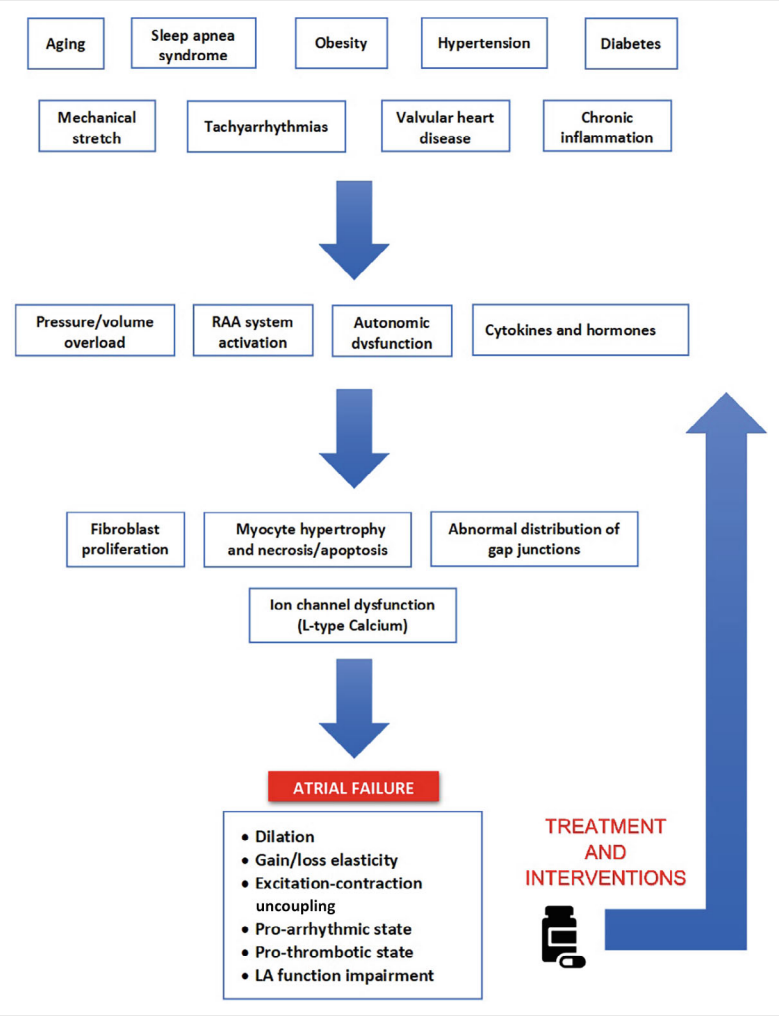
Graphical Abstract



Pathogenetic mechanism of atrial failure. Left atrial (LA) remodelling is a multifactorial clinical entity driven by different electrical, mechanical and metabolic stressors. These ones lead to volume/pressure overload, activate the renin–angiotensin–aldosterone (RAA) system and determine the release of different cytokines and hormones. The time-dependent adaptation of atrial myocytes finally results in a chronic LA dilatation and a loss of elasticity, with a consequent stiffer chamber, less affected by changes in pressure. Without removing the causative stressor, this adaptive process inexorably progresses and the alterations become persistent. However, by treating the underlying diseases or risk factors and with heart failure therapies, atrial failure progression may be halted and, in some cases, reversed.

Keywords Heart failure • Left atrium • Reverse remodelling

Introduction

The left atrium (LA) is a thin-walled dynamic chamber that plays an important role in global cardiac performance, contributing to left ventricle (LV) filling and cardiac output and maintaining a dynamic interaction with the LV.[1] In response to varying stressors (i.e. electrical, mechanical and metabolic), the LA can undergo a remodelling process resulting in its persistent dilatation with functional impairment.[2,3] LA enlargement and dysfunction are well-established markers of diastolic[4] and systolic dysfunction,[5] as well as predictors of cardiovascular (CV) outcomes, including atrial fibrillation (AF),[6,7] stroke,[8,9] heart failure (HF), and subsequent mortality.[10] This relationship is highly related to LV function and has been shown across all the ejection fraction,[11–14] even in advanced HF.[15] However, recent data suggest a possible independent contribution of LA dysfunction in HF.[16]

In the past decades, the concept of LA remodelling has evolved, and the contribution of the LA to the pathophysiology of HF has grown in appreciation.[2,17–20] Indeed, changes in LA structure and function may be either a marker of HF severity or a mechanism actively contributing to the progression of cardiac dysfunction. One manifestation of LA disease, AF, contributes substantially to morbidity in patients with HF. Recent data suggest that timely therapeutic intervention may attenuate the process of deleterious LA remodelling and potentially promote reverse LA remodelling with a consequent improvement in clinical symptoms and outcomes.[2,21] In contrast, age and endurance exercise are related to LA enlargement even in absence of LA disease.[22,23]

Prevention of LA dysfunction and treatment of LA disease may therefore be of critical importance. The relationship between changes in LV structure and function and subsequent CV outcome is well established.[24] We propose here a similar conceptual approach to the LA reflecting dynamic changes in relation to HF progression. The aim of this review is to summarize the concepts and the pathophysiologic mechanisms behind the potential beneficial effects of directed medical therapy on LA reverse remodelling and its clinical implications across all HF stages.

Definition of left atrial reverse remodelling

Atrial disease, as stated in the recent European Society of Cardiology (ESC) HF guidelines, can be defined as a complex of subclinical structural, electrophysiological, and functional changes that affect the atria with the potential to produce clinical consequences[25] (*Graphical Abstract*). Signs and symptoms may be those of HF and/or of atrial arrhythmias and be due to both a failing LV and a dysfunctional LA, proving the active role of atrial disease in HF pathophysiology[18,26] and in other pathophysiological processes.[27] Impaired atrial contractile reserve and LA enlargement independently predict mortality and CV morbidity, as well as AF onset or recurrence and severity of functional impairment in HF patients.[14,28–30]

The temporal process occurring after the removal of external stressors,[21] leading to a reduction in LA volume and/or a restoration of specific functional parameters[2] is called reverse remodelling.

Only recently the attention shifted to quantifying and evaluating LA reverse remodelling as a potential biomarker that responds to specific therapeutic interventions, potentially providing prognostic information. One critical aspect is that the response to therapeutic interventions is potentially different in the acute or chronic settings or in the early or late stage of atrial failure. In the early stage, the LA is less abnormal and potentially more capable of responding to the changes in myocardial structure and function. When stressors act for a longer time, LA remodelling progresses and reversal might be less likely (*Figure 1*). Reversibility and, ultimately, the clinical significance of LA reverse remodelling in the late stages of atrial failure, have to be proven, yet. Some studies have indicated that LA dysfunction may precede changes in LA volume in different clinical settings[31–34] and in normal subjects.[35,36] Thus, changes in LA function may be more sensitive than changes in LA volume to detect abnormal myocardial function and the effects of therapeutic interventions. However, this has not been proven, yet.

Assessment of left atrial reverse remodelling

Assessment of LA remodelling is based on various non-invasive parameters. To date, there are no definite cutoffs identifying a clinically relevant LA reverse remodelling. Hence, monitoring LA remodelling without such standardization makes routine examination challenging. Another major limitation of current evaluations of changes in LA function is that they are almost completely based on LA size. Measurements of LA strain and the different passive and active components might, on the other hand, better define atrial function in different clinical settings (*Table 1*).[37–40] *Table 2* shows some of the definitions of LA reverse remodelling reported from the literature.[16,41–48] Most reports have used arbitrarily a 15% change of LA volume measured with either echocardiography and/or cardiac magnetic resonance (CMR). Functional aspects of LA reverse remodelling have been extensively described using strain analysis. A recent systematic review and meta-analysis including more than 2500 patients showed reference values for reservoir, conduit and contractile strains. The variability was mostly explained by heart rate, body surface area, and sample size.[49] Nevertheless, little is known about the percentage change of LA strain which may be clinically significant. The difficulties related to the assessment of LA reverse remodelling are due to time-consuming issues, the reliability of the measurement and the lack of standardization across inter-vendor packages. However, the reproducibility of both LA volume and LA strain seems acceptable.[50,51]

Stages of heart failure

In line with the 2021 HF Society of America, HF Association of the ESC and Japanese HF Society universal definition of HF,[52] a four-stage classification has been proposed for atrial disease. We discuss below the potential benefits of prevention and treatment on LA reverse remodelling, across the four HF stages.

Patients at risk for heart failure and with pre-heart failure (stages A and B)

The importance of adopting effective measures to control risk factors and thus to prevent future HF development is an emerging public health need.[53] Even in the absence of overt HF, LA remodelling has a crucial role in this process. LA structural and functional reverse remodelling has been used to assess the therapeutic utility of different treatments, both in animal models and in humans (*Table 3*).[43,47,54–75] Risk of HF and pre-HF, i.e. structural heart disease and/or abnormal cardiac function in the absence of symptoms (stages A and B) represent two crucial steps of the progression of LA remodelling in which preventive measures and targeted treatments have shown favourable results.

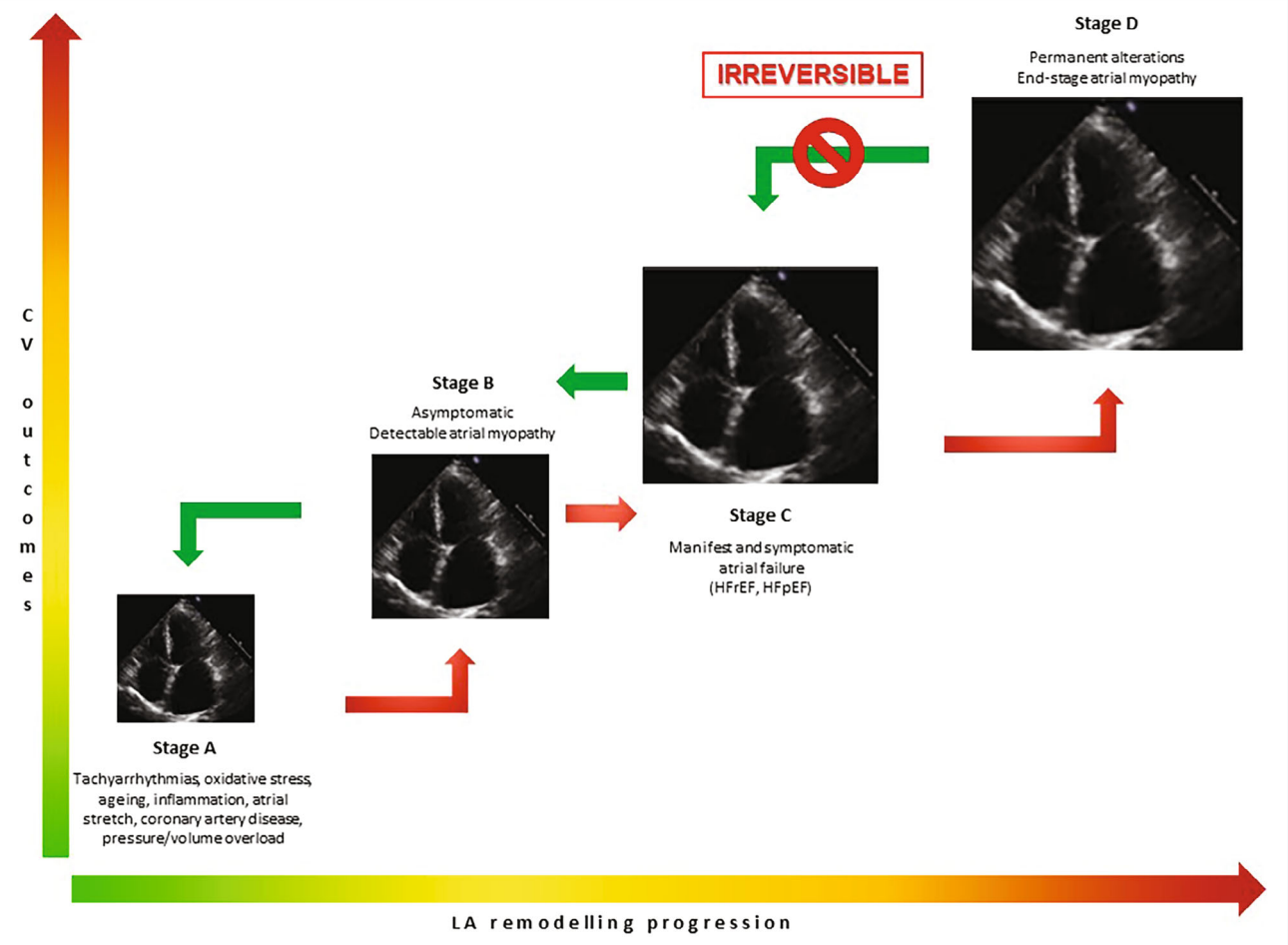


Figure 1 Progression of left atrial remodelling. The progression of left atrial remodelling goes through several stages, along with progressive worse cardiovascular outcomes. When causative stressors are not removed (by preventive measures or treatments), worsening atrial failure inexorably reaches an irreversible stage. On contrast, acting in the earlier phases may arrest and also reverse the pathophysiologic process. CV, cardiovascular; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Hypertension

In hypertensive patients, evidence of LA reverse remodelling has been provided by the efficacy of specific therapies and a better blood pressure (BP) control.[76] In fact, some studies have demonstrated a reversal of LA dimension with associated functional improvement[54–56,77,78] (*Table 3*). Telmisartan showed a reduction in LA maximum and minimum volumes along with an increase in atrial ejection force and a decrease in BP, after 12 months of treatment.[55] Along with structural reverse remodelling, the use of antihypertensive therapy has also been shown to be associated with functional improvement in measures of LA strain. In a group of 160 patients treated with irbesartan or nebivolol, speckle tracking analysis showed a significant improvement in LA global peak reservoir strain after 12 months (from 37% to 40% and from 36% to 41% for irbesartan and nebivolol, respectively).[78] Whether these results may be translated to a clinically relevant LA reverse remodelling has yet to be demonstrated. Also, given the observational nature of these studies, results should be considered as exploratory.

The use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs) has been hypothesized to be associated with LA reverse remodelling by a dual mechanism: an improved haemodynamic status, mediated by BP reduction, with a secondary improvement in LV diastolic function and a direct anti-fibrotic effect.[56]

Accordingly, careful monitoring of LA structure and function over time may serve as a surrogate marker to assess the efficacy of antihypertensive therapies. However, no study to date has assessed the prognostic significance of LA reverse remodelling among hypertensive patients.

Atrial fibrillation

The relationship between LA remodelling and AF is reciprocal.[79] The progression of LA disease may predispose to the occurrence

Table 1 **Imaging evaluation of left atrial reverse remodelling. Evaluation of left atrial size and function**

Parameter	Meaning	Advantages	Disadvantages
LA volume 2D-TTE	↓ LA volume = LA reverse remodelling	Large body of evidence Good reproducibility	Underestimation compared to 3D-TTE, CT and CMR No LA functional assessment
LA volume 3D-TTE	↓ LA volume = LA reverse remodelling	Less geometric assumptions → correlation with CT and CMR	Time-consuming Low frame rate for 3D acquisition and consequent poor spatial resolution Few evidences of LA reverse remodelling
Peak LA longitudinal strain	Quantification of functional reverse remodelling ↑ LA strain = ↓ LA fibrosis = LA reverse remodelling	Semi-automated Angle-independent Less load-dependent[37] Evaluation of phasic LA function[38] Acceptable reproducibility	Time-consuming Inter-vendor variability Lack of standardization
LA volume CT	↓ LA volume = LA reverse remodelling ↑ LA ejection fraction	Short time for scanning and analysis More accurate than TTE Good correlation with CMR Anatomical characterization for AF ablation	Need for contrast agent Need for breath-hold
LA volume CMR	↓ LA volume is the surrogate measure of LA reverse remodelling ↓ LA fibrosis = ↓ DE[39]	Gold standard for LA volume assessment High spatial and temporal resolution Tissue characterization (DE)	Time-consuming Challenging with current technology Expensive Renal function Lack of evidence Availability/access

2D, two-dimensional; 3D, three-dimensional; AF, atrial fibrillation; CMR, cardiac magnetic resonance; CT, computed tomography; DE, delayed enhancement; LA, left atrium; TTE, transthoracic echocardiography.

Table 2 Definitions of left atrial reverse remodelling

Author	Imaging modality	Definition	Type of choice	Reproducibility and agreement
Westenberg *et al.*[41]	CMR	≥15% LAV reduction	Arbitrary, pre-specified	Assessed: good
Antonini-Canterin *et al.*[42]	TTE	≥15% LAV reduction	Arbitrary, pre-specified Based on previously reported data	Assessed on 10 pts: good
Tops *et al.*[43]	TTE	≥15% LAV reduction	Arbitrary, pre-specified	Assessed on 15 pts: good
Brenyo *et al.*[44]	TTE	High responders: ≥20% LAV reduction Low responders: <20% LAV reduction	Arbitrary ≥lower-quartile response in the CRT-D group vs. <lower-quartile response in the CRT-D group	Not mentioned
Marsan *et al.*[45]	3D-TTE	≥15% LAV reduction	Arbitrary Based on previously reported data	Assessed on 20 pts: acceptable
Candan *et al.*[46]	TTE	>15% LAV index reduction	Arbitrary, pre-specified	Assessed on 20 pts: good
Gelsomino *et al.*[47]	TTE	≥15% LAV reduction	Arbitrary, pre-specified	Assessed: acceptable
Kloosterman *et al.*[16]	TTE	≥10% reduction in LAV	Arbitrary, pre-specified	Not mentioned
Mathias *et al.*[48]	TTE	>30% LAV reduction	Arbitrary Median value of LAV percent decrease	Not mentioned

3D, three-dimensional; CMR, cardiac magnetic resonance; CRT-D, cardiac resynchronization therapy-defibrillator; LAV, left atrial volume; pts, patients; TTE, transthoracic echocardiography.

of AF and, on the other hand, AF perpetuates and might worsen adverse LA remodelling in a vicious circle. The basis of this process seems to be related, at least in part, to an inflammatory state and the development of fibrosis.[80] In addition, the structural alterations associated with an enlarged LA lead to electrical remodelling.[81]

Reverse remodelling identified by a shrinking LA volume has been associated with fewer AF recurrences in HF patients.[82–84] Several studies have demonstrated the benefits of both medical therapy and catheter ablation on LA reverse remodelling (*Table 3*). Even in animal models of HF due to rapid atrial pacing, the use of ACEi or ARB resulted in a significant LA size reduction and decreased amount of fibrosis.[85,86] The reduction of LA fibrosis has also been reported in one human study. The amount of collagen I was higher in AF versus sinus rhythm patients undergoing cardiac surgery. Interestingly, when divided into groups with or without ACEi treatment, there was a significant lower expression of collagen in AF with ACEi versus AF without ACEi.[63]

The extent of pre-existing fibrosis is a crucial determinant of interventional success in patients undergoing AF treatment.[87,88] Pre-procedural LA strain is associated with rhythm outcome after LA catheter ablation.[89] Despite ablation itself may result in increased LA fibrosis,[90,91] performing the procedure has shown to favour LA reverse remodelling. Two studies reported LA response to catheter ablation or surgical treatment of AF.[43,47] In one study, LA reverse remodelling (*Table 2*) occurred in 63% of patients undergoing radiofrequency catheter ablation.[43] While LA maximum volume and LA minimum volume significantly decreased in the overall population, only the responder group reported a significant increase in LA strain. In this study, baseline LA strain and LA maximum volume were independent predictors of LA reverse remodelling. Similarly, in a cohort of patients who underwent surgical treatment of AF, 73% had LA reverse remodelling after a 12-month follow-up.[47]

Coronary artery disease

Left atrial volume increases in patients with recent myocardial infarction (MI), especially in the early phase. LA remodelling after 1 month and baseline LA size are both independent predictors of morbidity and mortality.[14] LA enlargement often occurs in parallel with LV remodelling, even in the absence of LV ejection fraction (LVEF) deterioration.[92,93]

Very few studies have assessed the direct effect of coronary interventions on LA reverse remodelling (*Table 3*). Ahn *et al.*[67] investigated the impact of myocardial perfusion on LA remodelling in 105 patients with acute MI treated with successful primary percutaneous coronary intervention. Despite no overall change of LA volume after 6 months, evidence of significant LA reverse remodelling according to myocardial perfusion grade was reported. In addition, perfusion grade and anterior MI location were independent determinants of LA remodelling at multivariate analysis (both $p < 0.001$).

In post-MI animal models, renin–angiotensin–aldosterone system (RAAS) inhibition produced some effects on LA remodelling, preventing LA enlargement (*Table 3*). The anti-fibrotic effect of ARBs was highlighted by a reduction in the expression of connexin 43.[66] Similarly, in ischaemic HF rats treated with ACEi, beta-blocker or mineralocorticoid receptor antagonists (MRAs), atrial hyperexcitability was reduced by all drugs, but only spironolactone reduced atrial fibrosis.[65] The hypothesis generating

Table 3 **Left atrial reverse remodelling in patients at risk of heart failure and pre-heart failure (stages A and B)**

Author	Type of study – sample	Population	Intervention/drug	Follow-up	LA outcomes	Clinical outcomes
Arterial hypertension						
Dernellis *et al.*[54]	Observational prospective – 48	Essential hypertension	Enalapril ± chlorthalidone vs. untreated	16 weeks	LARV: 35.4 to 29.3 ml (−17%), $p < 0.05$ LACV: 43.8 to 51.3 ml (+17%), $p < 0.05$ LA ejection force: 20.9 to 18.1 kdynes (−13%), $p < 0.05$	
Mattioli *et al.*[55]	Observational prospective – 120	Hypertensive patients with mild to moderate LV hypertrophy	Telmisartan	12 months	LAV max: 35 to 32 ml (−9%), $p < 0.05$	
Matsuyama *et al.*[56]	Observational	Animal: hypertension	Olmesartan	8 weeks	↓ LA fibrosis No difference in LA action potentials	
Matsuyama *et al.*[56]	Observational prospective – 174	Hypertension	Irbesartan or nebivolol	12 months	LAV max: Irbesartan 45.1 to 39.9 ml (−12%), $p < 0.001$ Nebivolol 47 to 40 ml (−15%), $p < 0.001$ LA-GLS: Irbesartan 37.71% to 40.45% (+ 7%), $p < 0.001$ Nebivolol 36.4 to 41.52 (+14%), $p < 0.001$	
Atrial fibrillation						
Shi *et al.*[57]	Observational prospective – 20	Animal: CHF due to rapid atrial pacing	Enalapril vs. control	5 weeks	↓ LA fractional area shortening (−42%, $p = 0.0001$) ↓ LA fibrosis	
Kumagai *et al.*[58]	Observational prospective – 20	Animal: sustained AF by rapid right atrial pacing	Candesartan vs. control	5 weeks	↓ LA fibrosis	↑ AF duration in control group
Cha *et al.*[59]	Observational prospective – 20	Animal: CHF due to rapid ventricular pacing	Omapatrilat vs. control	5 weeks	↑ LA area index	
Lee *et al.*[60]	Observational prospective – 15	Animal: CHF due to rapid ventricular pacing	Pirfenidone vs. control	3 weeks	↓ LA fibrosis	↓ Arrhythmogenic atrial remodelling ↓ AF vulnerability
Li *et al.*[61]	Observational prospective – 27	Animal: persistent AF by rapid right atrial pacing	Cilazapril or valsartan vs. control	6 weeks	↓ LAV ↑ LA ejection fraction	↓ AF inducibility and duration
Kunamalla *et al.*[62]	Observational prospective – 21	Animal: CHF due to rapid ventricular pacing	Gene-based expression of dominant-negative type II TGF-β receptor	3/4 weeks	↓ Increase in conduction inhomogeneity ↓ LA fibrosis	↓ AF episodes
Boldt *et al.*[63]	Observational prospective – 261	Permanent AF versus sinus rhythm	ACEi (various) vs. control	6 months	↓ Collagen I expression	
Perea *et al.*[64]	Observational prospective – 90	Paroxysmal AF	Catheter ablation	4–6 months	Recurrence of AF: LAV (CMR) 126.2 to 103.5 ml (−17%), $p < 0.001$ No recurrence of AF: LAV (CMR) 98 to 84.9 ml (−13%), $p < 0.001$	
Tops *et al.*[43]	Observational prospective – 148	Paroxysmal or persistent AF	Catheter ablation	13.2 ± 6.7 months	Responders (63%): LAVI max 31 to 22 ml/m^2 (−29%), $p < 0.05$ Non-responders (37%): LAVI max 29 to 31 ml/m^2 (+ 7%), $p < 0.05$ p-value between groups: <0.001 Responders: LA strain 19% to 22% (+16%), $p < 0.05$ Non-responders: LA strain 14% to 15% (+ 7%), NS p-value between groups: <0.001	Baseline LA strain and LAVI max predictor of LARR at multivariate analysis

Table 3 (Continued)

Author	Type of study – sample	Population	Intervention/drug	Follow-up	LA outcomes	Clinical outcomes
Gelsomino *et al.*[47]	Observational prospective – 33	Paroxysmal AF	Minimally invasive atrial fibrillation surgery	12 months	↓ LAVI (LARR in 72%) ↑ LA strain	
Coronary artery disease						
Milliez *et al.*[65]	Randomized – 88	Animal: acute MI	Spironolactone ± lisinopril ± atenolol vs. untreated	3 months	↓ LA hyperexcitability ↓ LA fibrosis (spironolactone > atenolol and lisinopril)	
Yoon *et al.*[66]	Randomized – 38	Animal: acute MI	Losartan vs. control	4 weeks	↓ Increase in LA diameter ↓ LA fibrosis (↓ connexin-43 expression)	AF inducibility and duration not different between groups
Ahn *et al.*[67]	Observational prospective – 105	Acute MI	PCI	6 months	Occurrence of LA reverse remodelling after 6 months according to myocardial perfusion grade	
Other risk factors						
Karason *et al.*[68]	Observational prospective – 63	Obese patients	Bariatric surgery vs. control	12 months	Surgery: LAV 71 to 63 ml (−11%), $p < 0.05$ Control: LAV 73 to 69 ml (−5%), NS p-value between groups: NS	
Willens *et al.*[69]	Observational prospective – 17	Obese patients	Bariatric surgery	7.6 ± 3.6 months	LA diameter: 35 to 37 mm (+ 6%), NS	
Di Bello *et al.*[70]	Observational prospective – 39	Obese patients	Bariatric surgery vs. control	6–24 months	LA diameter: 37.9 to 33.5 (−12%), $p < 0.05$	
Owan *et al.*[71]	Observational prospective – 882	Obese patients	Bariatric surgery vs. untreated	24 months	LAV: 55.3 to 54.4 ml (−2%), NS	
Luaces *et al.*[72]	Observational prospective – 41	Obese patients	Bariatric surgery	12 months	LAVI: 31.31 to 32.83 ml/m^2 (+ 5%), NS	
Pathak *et al.*[73]	Observational prospective – 149	Human: AF patients with BMI ≥27 kg/m^2 and ≥1 CV risk factor	Risk factors management (more intensive vs. treating physician) after AF ablation	42 months	Intensive: LAVI 42.5 to 30.4 ml/m^2 (−28%), $p < 0.001$ Control: LAVI 42.4 to 39.5 ml/m^2 (−7%), NS p-value between groups: < 0.001	Arrhythmia-free survival greater and less symptoms in intensive management group
Pathak *et al.*[74]	Observational prospective – 308	Paroxysmal/persistent AF and BMI ≥27 kg/m^2	Exercise programme and individual risk factors management; AF: medical therapy or ablation	49 ± 19 months	No significant difference in LAVI between patients with cardiorespiratory fitness gain and without	Cardiorespiratory fitness predicts arrhythmia recurrence in obese individuals with symptomatic AF
Pathak *et al.*[75]	Observational prospective – 355	AF and BMI ≥27 kg/m^2	Weight loss	48 months	WL ≥10%: 37.6 to 30.9 ml/m^2 (−18%), $p < 0.001$ WL 3%–9%: 39.5 to 34.7 ml/m^2 (−12%), $p < 0.001$ WL <3%: 39 to 40.4 ml/m^2 (+4%), $p = 0.02$ p-value between groups: < 0.001	Long-term sustained WL is associated with significant reduction in AF burden and maintenance of sinus rhythm

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; BMI, body mass index; CHF, chronic heart failure; CMR, cardiac magnetic resonance; CV, cardiovascular; LA, left atrium; LACV, left atrial conduit volume; LA-GLS, left atrial global longitudinal strain; LARR, left atrial reverse remodelling; LARV, left atrial reservoir volume; LAV, left atrial volume; LAVI, left atrial volume index; LV, left ventricle; MI, myocardial infarction; NS, not significant; PCI, percutaneous coronary intervention; TGF-β, transforming growth factor-beta; WL, weight loss.

nature of these findings should be replicated in humans to validate consistency in clinical practice.

Other risk factors

Recent evidence showed that dietary modification, physical activity and weight loss may reverse atrial abnormalities and may impact on arrhythmias incidence and recurrence in obese patients[2] (*Table 3*).

A recent meta-analysis reported conflicting data about cardiac structural and functional changes after bariatric surgery.[94] Karason *et al.*[68] demonstrated LA reverse remodelling in obese patients following bariatric surgery when compared to the group with only dietary restrictions. Nevertheless, the difference in LA volume between the interventional and the dietary group was not significant either at baseline and after 1-year follow-up. In general, LA reverse remodelling occurred in parallel with LV mass reduction and LV filling pressure improvement.

Even in the absence of surgery, weight loss influenced LA reverse remodelling. Dietary modifications among obese patients have been shown to decrease LA volume along with a decrease in body mass index.[75]

Other potentially modifiable risk factors such as sleep apnoea syndrome and arterial stiffness are associated with AF recurrence and LA remodelling.[95,96] Future studies will clarify whether targeted treatment of these conditions can reverse atrial remodelling and whether such changes are associated with a reduction in symptoms.

As opposed to LA reverse remodelling, exercise training may also be associated with LA enlargement. Young athletes tend to have larger LA volume when compared to active but not trained patients.[23] LA volume of athletes without AF showed considerable overlap with non-athletes with AF. However, LA reservoir strain in AF patients was significantly impaired compared with patients in sinus rhythm, regardless of training status,[97] reflecting that the dysfunction acts as the basis of the arrhythmia.

Patients with heart failure (stage C)

Heart failure with reduced ejection fraction

Myocardial injury, haemodynamic changes, and neuro-hormonal activation cause heart remodelling and this is a key factor for progression of HF with reduced ejection fraction (HFrEF). LA remodelling is a well-studied entity, as it is associated with adverse CV events. LV reverse remodelling is a critical finding as a surrogate of the beneficial effects of most HF treatments and is associated with an improved prognosis.[98] Although some evidence on LA reverse remodelling has been reported from several HFrEF trials, the real impact on clinical outcomes remains less explored (*Table 4*)[16,42,44–46,48,99–119].

The Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodelling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF) study[100] showed a reduction in LA volume index (from 37 to 29 ml/m^2, $p < 0.001$) after 12 months in patients treated with angiotensin receptor–neprilysin inhibitor (ARNI), along with an increase in LVEF and decrease in LV volumes and E/e′ ratio. Similarly, in the multicentre randomized EVALUATE-HF trial,[99] the ARNI group showed significant greater reductions in LA volume index, LV volumes and E/e′ ratio as compared to enalapril, while no significant change in LVEF was observed.

The rapid drop in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels during treatment with ARNI[100,120] testifies the direct effect of sacubitril/valsartan on ventricular wall stress and a possible acute effect on filling pressures, perhaps related to increased venous capacitance or natriuresis. It has been demonstrated that the significant reduction in circulating NT-proBNP (and high-sensitivity cardiac troponin T) is correlated to the LA volume index reduction among HFrEF patients treated with ARNI.[121]

Left atrial reverse remodelling can be considered an active player of the so-called 'complete left-sided reverse remodelling'.[16,48] This concept has been elucidated by trials testing the structural response to cardiac resynchronization therapy (CRT) (*Table 4*). Results from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)[44] study showed that reductions in LA volume with CRT-defibrillator (CRT-D) at 1 year were highly associated with reduction in LV volume, suggesting a cause–effect relationship. In this trial, most CRT-D patients experienced ≥20% reduction in LA volume, while the implantable cardioverter-defibrillator (ICD)-only group had a significantly lower LA response. Patients who showed a favourable LA response to CRT-D experienced a subsequent reduction in the risk of atrial tachycardia, HF events and death. Importantly, atrial tachycardia risk reduction appeared to be related to LA response independently of LV structural changes.

Two studies revealed that 20%–45% of patients with CRT showed LA reverse remodelling in absence of LV reverse remodelling[16,48] and contrasting results in terms of outcome have been reported (*Table 4*). Kloosterman *et al.*[16] retrospectively assessed LA reverse remodelling in 365 patients who were eligible for CRT. They reported that discordant left side reverse remodelling (LA without LV reverse remodelling) showed comparable mortality and HF hospitalization risk to patients with both LA and LV reverse remodelling. Thus, successful CRT can reduce LA size and improve LA pump function and LA reverse remodelling might improve outcome in CRT patients, even in the absence of LV remodelling.

The LA plays an active role in HFrEF pathophysiology and appears as a promising target to evaluate the efficacy of HF treatments. Although trials showed variable results, additional efforts should be addressed to clarify whether the assessment of LA reverse remodelling, as an independent entity, can provide prognostic information.

Heart failure with preserved ejection fraction

The assessment of LA response to different interventions in HF with preserved ejection fraction (HFpEF) patients has not been fully evaluated and available data have shown contrasting results.

Mineralocorticoid receptor antagonists decrease extracellular matrix turnover and myocardial collagen, one of the mechanisms of atrial disease. Studies investigating the impact of MRAs on cardiac

Table 4 Left atrial reverse remodelling in heart failure (stage C)

Author	Type of study – sample	Stage of HF – NYHA class	Intervention	Follow-up	LA outcomes	Clinical outcomes
Reduced ejection fraction						
Desai *et al.*[99]	RCT – 413	Stage C – NYHA I–III	ARNI vs. enalapril	12 weeks	ARNI: LAVI 30.4 to 28.2 ml/m^2 (−7%) Enalapril: LAVI 29.8 to 30.5 ml/m^2 (+2%) *p*-value between groups: ≤ 0.001	
Januzzi *et al.*[100]	Observational prospective – 794	Stage C – NYHA II–IV	ARNI	6 months 12 months	ARNI: LAVI 37.76 to 32.80 (−13%) to 29.32 (−22%) ml/m^2 (both $p < 0.001$)	↓ NT-proBNP ($p < 0.001$)
Brenyo *et al.*[44]	RCT (sub-study) – 1378	Stage C – NYHA II–III	CRT vs. ICD-only	12 months	Median LAV reduction: 29% (CRT; IQR 20%–36%) vs. 10% (ICD-only; IQR 5%–14%)	↓ Risk of supraventricular tachyarrhythmias, HF and deaths
Kloosterman *et al.*[16]	Observational retrospective – 365	Stage C – NYHA II–IV	CRT	6 months	LA + LVRR: LAVI 44 to 34 ml/m^2 (−3%) LARR: LAVI 45 to 36 ml/m^2 (−20%) LVRR: LAVI 40 to 42 ml/m^2 (+5%) noRR: LAVI 43 to 47 ml/m^2 (+9%) *p*-value between groups: <0.001	HFH and deaths: LARR not different from LARR + LVRR
Mathias *et al.*[48]	RCT (sub-study) – 533	Stage C – NYHA I–II	CRT vs. ICD-only	12 months	>30% LAV reduction in 60% of patients	Lower rate of HFH and deaths with LA + LVRR vs. LARR or noRR Lower rate of HFH and deaths with LARR vs. noRR
Valzania *et al.*[101]	Observational prospective – 30	Stage C – NYHA III	CRT	12 months	LA area: 26.6 to 23.1 cm^2 (−13%) $p < 0.05$ LA strain: 11.4% to 16.5% (+45%) $p < 0.05$	↓ AF incidence ($p = 0.05$) ↓ NYHA class ($p < 0.001$) No difference for HFH
St John Sutton *et al.*[102]	RCT – 419	Stage C – NYHA I–II	CRT-ON vs. CRT-OFF (excluded from analysis)	5 years (assessment every 6 months)	Overall LA area change not significant ($p = 0.95$)	No effect of LA area on mortality/morbidity
Singh *et al.*[103]	RCT – 56	Stage C	Dapagliflozin vs. placebo	12 months	LAVI: −2.6 ml/m^2 ($p = 0.464$)	
Lee *et al.*[104]	RCT – 92	Stage C – NYHA II–IV	Empagliflozin vs. placebo	36 weeks	Empagliflozin: LAV (on CMR) 79 to 75.5 ml (−4%) Placebo: LAV (on CMR) 87.9 to 86.3 ml (−2%) *p*-value between groups: 0.22	
Preserved ejection fraction						
Tsang *et al.*[105]	RCT – 21	Diastolic dysfunction + LA enlargement	Quinapril vs. placebo	6 and 12 months	Quinapril: LAVI 43 to 40 to 39 ml/m^2 (−9%) Placebo: LAVI 38 to 40 to 44 ml/m^2 (+16%) *p*-value between groups: <0.05	
Mak *et al.*[106]	RCT – 44	Stage C – NYHA II–IV	Eplerenone vs. placebo	6 and 12 months	Eplerenone: LAVI 50 to 49 to 52 ml/m^2 (+4%) Placebo: LAVI 45 to 44 to 53 ml/m^2 (+18%) Non-significant difference between groups	
Kayrak *et al.*[107]	RCT – 110	Post-MI	Spironolactone vs. standard therapy	6 months	Spironolactone: LAVI 52.3 to 52.2 ml/m^2 (−0.2%) Control: LAVI 50.2 to 49.2 ml/m^2 (+2%) Non-significant difference between groups Spironolactone: LAEF 53% to 57% (+8%) Control: LAEF 50% to 47% (−6%) *p*-value between groups: 0.013	

Table 4 (Continued)

Author	Type of study – sample	Stage of HF – NYHA class	Intervention	Follow-up	LA outcomes	Clinical outcomes
Edelmann *et al.*[108]	RCT – 64	Stage C – NYHA II–III	Supervised exercise training vs. usual care	3 months	Training: LAVI 27.9 to 24.3 ml/m^2 (−13%) Control: LAVI 28.2 to 28.6 ml/m^2 (+1%) *p*-value between groups: 0.001	Improved maximal exercise capacity
Solomon *et al.*[109]	RCT – 149	Stage C – NYHA I–III	ARNI vs. valsartan	36 weeks	ARNI: LAVI 35 to 32.4 ml/m^2 (−7%) Valsartan: LAVI 36.8 to 37.1 ml/m^2 (+1%) *p*-value between groups: 0.007	↓ NYHA class ($p = 0.05$)
Deswal *et al.*[110]	RCT – 44	Stage C – NYHA II–III	Eplerenone vs. placebo	26 weeks	Eplerenone: LAV 73 to 64 ml (−12%) $p = 0.02$ Placebo: LAV 80 to 73 ml (−9%) $p = 0.09$ Non-significant difference between groups	
Edelmann *et al.*[111]	RCT – 422	Stage C – NYHA II–III	Spironolactone vs. placebo	12 months	Spironolactone: LAVI 28.2 to 27.5 ml/m^2 (−2%) Placebo: LAVI 27.8 to 27.6 ml/m^2 (−1%) Non-significant difference between groups	
Kurrelmeyer *et al.*[112]	RCT – 48 (only women)	Stage C – NYHA II–III	Spironolactone vs. placebo	6 months	Spironolactone: LAVI 32.5 to 33.3 ml/m^2 (+3%) Placebo: LAVI 35.7 to 36.7 ml/m^2 (+3%) Non-significant difference between groups ↓ Type III collagen levels	
Shah *et al.*[113]	RCT – 239	Stage C – NYHA I–IV	Spironolactone vs. placebo	12–18 months	Spironolactone: LAV 59.3 to 60.3 ml (+2%) Placebo: LAVI 58.1 to 60.3 ml (+4%) Non-significant difference between groups	Reduced composite endpoint of cardiovascular death, HFH, or aborted cardiac arrest due to overall LAV reduction
Soga *et al.*[114]	Observational prospective – 58	Stage C (69% HFpEF, 13% HFrEF)	Dapagliflozin	6 months	LAVI 31 to 26 ml/m^2 (−16%) $p = 0.001$	
Valvular heart disease						
Antonini-Canterin *et al.*[42]	Observational retrospective – 79	Stage C	Mitral valve surgery (repair or replacement) for severe degenerative MR	6 months	LAVI 68 to 47 ml/m^2 (−29%) $p < 0.001$ 80% LARR Lower LAVI reduction in >45 years old and hypertensive patients	
Kim *et al.*[115]	Observational prospective – 303	Stage C – NYHA II–III	Percutaneous mitral valvuloplasty	After procedure, 1 year and 8 years	Total: LAVI 60.2 to 44.8 (−25%) to 69.1 (+15%) ml/m^2, $p < 0.001$ SR: LAVI 48.8 to 35.7 (−27%) to 55.1 (+13%) ml/m^2, $p < 0.001$ AF: LAVI 85.5 to 65 (−24%) to 100.9 (+18%) ml/m^2, $p < 0.001$	Pre-procedural LAVI and percentage change of LAV immediately after procedure independent predictor of event-free survival
Marsan *et al.*[45]	Observational prospective – 65	Stage C	Early repair for severe MR (prolapse)	6 and 12 months	LAVI 43 to 25 to 23 (−47%) ml/m^2, both $p < 0.05$ 85% LARR (1 year)	
D'Ascenzi *et al.*[116]	Observational prospective – 32	Stage C – NYHA II–III–IV	TAVR	40 days and 3 months	LAVI 47.3 to 42.8 to 43.5 (−8%) ml/m^2, both $p < 0.05$ PALS 14.4% to 19% to 19.1% (+33%), $p < 0.05$ and $p < 0.001$	
Candan *et al.*[46]	Observational prospective – 53	Stage C – NYHA I–II–III	Mitral valve surgery (repair or replacement) for severe MR	6 months	LAVI 58.2 to 43.9 (−25%) ml/m^2, $p = 0.001$ No difference between type of surgery	

Table 4 (Continued)

Author	Type of study – sample	Stage of HF – NYHA class	Intervention	Follow-up	LA outcomes	Clinical outcomes
Hatani *et al.*[117]	Observational retrospective – 83	Stage C	Surgical AVR	1 month, 1 year and 3 years	LAVI 51.3 to 43.7 (−15%) to 44.7 to 46.1 ml/m^2, $p < 0.001$	Residual LA dilatation at 1 year after AVR was associated with reduced event-free survival
Toprak *et al.*[118]	Observational prospective – 25	Stage C – NYHA II–IV (60%)	Transcatheter mitral valve repair (MitraClip implantation)	12 months	2D-LAVI max: 51.5 to 50 ml/m^2 (−3%) $p = 0.512$ 3D-LAVI max: 55.2 to 51.5 ml/m^2 (−7%) $p = 0.018$ LA reservoir strain: 7.66% to 11.15% (+46%), $p < 0.001$	Pre-procedural 3D-LAV and LA reservoir strain associated with MACE (univariate analysis) LA reservoir strain and 3D-LAV min correlated with ↓ MR, ↓ NYHA class, ↑ 6MWD
Avenatti *et al.*[119]	Observational retrospective – 35	Stage C – NYHA III	Transcatheter mitral valve repair (MitraClip implantation)	30 days	LAVI max: 74 to 53 ml/m^2 (−28%), $p = 0.008$ LAVI max functional MR: 70 to 55 ml/m^2 (−21%), $p < 0.05$ LAVI max primary MR: 65 to 49 ml/m^2 (−25%), $p < 0.05$ ↓ LA stiffness	Significant inverse correlation between LA stiffness change and 6MWD in 14 patients

3D, three-dimensional; 6MWD, 6-min walking distance; 6MWT, 6-min walking test; AF, atrial fibrillation; ARNI, angiotensin receptor–neprilysin inhibitor; AVR, aortic valve replacement; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; HF, heart failure; HFH, hospitalization for heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LA, left atrium; LAEF, left atrial emptying fraction; LARR, left atrial reverse remodelling; LAV, left atrial volume; LAVI, left atrial volume index; LV, left ventricle; LVRR, left ventricular reverse remodelling; MACE, major adverse cardiovascular event; MI, myocardial infarction; MR, mitral regurgitation; NYHA, New York Heart Association; PALS, peak atrial longitudinal strain; RCT, randomized clinical trial; RR, reverse remodelling; SR, sinus rhythm; TAVR, transcatheter aortic valve replacement.

function did not show significant LA reverse remodelling, despite many of them reported improvement in certain parameters of LV diastolic function (*Table 4*). In the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOP-CAT)[113] echocardiographic sub-study, while spironolactone was not associated with significant change in either LA and LV structure over time, the overall reduction in LA volume was associated with an independent lower risk of subsequent occurrence of CV death, HF hospitalization, or aborted cardiac arrest. The reasons why the effects of antagonizing aldosterone activity did not show a direct effect on LA structure are uncertain. It is possible that the anti-fibrotic effect of MRAs may require a longer time to result in functional or structural reverse remodelling.

In the phase II Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) trial,[109,122] while the use of ARNI did not show a significant effect on changes of LV structure or function, diastolic function, or LV mass after 12 and 36 weeks of treatment, LA size and volume significantly decreased after 36 weeks (*Table 4*). The concomitant inhibition of RAAS activity and the augmentation of the actions of natriuretic peptides have incremental effects on cardiac haemodynamics and structural remodelling. In the aforementioned study, the use of ARNI rapidly reversed LA remodelling without an apparent effect on LV size or diastolic function. This result may be explained by a rapid decrease in LV filling pressure, testified by the reduction of NT-proBNP levels. LA remodelling reflects increased LV filling pressure in a more robust way than Doppler-derived measures of diastolic function which are subject to greater variability. Also, the improvement of New York Heart Association (NYHA) functional class after 36 weeks may possibly explain the independent contribution of LA reverse remodelling to improvement of symptoms in HFpEF patients.

The Exercise training in Diastolic Heart Failure (Ex-DHF)[108] study assessed the effect of structured exercise training compared to usual care in 64 patients with HFpEF. It demonstrated that exercise training positively affected exercise capacity and quality of life in HFpEF, through improvement in LV diastolic function and reduction in LA volume. BP values and body mass index did not change in either group, hence the effect on LA size reduction is not likely to be due to the haemodynamic effect. In fact, a significant reduction of procollagen type I plasma levels induced by exercise training was reported. It seems reasonable that LA reverse remodelling may be related to reduced collagen turnover.

The link between LA reverse remodelling and outcomes in patients with HFpEF needs to be evaluated in larger trials, possibly with longer follow-up. However, targeting therapies based on LA response in HFpEF seems to be a rational approach.

Valvular heart disease

Mitral valve disease is a well-studied model that represents the consequences of haemodynamic impairment on the LA. In mitral regurgitation (MR), volume overload has a direct effect on the LA causing chamber enlargement and myocyte hypertrophy to compensate the haemodynamic stress and to prevent pulmonary

congestion.[123] At a cellular level, atrophy and interstitial fibrosis progressively impair LA function and decrease atrial elasticity.[124]

Candan *et al.*[46] assessed the relationship between LA peak longitudinal reservoir strain and LA reverse remodelling in 53 patients with severe MR undergoing surgical valve repair or replacement (*Table 4*). LA volume index significantly decreased after surgery, regardless of the type of intervention. Also, pre-operative higher LA volume, younger age and higher peak LA longitudinal strain values were independent predictor of LA reverse remodelling.

Left atrial function assessed by speckle tracking echocardiography has been associated with CV outcomes in patients with primary degenerative moderate asymptomatic MR.[125] Data from 87 subjects with degenerative MR enrolled in the Endovascular Valve Edge-to-Edge Repair Study II (EVEREST II) trial[126] displayed LA strain changes after both surgical or transcatheter mitral valve repair. LA strain improvement was dependent on baseline LA function as only in patients with normal or high baseline strain values, MR reduction resulted in normalization of LA strain. Moreover, in a cohort of 25 patients undergoing MitraClip, pre-operative LA volume measured by three-dimensional echocardiography (but not by two-dimensional) and LA reservoir strain were associated with 1-year major adverse CV events.[118]

Recently, transcatheter indirect mitral annuloplasty showed benefits in reducing functional MR in HFrEF patients with a high procedural successful rate; an improvement in NYHA class was reported too.[127] One individual patient data meta-analysis found that Carillon device implantation resulted in significant left-sided reverse remodelling, as demonstrated by reduction in LV end-diastolic and end-systolic volume and reduction in LA volume.[128]

The mechanisms behind LA remodelling in aortic stenosis (AS) are thought to be related to LV hypertrophy and increased LV filling pressure due to high afterload. The impact of aortic valve replacement (AVR) has yet to be explained. LV and LA reverse remodelling have been assessed in one cohort of patients with severe AS undergoing AVR[117] (*Table 4*). LA volume index rapidly decreased after 1 month along with a reduction in LV mass index. Patients who did not experience LA and LV reverse remodelling appeared to exhibit worse long-term outcomes.

Even transcatheter AVR (TAVR) has been demonstrated to be associated with significant LA reverse remodelling. D'Ascenzi *et al.*[116] reported a significant reduction of LA size at a 40-day follow-up after TAVR. Alongside the recovery of LA structure, TAVR was accompanied by a significant increase in global peak atrial longitudinal reservoir strain. Pre-procedural LA volume and trans-aortic mean gradient change were reported as predictors of LA volume reduction 3 months following TAVR.

Advanced heart failure (stage D)

When reversal of LA remodelling fails to occur, the disease progresses to stage D of atrial disease.[1] The lack of LA volume reduction despite treatment identifies the irreversible advanced end-stage, mainly related to a larger amount of fibrosis. Albeit not largely proven, in this stage, no therapeutic intervention may have beneficial consequences on LA function or structure. Only acting at earlier stages may prevent LA remodelling progression (*Figure 1*).

New treatments and future perspectives

While the effects of sodium–glucose cotransporter 2 inhibitors on atrial function have not been assessed, to date,[104,129–131] new drugs acting directly on cardiac function may have an impact also on the LA. Compared with placebo, the myosin activator omecamtiv mecarbil improved LA function, as shown by a reduced LA minimal volume and a larger emptying fraction, in the Chronic Oral Study of Myosin Activation to Increase Contractility in HF (COSMIC-HF) trial and reduced the risk of new-onset AF and stroke, likely through an improvement in LA function, in the larger Global Approach to Lowering Adverse Cardiac outcomes Through Improving Contractility in HF (GALACTIC-HF) trial.[132–135]

Rhythm control for AF may improve LA function and this may improve patients' outcomes.[130] These effects, shown also after pulmonary vein isolation, may be particularly effective in patients with HFpEF such as 79% of the patients analysed in the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial.[136] Improvement in LA function, as well as in outcomes, has been shown also in the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial, enrolling patients with reduced LVEF.[137]

Our review shows that LA reverse remodelling may occur in clinical practice and be related with better outcomes. Changes in LA size and function may be related with progression of cardiac function and thus be a target of treatment or rather be a surrogate measurement of the severity of cardiac dysfunction. Also in this last case, changes in LA function may allow a more complete assessment of cardiac function and of the risk of cardiac events. LA function depends on both systolic and diastolic LV function and may predict not only HF events, as related with intracardiac pressure and congestion, but also other events including stroke and AF. However, even if measurements of LA function seem more stable than others, more data regarding their reproducibility and their clinically meaningful threshold are warranted. Future studies will also show whether LA function can be a target of treatment. Some interventions, such as pulmonary vein isolation for rhythm control in patients with AF may favourably affect LA function and this may mediate their effects on outcomes.[135–138] Also percutaneous treatment of MR may have an effect on LA function that may be larger than on LV function.[123]

Conclusions

Left atrial remodelling and LA disease are markers of CV disease and may also have an impact on clinical outcomes. Counteracting the underlying mechanisms and removing the causative factors may restore LA structure and function. Increasing evidence indicates significant LA reverse remodelling after initiation of medical therapy across all the stages of development and progression of HF.

Although a clear definition of LA reverse remodelling is needed, assessing LA response to targeted therapies appears to be a valid parameter to re-define patients' risk stratification. Prospective clinical trials are required to establish the role of LA reverse remodelling as a marker of therapeutic response in clinical practice and to assess its potential independent role as a mechanism of development and progression of HF.

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References

1. Shen MJ, Arora R, Jalife J. Atrial myopathy. *JACC Basic Transl Sci.* 2019;**4**:640–54.
2. Thomas L, Abhayaratna WP. Left atrial reverse remodeling: mechanisms, evaluation, and clinical significance. *JACC Cardiovasc Imaging.* 2017;**10**:65–77.
3. Wakili R, Voigt N, Kääb S, Dobrev D, Nattel S. Recent advances in the molecular pathophysiology of atrial fibrillation. *J Clin Invest.* 2011;**121**:2955–68.
4. Thomas L, Marwick TH, Popescu BA, Donal E, Badano LP. Left atrial structure and function, and left ventricular diastolic dysfunction: JACC state-of-the-art review. *J Am Coll Cardiol.* 2019;**73**:1961–77.
5. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2016;**17**:1321–60.
6. Hsu PC, Lee WH, Chu CY, Lee HH, Lee CS, Yen HW, et al. Prognostic role of left atrial strain and its combination index with transmitral E-wave velocity in patients with atrial fibrillation. *Sci Rep.* 2016;**6**:17318.
7. Jarasunas J, Aidietis A, Aidietiene S. Left atrial strain – an early marker of left ventricular diastolic dysfunction in patients with hypertension and paroxysmal atrial fibrillation. *Cardiovasc Ultrasound.* 2018;**16**:29.
8. Sajeev JK, Kalman JM, Dewey H, Cooke JC, Teh AW. The atrium and embolic stroke: myopathy not atrial fibrillation as the requisite determinant? *JACC Clin Electrophysiol.* 2020;**6**:251–61.
9. Yaghi S, Kamel H, Elkind MSV. Atrial cardiopathy: a mechanism of cryptogenic stroke. *Expert Rev Cardiovasc Ther.* 2017;**15**:591–9.
10. Huynh QL, Kalam K, Iannaccone A, Negishi K, Thomas L, Marwick TH. Functional and anatomic responses of the left atrium to change in estimated left ventricular filling pressure. *J Am Soc Echocardiogr.* 2015;**28**:1428–1433.e1.
11. Blume GG, Mcleod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM, et al. Left atrial function: physiology, assessment, and clinical implications. *Eur J Echocardiogr.* 2011;**12**:421–30.
12. Patel DA, Lavie CJ, Milani RV, Shah S, Gilliland Y. Clinical implications of left atrial enlargement: a review. *Ochsner J.* 2009;**9**:191–6.
13. Ristow B, Ali S, Whooley MA, Schiller NB. Usefulness of left atrial volume index to predict heart failure hospitalization and mortality in ambulatory patients with coronary heart disease and comparison to left ventricular ejection fraction (from the Heart and Soul study). *Am J Cardiol.* 2008;**102**:70–6.
14. Meris A, Amigoni M, Uno H, Thune JJ, Verma A, Køber L, et al. Left atrial remodelling in patients with myocardial infarction complicated by heart failure, left ventricular dysfunction, or both: the VALIANT Echo study. *Eur Heart J.* 2009;**30**:56–65.
15. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail.* 2015;**8**:295–303.
16. Kloosterman M, Rienstra M, Mulder BA, Van Gelder IC, Maass AH. Atrial reverse remodelling is associated with outcome of cardiac resynchronization therapy. *Europace.* 2016;**18**:1211–9.
17. Khan MS, Memon MM, Murad MH, Vaduganathan M, Greene SJ, Hall M, et al. Left atrial function in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Heart Fail.* 2020;**22**:472–85.
18. Reddy YNV, Borlaug BA. Left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail.* 2020;**22**:486–8.
19. Tamargo M, Obokata M, Reddy YNV, Pislaru SV, Lin G, Egbe AC, et al. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail.* 2020;**22**:489–98.
20. Pritchett AM, Mahoney DW, Jacobsen SJ, Rodeheffer RJ, Karon BL, Redfield MM. Diastolic dysfunction and left atrial volume: a population-based study. *J Am Coll Cardiol.* 2005;**45**:87–92.
21. Rossi A, Gheorghiade M, Triposkiadis F, Solomon SD, Pieske B, Butler J. Left atrium in heart failure with preserved ejection fraction: structure, function, and significance. *Circ Heart Fail.* 2014;**7**:1042–9.
22. Rønningen PS, Berge T, Solberg MG, Enger S, Nygård S, Pervez MO, et al. Sex differences and higher upper normal limits for left atrial end-systolic volume in individuals in their mid-60s: data from the ACE 1950 study. *Eur Heart J Cardiovasc Imaging.* 2020;**21**:501–7.
23. Cuspidi C, Tadic M, Sala C, Gherbesi E, Grassi G, Mancia G. Left atrial function in elite athletes: a meta-analysis of two-dimensional speckle tracking echocardiographic studies. *Clin Cardiol.* 2019;**42**:579–87.
24. Kim GH, Uriel N, Burkhoff D. Reverse remodelling and myocardial recovery in heart failure. *Nat Rev Cardiol.* 2018;**15**:83–96.
25. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur J Heart Fail.* 2022;**24**:4–131.
26. Mateescu AD, Călin A, Beladan CC, Roşca M, Enache R, Băicuş C, et al. Left atrial dysfunction as an independent correlate of heart failure symptoms in patients with severe aortic stenosis and preserved left ventricular ejection fraction. *J Am Soc Echocardiogr.* 2019;**32**:257–66.
27. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol.* 2006;**47**:2357–63.
28. Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, et al.; I-PRESERVE Investigators. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation.* 2011;**124**:2491–501.
29. Cameli M, Sciaccaluga C, Loiacono F, Simova I, Miglioranza MH, Nistor D, et al. The analysis of left atrial function predicts the severity of functional impairment in chronic heart failure: the FLASH multicenter study. *Int J Cardiol.* 2019;**286**:87–91.
30. Cameli M, Pastore MC, Mandoli GE, Nistor D, Lisi E, Tok ÖÖ, et al. Prognosis and risk stratification of patients with advanced heart failure (from PROBE). *Am J Cardiol.* 2019;**124**:55–62.
31. Minamisawa M, Inciardi RM, Claggett B, Cuddy SAM, Quarta CC, Shah AM, et al. Left atrial structure and function of the amyloidogenic V122I transthyretin variant in elderly African Americans. *Eur J Heart Fail.* 2021;**23**:1290–5.
32. Kadappu KK, Abhayaratna K, Boyd A, French JK, Xuan W, Abhayaratna W, et al. Independent echocardiographic markers of cardiovascular involvement in

chronic kidney disease: the value of left atrial function and volume. *J Am Soc Echocardiogr.* 2016;**29**:359–67.
33. Inciardi RM, Claggett B, Minamisawa M, Shin SH, Selvaraj S, Gonçalves A, et al. Association of left atrial structure and function with heart failure in older adults. *J Am Coll Cardiol.* 2022;**79**:1549–61.
34. Inciardi RM, Claggett B, Gupta DK, Cheng S, Liu J, Echouffo Tcheugui JB, et al. Cardiac structure and function and diabetes-related risk of death or heart failure in older adults. *J Am Heart Assoc.* 2022;**11**:e022308.
35. Morris DA, Takeuchi M, Krisper M, Köhncke C, Bekfani T, Carstensen T, et al. Normal values and clinical relevance of left atrial myocardial function analysed by speckle-tracking echocardiography: multicentre study. *Eur Heart J Cardiovasc Imaging.* 2015;**16**:364–72.
36. Boyd AC, Richards DAB, Marwick T, Thomas L. Atrial strain rate is a sensitive measure of alterations in atrial phasic function in healthy ageing. *Heart.* 2011;**97**:1513–9.
37. Gan GCH, Ferkh A, Boyd A, Thomas L. Left atrial function: evaluation by strain analysis. *Cardiovasc Diagn Ther.* 2018;**8**:29–46.
38. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to Standardize Deformation Imaging. *J Am Soc Echocardiogr.* 2015;**28**:183–93.
39. Kuppahally SS, Akoum N, Burgon NS, Badger TJ, Kholmovski EG, Vijayakumar S, et al. Left atrial strain and strain rate in patients with paroxysmal and persistent atrial fibrillation: relationship to left atrial structural remodeling detected by delayed-enhancement MRI. *Circ Cardiovasc Imaging.* 2010;**3**:231–9.
40. Inciardi RM, Galderisi M, Nistri S, Santoro C, Cicoira M, Rossi A. Echocardiographic advances in hypertrophic cardiomyopathy: three-dimensional and strain imaging echocardiography. *Echocardiography.* 2018;**35**:716–26.
41. Westenberg JJM, van der Geest RJ, Lamb HJ, Versteegh MIM, Braun J, Doornbos J, et al. MRI to evaluate left atrial and ventricular reverse remodeling after restrictive mitral annuloplasty in dilated cardiomyopathy. *Circulation.* 2005;**112**(9 Suppl):I437–42.
42. Antonini-Canterin F, Beladan CC, Popescu BA, Ginghina C, Popescu AC, Piazza R, et al. Left atrial remodelling early after mitral valve repair for degenerative mitral regurgitation. *Heart.* 2008;**94**:759–64.
43. Tops LF, Delgado V, Bertini M, Marsan NA, Den Uijl DW, Trines SAIP, et al. Left atrial strain predicts reverse remodeling after catheter ablation for atrial fibrillation. *J Am Coll Cardiol.* 2011;**57**:324–31.
44. Brenyo A, Link MS, Barsheshet A, Moss AJ, Zareba W, Wang PJ, et al. Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). *J Am Coll Cardiol.* 2011;**58**:1682–9.
45. Marsan NA, Maffessanti F, Tamborini G, Gripari P, Caiani E, Fusini L, et al. Left atrial reverse remodeling and functional improvement after mitral valve repair in degenerative mitral regurgitation: a real-time 3-dimensional echocardiography study. *Am Heart J.* 2011;**161**:314–21.
46. Candan O, Ozdemir N, Aung SM, Hatipoglu S, Karabay CY, Guler A, et al. Atrial longitudinal strain parameters predict left atrial reverse remodeling after mitral valve surgery: a speckle tracking echocardiography study. *Int J Cardiovasc Imaging.* 2014;**30**:1049–56.
47. Gelsomino S, Lucà F, Rao CM, Parise O, Pison L, Wellens F, et al. Improvement of left atrial function and left atrial reverse remodeling after surgical treatment of atrial fibrillation. *Ann Cardiothorac Surg.* 2014;**3**:70–4.
48. Mathias A, Moss AJ, McNitt S, Zareba W, Goldenberg I, Solomon SD, et al. Clinical implications of complete left-sided reverse remodeling with cardiac resynchronization therapy: a MADIT-CRT substudy. *J Am Coll Cardiol.* 2016;**68**:1268–76.
49. Pathan F, D'Elia N, Nolan MT, Marwick TH, Negishi K. Normal ranges of left atrial strain by speckle-tracking echocardiography: a systematic review and meta-analysis. *J Am Soc Echocardiogr.* 2017;**30**:59–70.e8.
50. Cho GY, Hwang IC. Left atrial strain measurement: a new normal for diastolic assessment? *JACC Cardiovasc Imaging.* 2020;**13**:2327–9.
51. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to Standardize Deformation Imaging. *Eur Heart J Cardiovasc Imaging.* 2018;**19**:591–600.
52. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail.* 2021;**23**:352–80.
53. Faggiano P, Bernardi N, Calvi E, Bonelli A, Faggiano A, Bursi F, et al. Stage a heart failure: modern strategies for an effective prevention. *Heart Fail Clin.* 2021;**17**:167–77.
54. Dernellis JM, Vyssoulis GP, Zacharoulis AA, Toutouzas PK. Effects of antihypertensive therapy on left atrial function. *J Hum Hypertens.* 1996;**10**:789–94.
55. Mattioli AV, Zennaro M, Bonatti S, Bonetti L, Mattioli G. Regression of left ventricular hypertrophy and improvement of diastolic function in hypertensive patients treated with telmisartan. *Int J Cardiol.* 2004;**97**:383–8.
56. Matsuyama N, Tsutsumi T, Kubota N, Nakajima T, Suzuki H, Takeyama Y. Direct action of an angiotensin II receptor blocker on angiotensin II-induced left atrial conduction delay in spontaneously hypertensive rats. *Hypertens Res.* 2009;**32**:721–6.
57. Shi Y, Li D, Tardif JC, Nattel S. Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. *Cardiovasc Res.* 2002;**54**:456–61.
58. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. *J Am Coll Cardiol.* 2003;**41**:2197–204.
59. Cha YM, Dzeja PP, Redfield MM, Shen WK, Terzic A. Bioenergetic protection of failing atrial and ventricular myocardium by vasopeptidase inhibitor omapatrilat. *Am J Physiol Heart Circ Physiol.* 2006;**290**:H1686–92.
60. Lee KW, Everett TH, Rahmutula D, Guerra JM, Wilson E, Ding C, et al. Pirfenidone prevents the development of a vulnerable substrate for atrial fibrillation in a canine model of heart failure. *Circulation.* 2006;**114**:1703–12.
61. Li Y, Li W, Gong Y, Li B, Liu W, Han W, et al. The effects of cilazapril and valsartan on the mRNA and protein expressions of atrial calpains and atrial structural remodeling in atrial fibrillation dogs. *Basic Res Cardiol.* 2007;**102**:245–56.
62. Kunamalla A, Ng J, Parini V, Yoo S, McGee KA, Tomson TT, et al. Constitutive expression of a dominant-negative TGF-β type II receptor in the posterior left atrium leads to beneficial remodeling of atrial fibrillation substrate. *Circ Res.* 2016;**119**:69–82.
63. Boldt A, Scholl A, Garbade J, Resetar ME, Mohr FW, Gummert JF, et al. ACE-inhibitor treatment attenuates atrial structural remodeling in patients with lone chronic atrial fibrillation. *Basic Res Cardiol.* 2006;**101**:261–7.
64. Perea RJ, Tamborero D, Mont L, De Caralt TM, Ortiz JT, Berruezo A, et al. Left atrial contractility is preserved after successful circumferential pulmonary vein ablation in patients with atrial fibrillation. *J Cardiovasc Electrophysiol.* 2008;**19**:374–9.
65. Milliez P, Deangelis N, Rucker-Martin C, Leenhardt A, Vicaut E, Robidel E, et al. Spironolactone reduces fibrosis of dilated atria during heart failure in rats with myocardial infarction. *Eur Heart J.* 2005;**26**:2193–9.
66. Yoon N, Cho JG, Kim KH, Park KH, Sim DS, Yoon HJ, et al. Beneficial effects of an angiotensin-II receptor blocker on structural atrial reverse-remodeling in a rat model of ischemic heart failure. *Exp Ther Med.* 2013;**5**:1009–16.
67. Ahn SG, Shin JH, Koh BR, Choi JH, Kang SJ, Choi BJ, et al. Impact of myocardial perfusion on left atrial remodeling following primary angioplasty for acute myocardial infarction. *Coron Artery Dis.* 2006;**17**:597–603.
68. Karason K, Wallentin I, Larsson B, Sjöström L. Effects of obesity and weight loss on cardiac function and valvular performance. *Obes Res.* 1998;**6**:422–9.
69. Willens HJ, Chakko SC, Byers P, Chirinos JA, Labrador E, Castrillon JC, et al. Effects of weight loss after gastric bypass on right and left ventricular function assessed by tissue Doppler imaging. *Am J Cardiol.* 2005;**95**:1521–4.
70. Di Bello V, Santini F, Di Cori A, Pucci A, Talini E, Palagi C, et al. Effects of bariatric surgery on early myocardial alterations in adult severely obese subjects. *Cardiology.* 2008;**109**:241–8.
71. Owan T, Avelar E, Morley K, Jiji R, Hall N, Krezowski J, et al. Favorable changes in cardiac geometry and function following gastric bypass surgery: 2-year follow-up in the Utah obesity study. *J Am Coll Cardiol.* 2011;**57**:732–9.
72. Luaces M, Cachofeiro V, García-Muñoz-Najar A, Medina M, González N, Cancer E, et al. Anatomical and functional alterations of the heart in morbid obesity. Changes after bariatric surgery. *Rev Esp Cardiol (Engl Ed).* 2012;**65**:14–21.
73. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol.* 2014;**64**:2222–31.
74. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, et al. Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: the CARDIO-FIT study. *J Am Coll Cardiol.* 2015;**66**:985–96.
75. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol.* 2015;**65**:2159–69.

76. Eshoo S, Ross DL, Thomas L. Impact of mild hypertension on left atrial size and function. *Circ Cardiovasc Imaging.* 2009;**2**:93–9.
77. Kokubu N, Yuda S, Tsuchihashi K, Hashimoto A, Nakata T, Miura T, et al. Noninvasive assessment of left atrial function by strain rate imaging in patients with hypertension: a possible beneficial effect of renin-angiotensin system inhibition on left atrial function. *Hypertens Res.* 2007;**30**:13–21.
78. Degirmenci H, Duman H, Demirelli S, Bakirci EM, Hamur H, Inci S, et al. Assessment of effect of irbesartan and nebivolol on the left atrium volume and deformation in the patients with mild-moderate hypertension. *Eur Rev Med Pharmacol Sci.* 2014;**18**:781–9.
79. Inciardi RM, Giugliano RP, Claggett B, Gupta DK, Chandra A, Ruff CT, et al.; ENGAGE AF-TIMI 48 Investigators. Left atrial structure and function and the risk of death or heart failure in atrial fibrillation. *Eur J Heart Fail.* 2019;**21**:1571–9.
80. Pessoa-Amorim G, Mancio J, Vouga L, Ribeiro J, Gama V, Bettencourt N, et al. Impaired left atrial strain as a predictor of new-onset atrial fibrillation after aortic valve replacement independently of left atrial size. *Rev Esp Cardiol (Engl Ed).* 2018;**71**:466–76.
81. Bukowska A, Lendeckel U, Bode-Böger SM, Goette A. Physiologic and pathophysiologic role of calpain: implications for the occurrence of atrial fibrillation. *Cardiovasc Ther.* 2012;**30**:e115–27.
82. Vermes E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: insight from the Studies of Left Ventricular Dysfunction (SOLVD) trials. *Circulation.* 2003;**107**:2926–31.
83. Khatib R, Joseph P, Briel M, Yusuf S, Healey J. Blockade of the renin-angiotensin-aldosterone system (RAAS) for primary prevention of non-valvular atrial fibrillation: a systematic review and meta analysis of randomized controlled trials. *Int J Cardiol.* 2013;**165**:17–24.
84. Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlöf B, et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study. *J Am Coll Cardiol.* 2005;**45**:712–9.
85. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. *Circulation.* 2000;**101**:2612–7.
86. Cha TJ, Ehrlich JR, Chartier D, Qi XY, Xiao L, Nattel S. Kir3-based inward rectifier potassium current: potential role in atrial tachycardia remodeling effects on atrial repolarization and arrhythmias. *Circulation.* 2006;**113**:1730–7.
87. Bax JJ, Marsan NA, Delgado V. Non-invasive imaging in atrial fibrillation: focus on prognosis and catheter ablation. *Heart.* 2015;**101**:94–100.
88. Leong DP, Delgado V, Bax JJ. Imaging for atrial fibrillation. *Curr Probl Cardiol.* 2012;**37**:7–33.
89. Motoki H, Negishi K, Kusunose K, Popović ZB, Bhargava M, Wazni OM, et al. Global left atrial strain in the prediction of sinus rhythm maintenance after catheter ablation for atrial fibrillation. *J Am Soc Echocardiogr.* 2014;**27**:1184–92.
90. Tsao HM, Hu WC, Wu MH, Tai CT, Chang SL, Lin YJ, et al. The impact of catheter ablation on the dynamic function of the left atrium in patients with atrial fibrillation: insights from four-dimensional computed tomographic images. *J Cardiovasc Electrophysiol.* 2010;**21**:270–7.
91. Wylie JV, Peters DC, Essebag V, Manning WJ, Josephson ME, Hauser TH. Left atrial function and scar after catheter ablation of atrial fibrillation. *Heart Rhythm.* 2008;**5**:656–62.
92. Yoon HJ, Jeong MH, Jeong Y, Kim KH, Song JE, Cho JY, et al. Progressive dilation of the left atrium and ventricle after acute myocardial infarction is associated with high mortality. *Korean Circ J.* 2013;**43**:731–8.
93. Popescu BA, Macor F, Antonini-Canterin F, Giannuzzi P, Temporelli PL, Bosimini E, et al.; GISSI-3 Echo Substudy Investigators. Left atrium remodeling after acute myocardial infarction (results of the GISSI-3 Echo substudy). *Am J Cardiol.* 2004;**93**:1156–9.
94. Cuspidi C, Rescaldani M, Tadic M, Sala C, Grassi G. Effects of bariatric surgery on cardiac structure and function: a systematic review and meta-analysis. *Am J Hypertens.* 2014;**27**:146–56.
95. Dimitri H, Ng M, Brooks AG, Kuklik P, Stiles MK, Lau DH, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. *Heart Rhythm.* 2012;**9**:321–7.
96. Lau DH, Middeldorp ME, Brooks AG, Ganesan AN, Roberts-Thomson KC, Stiles MK, et al. Aortic stiffness in lone atrial fibrillation: a novel risk factor for arrhythmia recurrence. *PLoS One.* 2013;**8**:e76776.
97. Sørensen E, Myrstad M, Solberg MG, Øie E, Tveit A, Aarønæs M. Left atrial function in male veteran endurance athletes with paroxysmal atrial fibrillation. *Eur Heart J Cardiovasc Imaging.* 2021;**23**:137–46.
98. Kramer DG, Trikalinos TA, Kent DM, Antonopoulos GV, Konstam MA, Udelson JE. Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach. *J Am Coll Cardiol.* 2010;**56**:392–406.
99. Desai AS, Solomon SD, Shah AM, Claggett BL, Fang JC, Izzo J, et al.; EVALUATE-HF Investigators. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial. *JAMA.* 2019; **322**:1077–84.
100. Januzzi JL, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, et al.; PROVE-HF Investigators. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA.* 2019;**322**:1085–95.
101. Valzania C, Gadler F, Boriani G, Rapezzi C, Eriksson MJ. Effect of cardiac resynchronization therapy on left atrial size and function as expressed by speckle tracking 2-dimensional strain. *Am J Cardiol.* 2016;**118**:237–43.
102. St John Sutton M, Linde C, Gold MR, Abraham WT, Ghio S, Cerkvenik J, et al. Left ventricular architecture, long-term reverse remodeling, and clinical outcome in mild heart failure with cardiac resynchronization: results from the REVERSE trial. *JACC Heart Fail.* 2017;**5**:169–78.
103. Singh JSS, Mordi IR, Vickneson K, Fathi A, Donnan PT, Mohan M, et al. Dapagliflozin versus placebo on left ventricular remodeling in patients with diabetes and heart failure: the REFORM trial. *Diabetes Care.* 2020;**43**:1356–9.
104. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation.* 2021;**143**:516–25.
105. Tsang TSM, Barnes ME, Abhayaratna WP, Cha SS, Gersh BJ, Langins AP, et al. Effects of quinapril on left atrial structural remodeling and arterial stiffness. *Am J Cardiol.* 2006;**97**:916–20.
106. Mak GJ, Ledwidge MT, Watson CJ, Phelan DM, Dawkins IR, Murphy NF, et al. Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone. *J Am Coll Cardiol.* 2009;**54**:1674–82.
107. Kayrak M, Bacaksiz A, Vatankulu MA, Ayhan SS, Ari H, Kaya Z, et al. The effects of spironolactone on atrial remodeling in patients with preserved left ventricular function after an acute myocardial infarction: a randomized follow-up study. *Coron Artery Dis.* 2010;**21**:477–85.
108. Edelmann F, Gelbrich G, Düngen HD, Fröhling S, Wachter R, Stahrenberg R, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise Training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol.* 2011;**58**:1780–91.
109. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al.; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet.* 2012;**380**:1387–95.
110. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). *J Card Fail.* 2011;**17**:634–42.
111. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, et al.; Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA.* 2013;**309**:781–91.
112. Kurrelmeyer KM, Ashton Y, Xu J, Nagueh SF, Torre-Amione G, Deswal A. Effects of spironolactone treatment in elderly women with heart failure and preserved left ventricular ejection fraction. *J Card Fail.* 2014;**20**:560–8.
113. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Deswal A, Anand IS, et al. Prognostic importance of changes in cardiac structure and function in heart failure with preserved ejection fraction and the impact of spironolactone. *Circ Heart Fail.* 2015;**8**:1052–8.
114. Soga F, Tanaka H, Tatsumi K, Mochizuki Y, Sano H, Toki H, et al. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. *Cardiovasc Diabetol.* 2018;**17**:132.
115. Kim KH, Kim YJ, Shin DH, Chang SA, Kim HK, Sohn DW, et al. Left atrial remodelling in patients with successful percutaneous mitral valvuloplasty: determinants and impact on long-term clinical outcome. *Heart.* 2010;**96**:1050–5.
116. D'Ascenzi F, Cameli M, Henein M, Iadanza A, Reccia R, Lisi M, et al. Left atrial remodelling in patients undergoing transcatheter aortic valve implantation: a speckle-tracking prospective, longitudinal study. *Int J Cardiovasc Imaging.* 2013;**29**:1717–24.
117. Hatani T, Kitai T, Murai R, Kim K, Ehara N, Kobori A, et al. Associations of residual left ventricular and left atrial remodeling with clinical outcomes

in patients after aortic valve replacement for severe aortic stenosis. *J Cardiol.* 2016;**68**:241–7.
118. Toprak C, Kahveci G, Kilicgedik A, Pala S, Kirma C, Tabakci MM, et al. Left atrial remodeling in patients undergoing percutaneous mitral valve repair with the MitraClip system: an advanced echocardiography study. *Echocardiography.* 2016;**33**:1504–11.
119. Avenatti E, Little SH, Barker CM, Nagueh SF. Changes in left atrial function after transcutaneous mitral valve repair. *Am J Cardiol.* 2018;**122**:1204–9.
120. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al.; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. *N Engl J Med.* 2019;**380**:539–48.
121. Murphy SP, Prescott MF, Maisel AS, Butler J, Piña IL, Felker GM, et al. Association between angiotensin receptor-neprilysin inhibition, cardiovascular biomarkers, and cardiac remodeling in heart failure with reduced ejection fraction. *Circ Heart Fail.* 2021;**14**:e008410.
122. Zile MR, Jhund PS, Baicu CF, Claggett BL, Pieske B, Voors AA, et al.; Prospective Comparison of ARNI With ARB on Management of Heart Failure With Preserved Ejection Fraction (PARAMOUNT) Investigators. Plasma biomarkers reflecting profibrotic processes in heart failure with a preserved ejection fraction: data from the Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction study. *Circ Heart Fail.* 2016;**9**:e002551.
123. Inciardi RM, Rossi A, Bergamini C, Benfari G, Maffeis C, Greco C, et al. Mitral regurgitation, left atrial structural and functional remodelling and the effect on pulmonary haemodynamics. *Eur J Heart Fail.* 2020;**22**:499–506.
124. Braunwald E, Awe WC. The syndrome of severe mitral regurgitation with normal left atrial pressure. *Circulation.* 1963;**27**:29–35.
125. Cameli M, Pastore MC, Righini FM, Mandoli GE, D'Ascenzi F, Lisi M, et al. Prognostic value of left atrial strain in patients with moderate asymptomatic mitral regurgitation. *Int J Cardiovasc Imaging.* 2019;**35**:1597–604.
126. Gucuk Ipek E, Singh S, Viloria E, Feldman T, Grayburn P, Foster E, et al. Impact of the MitraClip procedure on left atrial strain and strain rate. *Circ Cardiovasc Imaging.* 2018;**11**:e006553.
127. Witte KK, Lipiecki J, Siminiak T, Meredith IT, Malkin CJ, Goldberg SL, et al. The REDUCE FMR trial: a randomized sham-controlled study of percutaneous mitral annuloplasty in functional mitral regurgitation. *JACC Heart Fail.* 2019;**7**:945–55.
128. Giallauria F, Di Lorenzo A, Parlato A, Testa C, Bobbio E, Vigorito C, et al. Individual patient data meta-analysis of the effects of the CARILLON® mitral contour system. *ESC Heart Fail.* 2020;**7**:3383–91.
129. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;**381**:1995–2008.
130. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al.; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;**383**:1413–24.
131. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;**385**:1451–61.
132. Teerlink JR, Felker GM, McMurray JJV, Solomon SD, Adams KF, Cleland JGF, et al.; COSMIC-HF Investigators. Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure (COSMIC-HF): a phase 2, pharmacokinetic, randomised, placebo-controlled trial. *Lancet.* 2016;**388**:2895–903.
133. Teerlink JR, Diaz R, Felker GM, McMurray JJV, Metra M, Solomon SD, et al.;, GALACTIC-HF Investigators. Cardiac myosin activation with omecamtiv mecarbil in systolic heart failure. *N Engl J Med.* 2021;**384**:105–16.
134. Biering-Sørensen T, Teerlink JR, Felker GM, McMurray JJ, Malik FI, Honarpour N, et al. Cardiac myosin activator omecamtiv mecarbil improves left atrial structure and function in chronic heart failure (COSMIC-HF). *Circulation.* 2016;**134**:A19108 (abstr).
135. Teerlink JR, Diaz R, Felker M, McMurray JJ, Solomon S, Metra M, et al.; GALACTIC-HF Investigators and Patients. The effect of omecamtiv mecarbil on stroke in patients with heart failure and reduced ejection fraction in GALACTIC-HF. Abstract 16605. Late-Breaking Science Abstracts and Featured Science Abstracts from the American Heart Association's Scientific Sessions 2021 and Late-Breaking Abstracts in Resuscitation Science from the Resuscitation Science Symposium 2021. *Circulation.* 2021;**144**:e564–93.
136. Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, et al.; CABANA Investigators. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA.* 2019;**321**:1261–74.
137. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al.; CASTLE-AF Investigators. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med.* 2018;**378**:417–27.
138. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, et al. 2019 AHA/ACC/HRS Focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation.* 2019;**140**:e125–51.