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CARDIAC REMODELING IN PATIENTS WITH HFrEF TREATED WITH SACUBITRIL/VALSARTAN: ECHOCARDIOGRAPHIC ANALYSIS

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Abstract

CARDIAC REMODELING IN PATIENTS WITH HFrEF TREATED WITH SACUBITRIL/VALSARTAN: ECHOCARDIOGRAPHIC ANALYSIS

Aim of the study: The aim of the present study was to assess reverse remodeling in patients with HFrEF after six months of treatment with sacubitril/valsartan through 3D echocardiography and two-dimensional Speckle Tracking echocardiography, which are known to allow automatic and reproducible assessment of ventricular volumes, ejection fraction, left atrium volume and global longitudinal strain of the left ventricle and left atrium. A further aim of the study was to analyze clinical and echocardiographic baseline characteristics of the patients in order to identify the presence of predictive factors of significant reverse remodelling, and, thus, of response to sacubitril/valsartan treatment.
Finally, the variation in atrial natriuretic peptides plasmatic levels after sacubitril/valsartan therapy was also evaluated.

Material and Methods: In this prospective longitudinal study, patients with HFrEF treated with sacubitril/valsartan were enrolled. The following were inclusion criteria: age over 18, EF ≤ 35%, NYHA class ≥ II, treatment with the maximum tolerated dosage of ACEi or ARB or patients naïve to ACEi or ARB, undergoing pre-treatment with one of theese drugs. Exclusion criteria were: symptomatic hypotension, systolic blood pressure <100mmHg, eGFR <30 ml/min/1.73 m^2, serum potassium levels >5.2 mmol/L, history of angioedema, adverse reactions during ACEi/ARB therapy, concomitant initiation of therapy that may induce reverse remodelling (for example, CRT implantation or coronary revascularization during follow-up or in the six months prior to enrolment), non-sinus rhythm, suboptimal acoustic window. Patients have been undergoing a clinical examination, 12-lead electrocardiogram, transthoracic echocardiogram (2D/3D parameters and 2D-Speckle Tracking), and dosage of natriuretic peptides before the start of therapy with sacubitril/valsartan and at the follow-up at 6 months. Functional assessment was performed using the NYHA classification.

Results: The final study population consisted of 32 patients. At the time of the follow up several echocardiographic parameters improved significantly in the entire study population. 13 (41%) of the patients in the study population were classified 'responders' and 19 (59%) were 'super responders'. In the 'responders' group more severe left ventricular remodelling before treatment was documented, in particular greater VTDi values and higher indexed atrial volumes.
An improvement in global ventricular and atrial strain was also observed in 'responders', although less marked than the 'super responders' group.

Conclusions: Sacubitril/valsartan significantly improves reverse remodeling in patients with HFrEF. This result tends to occur in patients with a ventricular dilation of lesser severity. In accordance with these considerations, the drug should be used early and independently of the apparent clinical "stability" to avoid further progression of ventricular remodelling. Further studies may lead to an indication of sacubitril/valsartan since an earlier stage of the disease.

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3. Study

Introduction

Heart failure with reduced ejection fraction (HFrEF), is a progressive disease with a history characterised by phases of apparent stability alternating with phases of instability and worsening, with frequent need for hospitalisation and subsequent high incidence of re-hospitalisation.

The PARADIGM-HF[2] study, the largest trial ever conducted to date in patients with HFrEF, introduced the greatest pharmacological innovation of recent years into the treatment of these patients: sacubitril/valsartan, the progenitor of a new generation of drugs known as 'ARNI' (angiotensin receptor neprilysin inhibitor), which on a pathophysiological level acts on two pathogenetic mechanisms of heart failure: the activation of the renin-angiotensin-aldosterone system (RAAS: Renin-Angiotensin-Aldosteron-System) and the decreased sensitivity to natriuretic peptides. Thanks to the presence of valsartan in the drug's composition, all the widely known positive effects of sartans (Angiotensin-Receptor-Blockers: ARB) are maintained; thanks to sacubitril, which causes an inhibition of neprilysin, a decreased degradation of natriuretic peptides is achieved, resulting in an increase in their plasmatic levels with their consequent vasodilator, natriuretic, antiproliferative and antifibrotic effects.

After a median follow-up of 27 months, the study was stopped early due to a net clinical benefit of sacubitril/valsartan compared to enalapril.

Compared to enalapril, sacubitril/valsartan reduced the primary endpoint, i.e. the risk of cardiovascular death and hospitalisation for heart failure, by 20% and mortality from all causes by 16%.

However, the PARADIGM-HF study did not include an echocardiographic follow-up. To date, there are still only a few studies available in literature[3-6] describing echocardiographic characteristics of the recovery of ventricular function and any reverse remodelling of the cardiac chambers after treatment with sacubitril/valsartan. Besides, none of these studies consider the currently most recommended methods for the assessment of ventricular function. In the echocardiographic assessment of cardiac function, there has been a rapid and progressive development: 3D echocardiography is currently the most accurate method of assessing ejection fraction. In addition, strain parameters derived from speckle tracking echocardiography, applied to the study of the ventricular and atrial myocardium, nowadays are of great importance, allowing a thorough, practical and non-invasive assessment of myocardial function.

The aim of the present study was to assess reverse remodelling in patients with HFrEF after treatment with sacubitril/valsartan, using innovative and accurate methods such as the HeartModel system, which provides a valid and reproducible estimation of ejection fraction within seconds. Alongside the 3D echocardiographic evaluation,

another aim was also to analyse changes in left ventricular and atrial longitudinal strain after medical therapy with sacubitril/valsartan. In addition to these more innovative and recent parameters, values for filling pressures, PAPS, and both ventricular and atrial diameters and volumes were also taken into account.
Finally, a further aim of the study was to analyse the main clinical and echocardiographic characteristics among patients who presented less significant reverse remodelling.

Bibliography

1 "*2021 ESC Guidelines for the diagnosis and treatment of Acute and Chronic Heart Failure"* European Heart Journal (2021) - doi:10.1093/eurheartj/ehab368

2 McMurray JJ et al.; *"PARADIGM-HF Investigators and Com- mittees. Angiotensin-neprilysin inhibition versus enalapril in heart failure."* N Engl J Med 2014;371:993-1004.

3 Almufleh A, Marbach J, Chih S, Stadnick E, Davies R, Liu P, Mielniczuk L **"***Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients."* Am J Cardiovascular Disease 2017 Dec 20;7(6):108-113. eCollection 2017.

4 Martens P, Beliën H, Dupont M, Vandervoort P, Mullens W.*"The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction."* Cardiovasc Ther. 2018 Aug;36(4):e12435. doi: 10.1111/1755-5922.12435. Epub 2018 Jun 7.

5 Kang DH, Park SJ, Shin SH, Hong GR, Lee S, Kim MS, Yun SC, Song JM, Park SW, Kim JJ. *"Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation: PRIME Study."* Circulation 2019;139:1354–1365. doi: 10.1161/CIRCULATIONAHA.118.037077

6 Januzzi JL et al. *"Rationale and methods of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF)."* Am Heart J. 2018 May;199:130-136. Epub 2018 Feb 13.

1. Heart failure

1.1 Definition, etiology, diagnosis

Heart failure is a complex clinical syndrome characterised by several typical symptoms and signs such as dyspnoea, asthenia, swollen ankles and legs, oedemas, jugular distension, and lung crackles. It can be caused by a structural or functional alteration that results in either an impaired blood ejection capacity and thus reduced cardiac output or impaired ventricular filling resulting in elevated intracardiac pressure at rest or during stress.
The terminology used to define heart failure has historically been based on the measurement of ejection fraction (FE). Using this parameter, three categories of heart failure can be distinguished: heart failure with preserved ejection fraction (HFpEF, EF >50%), with mildly reduced EF (HFmrEF, EF between 41 and 49%), and with reduced EF (HFrEF with FE < 40%).[1]

Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	-	-	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

"*2021 ESC Guidelines for the diagnosis and treatment of Acute and Chronic Heart Failure*" European Heart Journal (2021)

Different epidemiologies and etiological profiles can be recognised for the different types of heart failure. Compared to heart failure with reduced EF, heart failure with preserved EF occurs more often in older, female patients, with a history of systemic arterial hypertension, atrial fibrillation, while a previous history of myocardial infarction is more rarely found in these patients.
In 20-30% of patients with HFrEF, the exact etiology is unknown; in these case the

cause may be non-ischaemic, familial dilated or idiopathic cardiomyopathy. Previous viral infections or exposure to toxins can also lead to dilated cardiomyopathy. Actually, there is not a classification system for the causes of heart failure, because there are many different pathologies responsible for HF, the identification of which should be an integral part of the diagnostic work-up, so that specific therapeutic opportunities can be guaranteed, with multidisciplinary care. With regard to diagnosis in a non-acute setting, the essential elements to be considered, which allow specific diagnostic algorithms to be applied, are patient's medical history, physical examination, electrocardiogram, natriuretic peptide plasmatic levels and echocardiogram. Gathering a detailed medical history is essential, as heart failure will rarely be present in patients without a relevant clinical history, in which a potential cause of cardiac damage is not recognised, while obviously some elements such as a history of myocardial infarction, previous myocardial revascularisation surgery or systemic arterial hypertension significantly increase the likelihood that the patient, who presents for the first time with typical signs or symptoms, really has a heart failure condition. Therefore, in the first steps of the diagnostic approach, the presenting symptoms, the physical examination and finally the resting ECG must be considered. If all these elements are normal, heart failure is highly unlikely and other diagnoses must be considered. If, however, at least one element is altered, plasma natriuretic peptide levels should be measured.[2]

Natriuretic peptides are very useful biomarkers and can guide the clinician both in the diagnosis of heart failure and in the therapeutic choices and prognostic evaluation of the patient. The most frequently used are B-type natriuretic peptide (BNP) and the N-terminal fragment of B-type natriuretic peptide (N-Terminal pro-B-type Natriuretic Peptide, NT-proBNP). They are released by cardiomyocytes and, considering their distribution predominantly in ventricles, they are believed to be indicative of ventricular stretch and synthesised in response to wall stress. Natriuretic peptide levels tend to increase progressively with worsening NYHA functional class and to be higher in HFrEF than in HFpEF, despite the independent contribution of diastolic function to their concentration. Patients with acute decompensated heart failure more often have higher BNP and NT-proBNP values than those with chronic stable heart failure. The upper limit of normality for the non-acute setting is for BNP 35 pg/mL and for NT-proBNP 125 pg/mL; in the acute setting, however, higher values for BNP < 100 pg/mL and for NT-proBNP < 300 pg/mL must be considered.[3]

Several important clinical variables interfere with BPN and NT- proBNP values. Both natriuretic peptides increase with age, probably due to the accumulation of cardiac structural alterations in older subjects, with renal insufficiency, partly due to slower clearance and in many other cardiac or non-cardiac pathological situations, such as atrial fibrillation, right ventricular dysfunction resulting from pulmonary embolism,

sepsis, and also obesity.[4] Once measured natriuretic peptides levels, if altered values are found, the diagnostic pathway must be continued by performing a colour-Doppler echocardiogram, which is the most readily available imaging modality, without any risks, as it does not even involve exposure to radiation, and can even be performed at patient's bedside. It can assess structure and function of myocardium and valves, providing important information on intracardiac pressures and flows.

In addition to the echocardiogram, many other imaging modalities are extremely important in the diagnosis of HF. Readily available and easily performed, chest X-ray is extremely important, especially in the acute form. Cardiac MRI is the gold standard for measurements of volumes, mass, and ejection fraction of both ventricles.[5] In patients with inconclusive echocardiographic examinations, especially imaging of the right heart and in those with complex congenital heart disease, MRI is the best exam.[6] Through different sequences, with or without gadolinium, it can highlight the characteristics of cardiac tissue and assess myocardial viability, allowing the distinction between ischaemic and non-ischemic cardiomyopathy, especially on the basis of the localization of areas with LGE (late gadolinium enhancement), which correspond to myocardial necrosis or fibrosis. Generally, in ischemic cardiomyopathies LGE is predominantly observed in subendocardial regions or with transmural extension, whereas in non-ischemic dilated cardiomyopathies it may be observed more frequently in intermediate or epicardial regions or not be present, or show specific patterns depending on the aetiology.[7,8]

Nuclear imaging techniques include methods useful in the study of heart failure too, such as PET and SPECT, which are mostly used for the assessment of myocardial ischaemia and heart viability.[9]

Coronarography is recommended in patients with heart failure and angina refractory to medical therapy or symptomatic for ventricular arrhythmias, and should be considered in patients with intermediate-high pre-test probability.[10] Coronary CT is preferred in patients who have undergone non-invasive stress testing with equivocal results and in those with low to intermediate pre-test probability.

Finally, among several other tests that can be performed, probably the one with the greatest importance and diagnostic value is the endomyocardial biopsy, which should be considered in patients with rapidly progressive heart failure, despite medical therapy, where there is a possibility to make a specific diagnosis, confirmed by myocardial histological examination, and to start an effective targeted medical therapy.

1.2 Echocardiography in the evaluation of patients with heart failure

1.2.1 Assessment of systolic function: 3D echocardiography and beyond

Echocardiography, which is routinely used for the evaluation of patients with heart failure, is a widely used imaging method that is safe, easy to perform, non-invasive, providing very important information regarding cardiac structure and function. It has also the fundamental role of guiding the clinician in making therapeutic decisions and monitoring response to treatment.

The pump function of the left ventricle can be expressed through various parameters. In clinical practice, ejection fraction tends to be used more frequently.

Current guidelines recommend the use of 3D to assess the dimensions of cardiac chambers and their function, because of its diagnostic accuracy and high reproducibility. In fact, 3D is not based on any kind of geometric assumption and there is no risk of assessing the volumes of the heart chambers incorrectly. The latest innovation in 3D echocardiography is the HeartModelA.I., an intuitive and validated diagnostic tool that provides a valid and reproducible ejection fraction in few seconds, and the simultaneous characterization of the volume of the left atrium, which has been shown to have an important cardiovascular prognostic value. The multicentre clinical study by Medvedofsky et al.[11] demonstrated the accuracy and reproducibility of 3D echocardiography performed with HeartModelA.I. and subsequently proved its superiority over manual 3D echocardiography.

This new automatic method, which is quick and easy to perform, is based on an algorithm built from a large number of 3D datasets obtained in patients with different types of left ventricle. The software simultaneously detects endocardial surfaces of left ventricle and atrium, identifying end diastolic and end systolic phases, in order to create three-dimensional casts of the cavities in the different phases of the cardiac cycle, from which the ventricular and atrial volumes can be derived directly, without the need for any geometric assumptions.

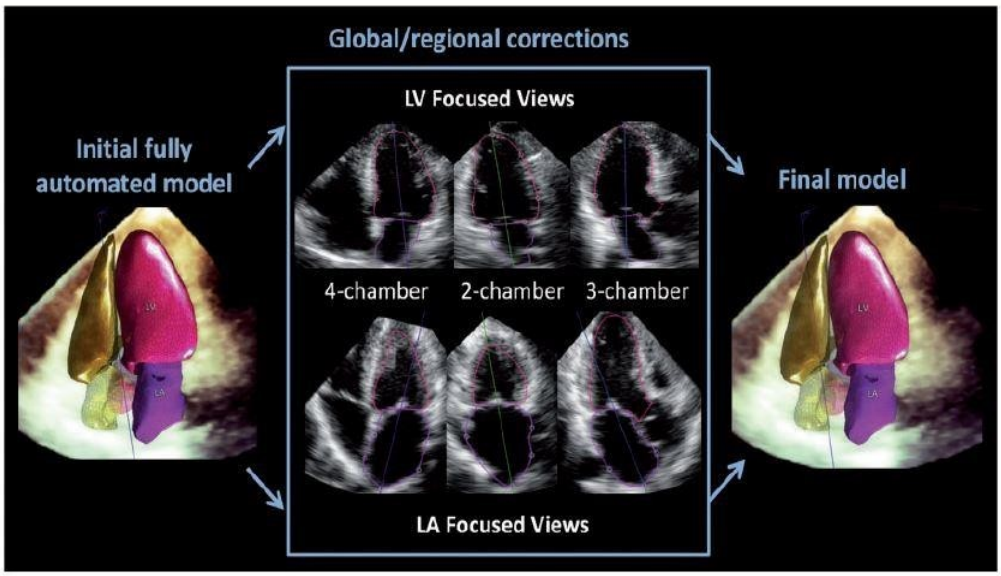


Figure 2 Automated technique for left-heart 3D chamber quantification. Following initial fully-automated detection of left ventricular and left atrial endocardial surfaces (left), the software allows the user to perform manual corrections of the endocardial boundaries when needed (centre), resulting in final 3D casts of the cardiac chambers. The optional correction are performed in anatomically correct non-foreshortened 2D planes showing focused long-axis views of the left ventricle (top) and left atrium (bottom), both automatically extracted from the 3D dataset.

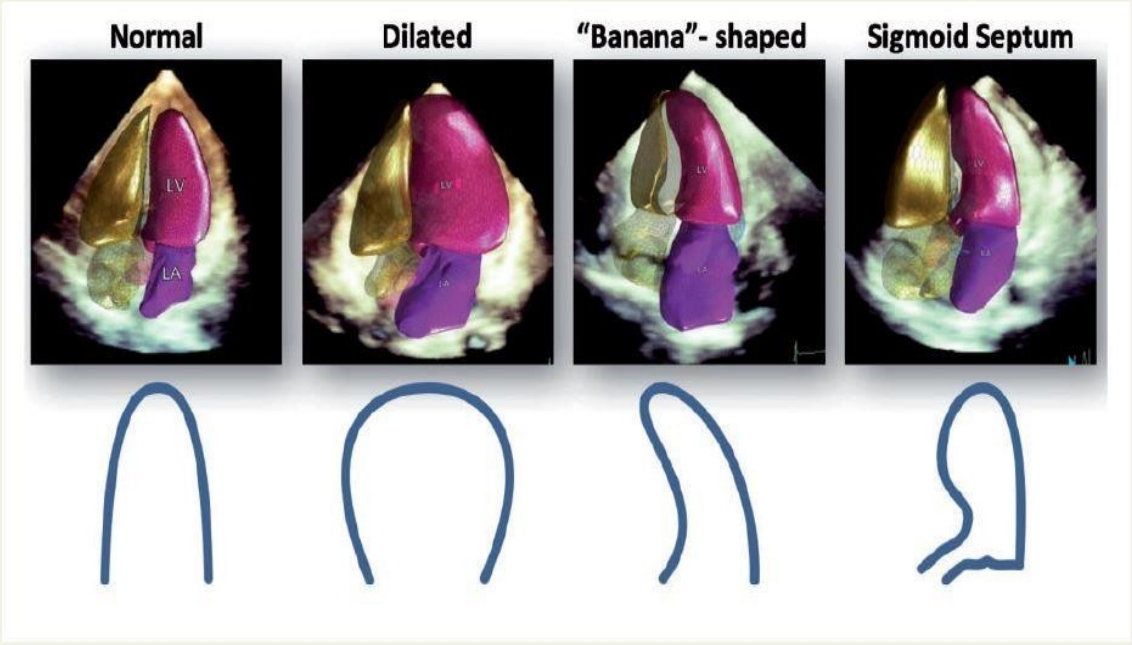


Figure 1 Different left ventricular shapes that the automated software was trained to recognize. In addition to normal ventricles, the training set included a number of common abnormal/asymmetrical ventricular shapes. (Note that the program displays RV and RA casts but no volume values are provided because they have not been validated).

D. Medvedofsky et al. *'Three-dimensional echocardiographic quantification of the left-heart chambers using an automated adaptive analytics algorithm: multicentre validation study'* European Heart Journal-Cardiovascular Imaging (2018) 19, 47-58

EF, when used alone, can sometimes confuse rather than clarify patient's functional characteristics. In fact, EF depends both on SV in a direct way and on end diastolic volume (EDV) of the left ventricle in an inverse way (EF = SV/EDV): this dependence of EF on the two factors makes clear how it is possible to observe a reduced EF associated with a normal SV (if EDV is increased) and, on the other hand, also a normal EF associated with a reduced SV (if EDV is reduced). So that, the assessment of EF in heart failure cannot be isolated but must always be combined with that of EDV and SV.[12]
Since EF is calculated from the difference in ventricular volumes, it merely represents the change in volume that occurs during ventricular systole, but does not clarify in which direction blood is eject. The fact that a reduced EF does not necessarily correspond to a reduced SV makes clear why resting EF in HF does not correlate with symptoms, exercise capacity and myocardial oxygen consumption.[13,14]
As previously mentioned, 3D echocardiography should be used for the calculation of left ventricular volumes and FE, as currently recommended by the guidelines. This method, however, is not yet available everywhere. Two-dimensional echocardiography should be used as an alternative with the biplane approach based on Simpson's method or, if endocardial borders are poorly recognisable, the area-length method.[15] Regarding SV, the method to be used for its assessment is the echo-Doppler, which has been also validated in patients with heart failure.

1.2.2 Assessment of left ventricular mass, geometry and remodeling

In patients with heart failure, the degree of left ventricular remodelling is an important prognostic factor. In addition to size, the change in ventricular shape is also a key element in determining the severity of heart failure. Different types of ventricular remodeling can be observed with different prognostic profiles.
In patients with HFpEF, myocardium generally responds with an increase in radial thickness of the muscle fibers and a greater deposition of extracellular collagen, resulting in concentric hypertrophy, characterized by an increase in parietal thickness and overall muscle mass.[16-17]
In some cases a concentric remodelling occurs, when total mass is not significantly increased, as opposed to parietal thickness. Distinguishing the two entities is important as concentric parietal hypertrophy is associated with a worse prognosis than concentric remodelling.[18-19]
In contrast, a lengthening of cardiomyocytes without an increase in their width is observed in patients with HFrEF. In addition, myocyte necrosis and extracellular

collagen degradation occur as a result of the increased activity of matrix metalloproteinases and similar enzymes.[17]
As a result, eccentric remodelling is observed, characterized by an increase in the size of the ventricular cavity, which is not associated with an increase in parietal thickness, which is sometimes actually thinned.
Moreover, left ventricle in these patients will tend to dilate, because it will tend to take on a more spherical shape, by virtue of the fact that spherical geometry allows larger volumes to be received for the same myocardial length.
However, the increased sphericity of the left ventricle is a maladaptation, associated with poorer prognosis, as it increases wall stress.[20]
Another index that can be easily derived on the basis of M- mode measurements and can provide useful pathophysiological and prognostic information is the relative wall thickness, which is calculated by dividing twice the posterior wall thickness by the left ventricular telediastolic diameter.
When the relative wall thickness is >0.42, it indicates concentric remodelling; conversely, it is suggestive of eccentric remodelling.
Since the transition from an ellipsoid shape to a more spherical geometry is generally associated with a progression of systolic dysfunction, it is important in this regard to make an assessment, which can be done visually or quantitatively through the ventricular sphericity index. It is also important to consider the extent of left ventricular dilatation: when it is very severe, i.e. when the end diastolic diameter is greater than 70 mm, reverse remodelling is less likely with medical therapy. Sudden dilatation in patients with left ventricular heart failure is associated with an increased risk of cardiac death. The BEST study by Grayburn et al.[21] showed that the indexed end diastolic volume is an independent prognostic predictor in HFrEF with a cut-off value of 120 ml/sqm.

1.2.3 Speckle-tracking echocardiography in patients with heart failure

Strain imaging is based on the study of three-dimensional myocardial deformation, a complex mechanism made possible by the left ventricular myocardial architecture, which has been accurately described by Torrent-Guasp et al,[22] based on the results of anatomopathological dissection of the heart.
These authors believe that left ventricle consists of a single myocardial band coiled in a spiral; consequently, the main mechanism responsible for left ventricular ejection would be a 'wringing' or 'squeezing motion' related to the spiral arrangement of the

myocardial architecture.
The subendocardial layer consists of fibers oriented longitudinally-obliquely from the base towards the apex, the intermediate layer of fibers arranged in a circular direction, while the subepicardial layer consists of fibers running longitudinally-obliquely from the apex towards the base. Because of the architecture described above, it is clear that the systolic contraction of the left ventricle cannot be compared to the shortening of any skeletal muscle, which, having specific tendon heads of insertion, shortens in a single direction. The systolic twisting of the left ventricle, in addition to being essential for blood ejection, also represents an important energy reserve. Near the end of systole, when the twisting is at its maximum, the muscle bundles begin to relax sequentially from the subepicardium to the subendocardium, resulting in an inverse deformation of the left ventricle: the base rotates in a counterclockwise direction while the apex rotates in a clockwise direction, a sort of recoiling also known as untwisting or recoil that occurs most during the phases of isovolumetric relaxation and early filling of the left ventricle. In this phase, the subepicardial fibers release and recoil back to their original position, the recoiling of the subepicardial fibers causes a tensile force to be exerted on the endocardium. Thus, a spring mechanism occurs between the epicardium and the endocardium that causes a negative transmural pressure; this causes an atrioventricular gradient responsible for mitral valve opening and early ventricular filling.
Decreased systolic torsion inevitably impairs the recoil phase of the left ventricle, leading to reduced early filling in diastole, which is precisely why patients with heart failure frequently have impaired diastolic function.
Longitudinal strain (LS) represents myocardial shortening along its longitudinal axis, is identified by negative curves during systole and positive curves in diastole, and can be assessed in apical 2, 3 and 4-chamber view. In addition to the strain of each individual myocardial segment, it is possible to assess the average of the regional strains to obtain the global longitudinal strain (GLS), which is an important index of global systolic and subclinical regional ventricular function before the alteration of EF.
Global radial strain (GRS) represents myocardial deformation in the radial direction and corresponds to the percentage systolic thickening of the myocardium. For this reason, normal systolic GRS curves are positive. The analysis is performed in parasternal short-axis view in 3 sections: base, papillary muscles and apex. In these same sections, global circumferential strain (GCS) is analysed, which represents the shortening of the myocardium circumferentially with negative curves.
The echocardiographic speckle tracking technique is a method that does not use the Doppler technique; therefore, compared to TDI it has the advantage of being independent of the angle between the flow direction and the ultrasound beam. It is based on the recognition of so-called speckles, i.e. a set of pixels that make up the

fundamental matrix of the two-dimensional echo, derive from the interaction of the ultrasounds with the myocardial tissue and can be recognised and tracked in an entire region throughout the cardiac cycle by the software in 2D or 3D, generating myocardial deformation curves in different directions. The principle is that if two consecutive frames are temporally close together, the small change in position of the speckles can be easily recognized by the software. The calculation capacity of the system allows this to be performed for dozens of regions simultaneously along the profile of a 2D image.[23]
Speckle Tracking analysis is performed on two-dimensional greyscale echocardiographic images, acquired during apnoea to minimise breath act-related shifts and synchronised with the electrocardiographic trace. Images should be acquired with a high frame-rate: the optimal range is between 60 and 110 Hz,[24] trying to set a value proportional to the patient's heart rate. Having a high frame rate means having a high temporal resolution; this allows the 'speckles' along the cardiac cycle to be followed more precisely.
Longitudinal strain parameters, obtained from 2D speckle tracking algorithms, are visualized through colour-coded regional/time strain curves and a 'bull's eye' graph.
While it is true that classifying heart failure as systolic or diastolic is erroneous and outdated, even the more recent designation described in the ESC 2021 guidelines of heart failure with reduced ejection fraction or preserved ejection fraction is not entirely complete, because it doesn’t consider the underlying myocardial mechanisms.[25]
In patients with HFpEF there is typically a reduction in GLS and GRS while GCS and twisting are often normal (or have values above normal), ensuring that EF is not reduced. In HFrEF there is also a reduction in GCS and twisting, demonstrating that all compensatory mechanisms are exhausted. The loss of circumferential fibers support results in dilation of the left ventricle.
In HFrEF, it has been shown that the peak of the twisting is reached later than normal, often during diastole, and so is the peak of the clockwise rotation of the apex. Impaired twisting negatively affects diastole as the energy released for untwisting is reduced.[26]
In patients with HFpEF, it has been observed that moderate diastolic dysfunction is associated with increased velocities of both twisting and untwisting as a possible compensatory mechanism for the reduction of various types of myocardial deformation; when diastolic dysfunction becomes advanced, with increased ventricular filling pressures, these velocities are normalised or reduced, as demonstrated by Park et al.[27]
Several studies comparing various software were carried out; from these studies emerged that the most reproducible parameter was the GLS, while the other strain parameters were subject to enormous variations and, therefore, not very reliable.[28]
Many studies have validated the existence of a good correlation between EF and

Longitudinal Strain. The GLS also allows an accurate and early identification of changes affecting the subendocardial longitudinal fibers layers after a myocardial damage, differently from EF. These fibers are the first to be affected in numerous pathologies, so GLS evaluation is particularly useful in patients with early-stage left ventricular dysfunction and still preserved FE.[29]

The search for subclinical ventricular dysfunction by means of GLS assessment can thus be carried out in hypertensive patients, diabetics and patients with valvular disease or cardiomyopathy.[30-31] Moreover, in patients with heart failure with preserved EF, it has also been shown that the GLS decreases proportionally to NYHA class.

The progressive reduction in GLS reflects the gradual development of left ventricular dysfunction that characterizes heart failure, from its earliest stages, and is therefore to be considered useful not only as an early diagnostic marker, but also as a prognostic marker.[32]

In patients with HFpEF and those with HFrEF, GLS is an index of myocardial fibrosis[33] and an independent predictor of all-cause mortality and major adverse cardiac events,[34] thus offering a very important additional prognostic value compared to EF.[35]

The LS of the right ventricle (right ventricular longitudinal strain, RVLS) has recently shown good feasibility and reproducibility.[36,37] The procedure for calculating the strain is similar to that described for the left ventricle. For this chamber, there are 6 segments of interest obtained in the 4-chamber view, with the same number of strain curves, from which the global RVLS is calculated as the mean value. The strain of the free wall of the VD alone can also be analysed by limiting the ROI to the basal, middle and apical segments of this wall. Speckle tracking echocardiography has also been applied to the analysis of left atrium function.[38]

The assessment of atrial strain has shown excellent sensitivity and specificity in predicting a pulmonary capillary pressure of 18 mmHg or higher in patients with heart failure, in particular a cut-off below 15% shows high diagnostic accuracy,[39] and it is especially important to emphasise that a good correlation with ventricular end diastolic pressure values has been demonstrated, using the Peak Atrial Longitudinal Strain (PALS), even in patients with reduced EF.[40] The inverse relationship between global PALS and elevated filling pressures can be explained by considering left ventricular end diastolic pressure as a kind of 'afterload' of left atrial function, whereby if left ventricular end diastolic pressure is elevated, the left atrium is mechanically stressed and its reservoir function is reduced, inducing progressive dilatation.[41] Furthermore, it has been shown that left atrial strain is closely correlated not only with left ventricular end diastolic pressure, but also with levels of natriuretic peptide, in particular BNP and NT-pro-BNP,42 which are produced by atrial and ventricular cardiomyocytes precisely in response to mechanical stress.

Left atrial strain can discriminate between patients with dysfunctional asymptomatic diastolic and patients with clinical evidence of HFpEF. In addition, it has been observed that atrial dysfunction is often present in patients with heart failure and may be the primum movens of clinical manifestations: in patients with new-onset dyspnoea, the reversibility of altered atrial strain may predict the reversibility of symptoms achievable with therapy. In patients with HFrEF and those with HFpEF, PALS has prognostic value and has a significant negative correlation with NYHA class.[43]

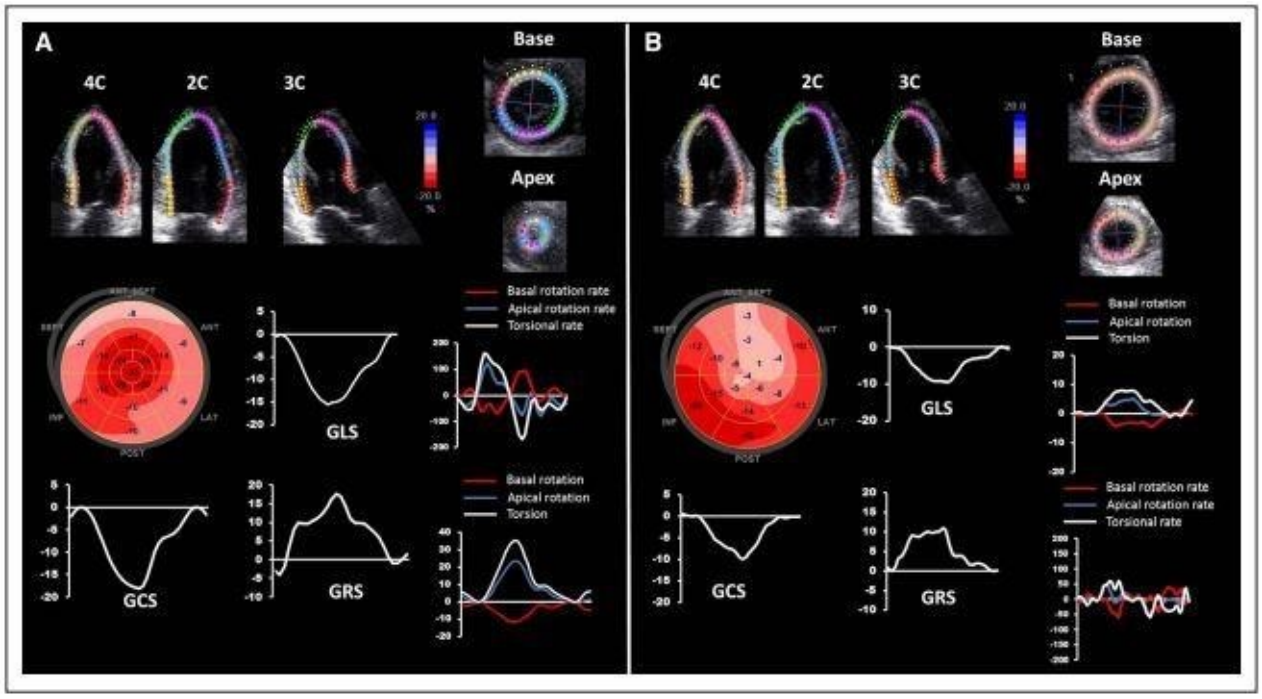
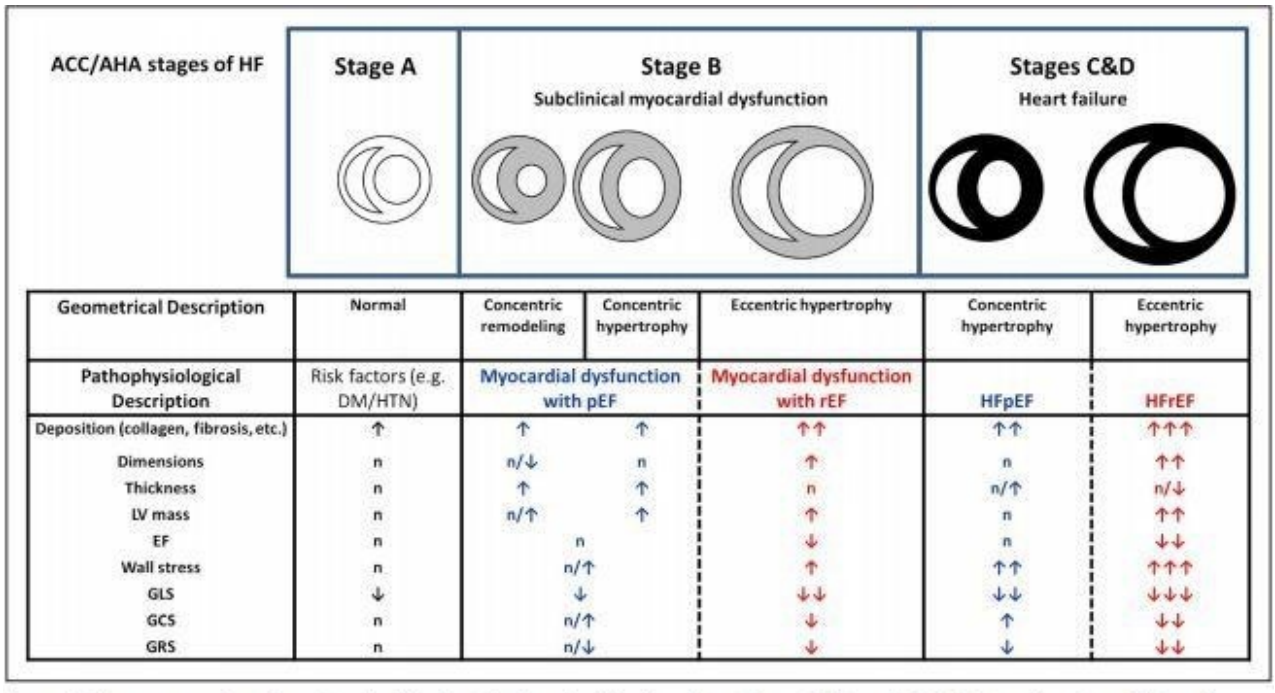


Figure 4. Speckle-tracking echocardiography–derived mechanics in patients with heart failure. A, An example of a patient with heart failure with preserved ejection fraction because of left ventricular hypertrophy caused by long-standing hypertension. GLS is blunted, whereas GCS and left ventricular torsion are exaggerated, thus, the preserved ejection fraction. Left ventricular untwist is delayed. **B**, An example of a patient with heart failure with reduced ejection fraction because of dilated cardiomyopathy. GLS is seen to be severely decreased compared with heart failure with preserved ejection fraction. In addition, mechanics in all other directions are also blunted, including reduced GCS, GRS, left ventricular torsion, and untwist rate, signifying the exhaustion of the compensatory mechanisms and the reduction of ejection fraction. 2C indicates 2-chamber; 3C, 3-chamber; 4C, 4 chamber; GCS, global circumferential strain; GLS, global longitudinal strain; and GRS, global radial strain.



Geometrical Description	Normal	Concentric remodeling	Concentric hypertrophy	Eccentric hypertrophy	Concentric hypertrophy	Eccentric hypertrophy
Pathophysiological Description	Risk factors (e.g. DM/HTN)	Myocardial dysfunction with pEF		Myocardial dysfunction with rEF	HFpEF	HFrEF
Deposition (collagen, fibrosis, etc.)	↑	↑	↑	↑↑	↑↑	↑↑↑
Dimensions	n	n/↓	n	↑	n	↑↑
Thickness	n	↑	↑	n	n/↑	n/↓
LV mass	n	n/↑	↑	↑	n	↑↑
EF	n	n		↓	n	↓↓
Wall stress	n	n/↑		↑	↑↑	↑↑↑
GLS	↓	↓		↓↓	↓↓	↓↓↓
GCS	n	n/↑		↓	↑	↓↓
GRS	n	n/↓		↓	↓	↓↓

Figure 1. The progression of mechanical dysfunction in subclinical and overt heart failure. ACC indicates American College of Cardiology; AHA, American Heart Association; DM, diabetes mellitus; EF, ejection fraction; GCS, global circumferential strain; GLS, global longitudinal strain; GRS, global radial strain; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; and LV, left ventricular.

Omar AM, Bansal M, Sengupta PP. *"Advances in Echocardiographic Imaging in Heart Failure With Reduced and Preserved Ejection Fraction."* Circ Res. 2016 Jul 8;119(2):357-74.

Bibliography

1 "*2021 ESC Guidelines for the diagnosis and treatment of Acute and Chronic Heart Failure"* European Heart Journal (2021) - doi:10.1093/eurheartj/ehab368

2 Krishnaswamy P et al. *"Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction."* Am J Med 2001;111:274–279

3 Maisel A et al. *"State of the art:using natriuretic peptide levels in clinical practice"*. Eur J Heart Fail 2008;10:824–839

4 Daniels LB et al. *"How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study."* Am Heart J 2006;151:999–1005.

5 Hundley WG et al. *"ACCF/ ACR/AHA/NASCI/SCMR 2010 expert consensus document on cardiovascular magnetic resonance: a report of the american college of cardiology foundation task force on expert consensus documents."* Circulation 2010;121:2462–2508. 102.

6 Kilner PJ et al. *"Recommendations for cardiovascular magnetic resonance in adults with congenital heart disease from the respective working groups of the European Society of Cardiology."* Eur Heart J 2010;31:794–805

7 Moon JC et al. *"Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement."* J Cardiovasc Magn Reson 2013;15:92. 104.

8 Yoshida A et al. *"Direct comparison of the diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy in patients with heart failure."* Eur J Heart Fail 2013;15:166–175

9 Beller GA, Heede RC. *"SPECT imaging for detecting coronary artery disease and determining prognosis by noninvasive assessment of myocardial perfusion and myocardial viability."* J Cardiovasc Transl Res 2011;4:416–424

10 Windecker S et al. *"2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI)."* Eur Heart J 2014;35:2541–2619

11 D.Medvedofsky et al. *"Three-dimensional echocardiographic quantification of the left-heart chambers using an automated adaptive analytics algorithm: multicentre validation study"* European Heart Journal-Cardiovascular Imaging (2018) 19, 47-58

12. Mele D. *"La frazione di eiezione del ventricolo sinistro: aspetti fisiopatologici e limiti intrinseci."* G Ital Cardiol 2012;13:793-808.

13 Cohen-Solaol A, Tabet JY, Logeart D, Bourgoin P, Tokmakova M, Dahan M. *"A non-invasively determined surrogate of cardiac
power ("circulatory power") at peak exercise is a powerful prognostic factor in chronic heart failure."* Eur Heart J 2002;23:806-14.

14 Smart N, Haluska B, Leano R, Case C, Mottram PM, Marwick TH. *"Determinants of functional capacity in patients with chronic heart failure: role of filling pressure and systolic and diastolic function."* Am Heart J 2005;149:152-8.

15 Lang RM, Badano LP, Mor-Avi V, et al. *"Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging."* J Am Soc Echocardiogr 2015;28:1-39.

16 Aurigemma GP et al. *"Contractile behavior of the left ventricle in diastolic heart failure: with emphasis on regional systolic function"* Circulation 2006;113:296-304

17 Van Heerebeek L. et al. *"Myocardial structure and function differ in systolic and diastolic heart failure"* Circulation 2006; 113: 1966-1973

18 Zile MR 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 201; 124. 2491-2501

19 Katz DH et al. "Prevalence, clinical characteristics, and outcomes associated with eccentric versus concentric left ventricular hypertrophy in heart failure with preserved ejection fraction" Am J Cardiol 2013;112: 1158-1164

20 Tischler et al. *"Relation between left ventricular shape and Doppler filling parameters in patients with left ventricular dysfunction secondary to coronary artery disease"* Am J Cardiol 1995; 76: 553-556

21 Grayburn PA et al. *"Echocardiographic predictors of morbidity and mortality in patients with advanced heart failure: the Beta-blocker Evaluation of Survival Trial (**BEST**)."* J Am Coll Cardiol. 2005 Apr 5;45(7):1064-71.

22 Torrent-Guasp F. *"Anatomia funcional del Corazon. La actividad ventricular diastolica y sistolica"* Madrid:Paz Montalvo,1957:11-94

23 Goffinet C et al. "Speckle tracking echocardiography" European Cardiovascular Disease 2007;3:1-3

24 J.U. Voigt, G. Pedrizzetti, P. Lysyansky, T.H. Marwick, H. Houle, R. Bauman, et al., *"Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of EACVI/ASE/Industry Task Force to standardize deformation imaging,"* Eur. Heart J. Cardiovasc. Imaging 16 (2015) 1–11.

25 Omar AM, Bansal M, Sengupta PP. *"Advances in Echocardiographic Imaging in Heart Failure With Reduced and Preserved Ejection Fraction."* Circ Res. 2016 Jul 8;119(2):357-74.

26 Sengupta PP,Narula J. *"Reclassifying heart failure: predominantly subendocardial, subepicardial and transmural"* Heart Fail Clin. 2008;4:379-382

27 Park SJ, Miyazaki C, Bruce CJ, Ommen S, Miller FA, Oh JK. *"Left ventricular torsion by two dimensional speckle tracking echocardiograph in patients with diastolic dysfunction and normal ejection fraction."* J Am Soc Echocardiogr 2008; 21:1129–1137.

28 Manovel A, Dawson D, Smith B et al, Europ J *"Assessment of left ventricular function by different speckle-tracking software"* Echocardiography 27 Feb 2011.

29 Edvardsen T, Helle-Valle T, Smiseth OA. *"Systolic dysfunction in hear failure with normal ejectio fraction: speckle-tracking echocardiography."* Prog Cardiovasc Dis 2006; 49:207–214.

30 Ng AC, Delgado V, Bertini M, et al. *"Findings from left ventricular strain and strain rate imaging in asymptomatic patients with type 2 diabetes mellitus."* Am J Cardiol 2009; 104:1398–1401.

31 Kosmala W, Plaksej R, Strotmann JM, et al. *"Progression of left ventricular functional abnormalities in hypertensive patients with heart failure: an ultrasonic two-dimensional speckle tracking study."* J Am Soc Echocardiogr 2008; 21:1309–1317

32 Motoki H et al. "Incremental prognostic value of assessing left ventricular myocardial mechanics in patients with chronic systolic heart failure" J Am Coll Cardiol 60(20):2074-2081

33 Cameli M et al. "Left ventricular deformation and myocardial fibrosis in patients with advanced heart failure requiring transplantation" J Card Fail 22(11):901-907

34 Stamphel MR et al. "Speckle strain echocardiography predicts outcome in patients with heart failure with both depressed and preserved left ventricular ejection fraction" Echocardiography 32(1):71-78

35 Cho GY et al. "Global2-dimensional strain as a new prognosticator in patients with heart failure"J Am Coll Cardiol 54:618-624

36 Cameli M, Lisi M, Righini FM, et al. *"Right ventricular longitudinal strain correlates well with right ventricular stroke work index in patients with advanced heart failure referred for heart transplantation"*. J Card Fail 2012;18:208-15.

37 Meris A, Faletra F, Conca C, et al. *"Timing and magnitude of regional right ventricular function: a speckle tracking-derived strain study of normal subjects and patients with right ventricular dysfunction."* J Am Soc Echocardiogr 2010;23:823-31.

38 Cameli et al. (2016) *"Left atrial strain: a new parameter for assessment of left ventricular filling pressure"* Heart Fail Rev 21(1):65-76

39 Cameli M. et al. *"Correlation of left atrial strain and Doppler measurements with invasive measurement of left ventricular and diastolic pressure in patients stratified for different values of ejection fraction"* Echocardiography 2015

40 Cameli M et al. *"Left atrial strain:a new parameter for assessment of left ventricular filling pressure"* Heart Fail rev 21(1):65-76

41 Machino-Ohtsuka T. et al. *"Left atrial stiffness relates to left ventricular diastolic dysfunction and recurrence after pulmonary vein isolation for atrial fibrillation"* J Cardiovasc Electrophysiol 22(9):999-1006

42 Kurt M. *"Relation of left ventricular end-diastolic pressure and N-terminal pro-brain natriuretic peptide level with left atrial deformation parameters"* Eur Heart J Cardiovasc Imaging 13(6):524-530

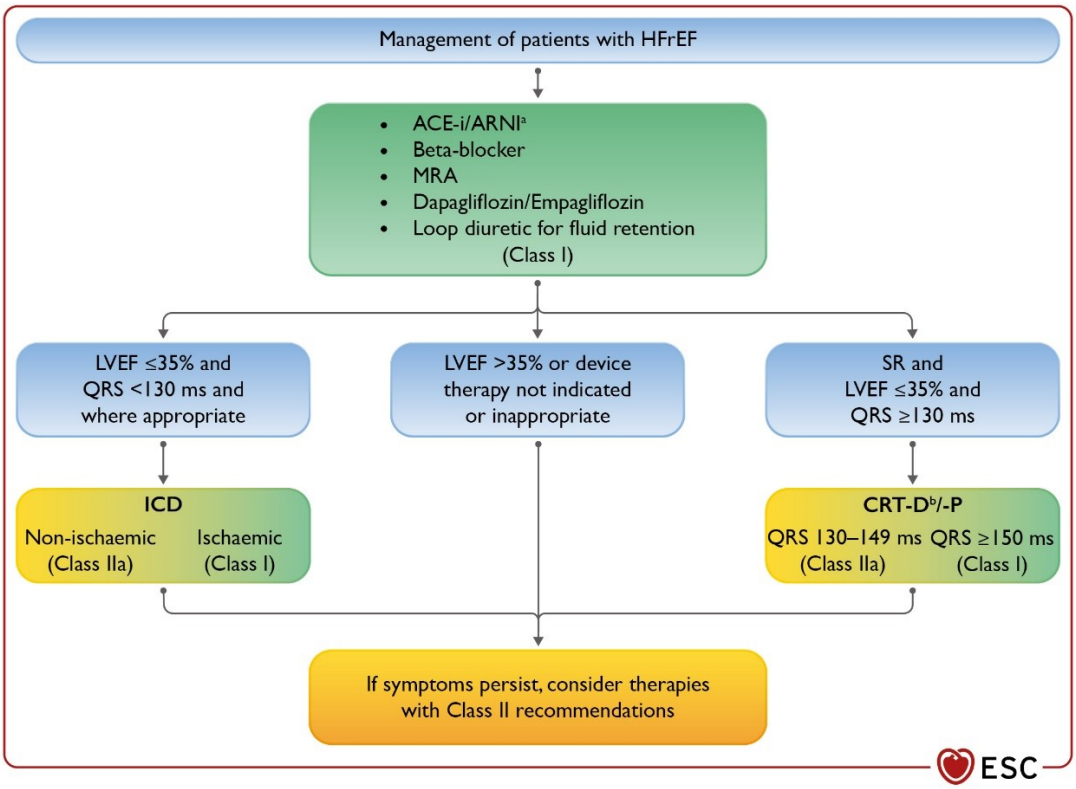
43 Rosca M. et al. (2010) *"Left atrial dysfunction as a correlate of heart failure symptoms in hypertrophic cardiomyopathy"* Drugs 2019 79: 1543-1556

1.3 Medical therapy in heart failure with reduced ejection fraction

In the treatment of HFrEF it is crucial to reduce the prolonged neuroendocrine activation, especially of the SNS and the RAAS system, which in the long term leads to deleterious consequences and is known to characterize the pathophysiology of heart failure.[1]

Pharmacological interventions are therefore aimed at restoring the neuroendocrine balance and especially at down-regulating the RAAS system through ACE-inhibitors[2-7] or sartans[8-11] (angiotensin receptor blockers: ARBs), aldosterone secretion[12-15] through mineral corticoid receptor antagonists (MRAs) and the SNS through beta-blockers.[16-21] The progenitor of the ARNI family of drugs, sacubitril/valsartan, combines the action of a sartan (valsartan) and a neprilysin inhibitor (sacubitril), which has been shown to be superior to the ACE inhibitor (enalapril) in reducing the risk of mortality and hospitalisation.[22] Triple therapy with beta-blockers, MRA and ace-inhibitors or sartans or ARNI, represents the cornerstone of medical therapy for patients with HFrEF, improving symptoms and quality of life, protecting against major fatal and non-fatal events, reducing hospitalisations and mortality.

The treatment of heart failure now includes a new class of drugs: the sodium-glucose cotransporter type 2 inhibitors, which have led to the establishment of a quadruple therapy. Further options in the treatment of the condition are diuretics, vasodilators such as nitrates, which are important for relieving the symptoms and signs of congestion, inotropic drugs, and also non-pharmacological tools such as the implantation of a cardiac defibrillator or resynchronisation therapy, or in the most severe cases the implantation of a ventricular assist device or a heart transplant.



"*2021 ESC Guidelines for the diagnosis and treatment of Acute and Chronic Heart Failure*" European Heart Journal (2021)

Bibliography

1 Packer M (1992) *'Pathophysiology of chronic heart failure.'* Lancet (Lond Engl) 340 (8811):88- 92

2 Sharpe, D.N., Murphy, J., Coxon, R. and Hannan, S.F. (1984) *"Enalapril in patients with chronic heart failure: a placebo-controlled, randomised, double-blind study."* Circulation **70**, 271-278

3 Captopril-Digoxin Multicenter Research Group (1988) *'Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure.'* JAMA **259**, 539-544

4 Captopril Multicenter Research Group (1983) *'A placebo-controlled trial of captopril in refractory chronic congestive heart failure.'* J. Am. Coll. Cardiol. **2**, 755-763

5 Le Jemtel, T.H., Keung, E., Frishman, W.H. and Ribner, H.S. (1982) *'Hemodynamic effects of captopril in patients with severe heart failure.'* Am. J. Cardiol. **49**, 1484-1488

6 SOLVD Investigators (1991) *"Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure."* N. Engl. J. Med. **325**, 293-302

7 Jong, P. and Yusuf, S. (2002) *"Extended follow-up of the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials."* European Society of Cardiology Meeting, Berlin, Germany, 31 August-4 September 2002

8 Cohn, J.N. and Tognoni, G. (2001) *'A randomised trial of the angiotensin-receptor blocker valsartan in chronic heart failure.'* N. Engl. J. Med. **345**, 1667-1675

9 Pfeffer, M.A., Swedberg, K., Granger, C.B., Held, P., McMurray, J.J., Michelson, E.L., Olofsson, B., Ostergren, J., Yusuf, S. and Pocock, S. (2003) *'Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme'* Lancet **362**, 759-766

10 McMurray, J.J., Ostergren, J., Swedberg, K., Granger, C.B., Held, P., Michelson, E.L., Olofsson, B., Yusuf, S. and Pfeffer, M.A. (2003) *"Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial."* Lancet **362**, 767-771

11 Yusuf,S. et al. (2003) "*Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial.*" Lancet **362**, 777-781

12 Zannad F. et al
"Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: integratin g evidence into clinical practice."
Eur Heart J.2012 Nov;33(22):2782-95. doi: 10.1093/eurheartj/ehs257. Epub 2012 Aug 31.

13 Pitt, B. et al (2003*) "Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction."* N. Engl. J. Med. **348**, 1309-1321

14 Zannad, F., McMurray, J.J., Drexler, H., Krum, H., van Veldhuisen, D.J., Swedberg, K., Shi, H., Vincent, J. and Pitt, B. (2010) *"Rationale and design of the Eplerenone in Mild Patients*

Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF)." Eur. J. Heart Fail. **12**, 617-622

15 Zannad, F., McMurray, J.J., Krum, H., van Veldhuisen, D.J., Swedberg, K., Shi, H., Vincent, J., Pocock, S.J. and Pitt, B. (2011) *'Eplerenone in patients with systolic heart failure and mild symptoms.'* N. Engl. J. Med. **364**, 11-21

16 Hjalmarson, A., Goldstein, S., Fagerberg, B., Wedel, H., Waagstein, F., Kjekshus, J., Wikstrand, J., El Allaf, D., V´ıtovec, J., Aldershvile, J. et al. (2000) *"Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF)."* MERIT-HF Study Group. JAMA **283**, 1295-1302

17 CIBIS II Investigators and Committees (1999) *'The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial.'* Lancet **353**, 9-13

18 FowlerMB *"Carvedilol prospectiverandomizedcumulativesurvival (COPERNICUS) trial: carvedilol in severe heart failure"* Am J Cardiol. 2004 May 6;93(9A):35B-9B.

19 Packer, M., Coats, A.J., Fowler, M.B., Katus, H.A., Krum, H., Mohacsi, P., Rouleau, J.L., Tendera, M., Castaigne, A., Roecker, E.B. et al. (2001) *"Effect of carvedilol on survival in severe chronic heart failure."* N. Engl. J. Med. **344**, 1651-1658

20 Flather, M.D., Yusuf, S., Køber, L., Pfeffer, M., Hall, A., Murray, G., Torp-Pedersen, C., Ball, S., Pogue, J., Moye´, L. et al. (2000) *"Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group."* Lancet **355**, 1575-1581

21 Piotr Ponikowski et al. *'2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure'*. Eur. J. Heart Fail. , **37**, 2129-2200

22 McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. *"Angiotensin-neprilysin inhibition versus enalapril in heart failure".* N Engl J Med. 2014 Sep 11;371(11):993-1004. Epub 2014 Aug 30.

2. Sacubitril/valsartan: new and effective drug in HFrEF

2.1 The new paradigm of ARNI

After the several historical studies that led to class IA recommendations for ACEIs/ARBs, beta-blockers and mineralocorticoid receptor antagonists or anti-aldosterone receptors (MRAs)[1] the last few decades have seen the failure of several therapeutic attempts, as was the case, for example, with aliskiren.[2] Furthermore, the possibility of using devices, when indicated, has been shown to further improve survival compared to medical therapy, for implantable defibrillator limited to patients in New York Heart Association (NYHA) class ≥II and FE ≤35%,[3] and cardiac resynchronisation therapy (CRT) limited to patients with FE ≤35% and left bundle branch block with QRS >130 ms. Finally, revascularization, regardless of how it is performed, should be pursued when possible and indicated, as it adds benefit over medical therapy.[4]

Despite available treatments, heart failure continues to have a poor prognosis, especially in patients who worsen and require hospitalization, reaching a 27% mortality rate at 1 year, with a high re-hospitalisation rate.[5]

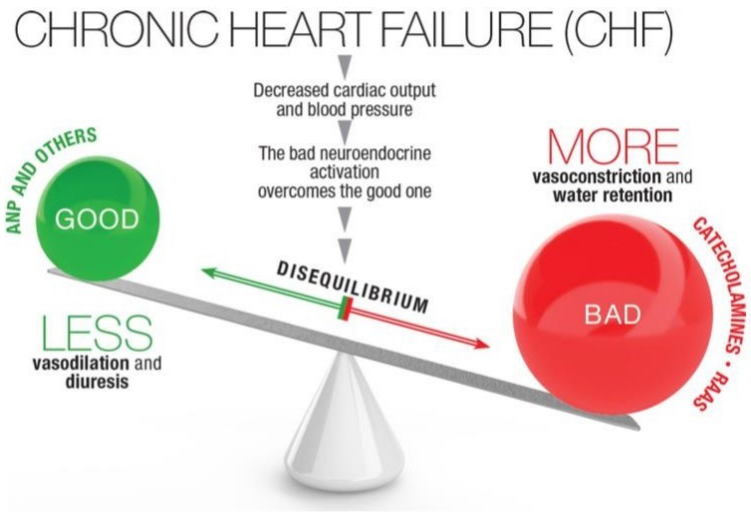
After many negative studies, two studies have recently reversed the trend, allowing the commercialisation of two new drugs capable of improving the prognosis of patients with HFrEF: ivabradine, studied vs placebo in the SHIFT trial (Systolic Heart failure treatment with the If inhibitor ivabradine Trial),[6] effective in patients with heart rates >70 b/min despite beta-blocker therapy (class IIb), and sacubitril/valsartan, compared vs enalapril in the PARADIGM-HF trial. [7]

The rationale behind the development of sacubitril/valsartan, the progenitor of ARNIs (angiotensin receptor neprilysin inhibitors), has born from recent evidence on the role of the natriuretic peptide system.[8]

As well known, in heart failure, due to the need to preserve cardiac output and blood pressure, a stereotyped neuronal response is activated, which is useful in the short term but deleterious in the long term. This response is mostly based on the activation of the adrenergic nervous system and the renin-angiotensin-aldosterone system, which cause an increase in salt and water retention, peripheral arterial vasoconstriction, contractility and, after prolonged overactivation, also an increase in inflammatory mediators, which are responsible for long-term cardiac remodelling. Concomitantly with the SNS and RAAS, which cause vasoconstriction and volume overload, other regulatory systems are also activated in heart failure: particularly that of natriuretic peptides, which are released in response to an increase in atrial or ventricular myocardial stretch, often

secondary to volume overload or an increase in transmural cardiac pressure. Natriuretic peptides, through a vasodilatory action, stimulating natriuresis and diuresis and inhibiting the release of renin and aldosterone, lead to a considerable hemodynamic improvement. Furthermore, through an antifibrotic and antiproliferative activity, they bring an enormous benefit from a structural point of view, because they positively interfere with ventricular remodelling, which is at the basis of the progression of left ventricular dysfunction.

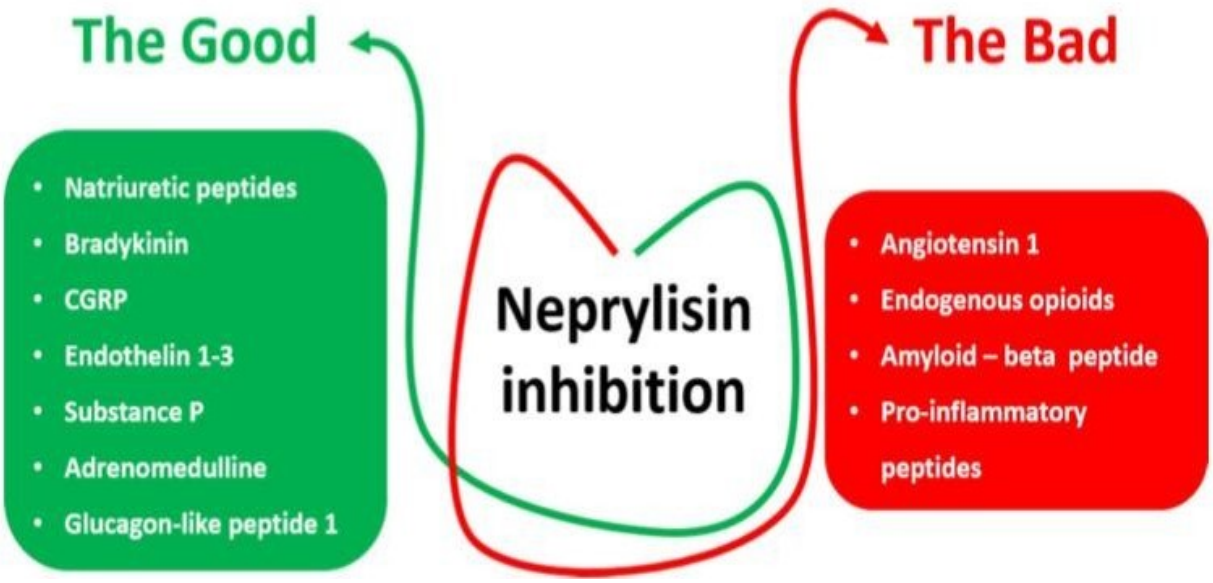
Thus, there are two opposing forces in HF: a so-called 'regulating' system, which causes vasoconstriction, water retention, hypertrophy, apoptosis, and fibrosis, and a so-called 'counter-regulating' system, which instead causes vasodilation and has anti-hypertrophic, anti-apoptotic and anti-fibrotic effects. However, over the time the good natriuretic and vasodilator influences are clearly overwhelmed by the bad ones.[9] The progression of the disease towards an advanced phase is characterized by the progressive loss of the endogenous ability exerted by vasoactive peptides to compensate for the negative effects of the SNS and RAAS, namely vasoconstriction and sodium retention.[10]



Roberto Ferrari et al *"ARNIs: balancing "the good and the bad" of neuroendocrine response to HF'* Clinical Research in Cardiology (2020) 109:599–610 DOI:10.1007/s00392-019-01547-2

Therefore it is clear how a pharmacological intervention aimed at enhancing the activity of endogenous PNs represents a further advantage over traditional therapy. The development of ARNI was based precisely on the possibility of considering the neurhormonal response from another point of view for the first time, assuming that its activation could also have favourable effects that could be exploited therapeutically. NT-proBNP is not a substrate for neprilysin, so it appears to be the best biomarker for

monitoring the effects of ARNI therapy. Substrate for NEP and angiotensin-converting enzyme (ACE) is bradykinin, which exerts positive cardio-renal and vasodilator effects, as well as being a strong anti-apoptotic agent capable of reducing both programmed myocyte and endothelial cell death.[12-15] In addition to NPs, there are also other substrates on which neprilysin acts, including Calcitonin Gene Related Peptides (CGRPs), a group of neuropeptides, mainly located in the heart, vessels and central and peripheral nervous system.[16-17] Both myocytes and blood vessels have specific receptors for CGRPs that are capable of causing considerable cardiovascular effects, including non-endothelium-dependent vasodilation, hypotension and a positive inotropic effect.[18] As observed both in experimental models and in humans,[19-20] all these peptides theoretically have important roles in HF such as limiting inflammation, reducing smooth muscle contraction, neutrophil adhesion and vascular permeability. NEP inhibition could also bring favourable metabolic effects in addition to the described hemodynamic effects. PARADIGM-HF data show that patients with diabetes, which had been present since screening, who received sacubitril/valsartan, had a greater long-term reduction in HbA1c and were less likely to start insulin than those who received enalapril. Of course, there are 'opposite' effects, and this also applies to neprilysin inhibition, the potential adverse consequences of which are important. An important substrate for NEP is angiotensin II, which in HF is overproduced by numerous enzymes including ACE. Its increased plasma levels cause vasoconstriction and water retention. Inhibition of NEP by further increasing angiotensin II would lead to deleterious effects if sacubitril were used alone, without the combination with valsartan, which by binding to the AT1 receptor of angiotensin II is capable of blocking all its negative effects. Other theoretical problems relating to the recent therapeutic concept of NEP inhibition concern its ability to also degrade endogenous opioids and the beta-amyloid peptide[12-21]. NEP's affinity for beta-amyloid peptide is higher than that of opioids, and among other things there is evidence that NEP, by degrading this peptide, may have protective activity against Alzheimer's[22]. It follows that chronic use of NEP inhibitors could instead cause or accelerate the disease, particularly in elderly patients such as those with HF. However, experimental data are controversial and in PARADIGM-HF no differences were observed in the incidence of cognitive impairment-related adverse events between patients treated with sacubitril/valsartan and those treated with enalapril.



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2.2 Sacubitril/valsartan and left ventricular remodelling: first studies on echocardiographic parameters

The single-centre, retrospective, cohort study by Aws Almufleh et al.[23] in 2017 investigated for the first time the effect of sacubitril/valsartan on ejection fraction and reverse ventricular remodelling parameters. In this study, 48 patients with HFrEF treated with sacubitril/valsartan for a mean period of 3 months were enrolled. Clinical and echocardiographic parameters were reviewed at three different time (pre-basal step i.e. 18 months before starting sacubitril/valsartan, basal step before starting treatment and post-sacubitril/valsartan). Cardiac imaging was performed through transthoracic echocardiography (80%), angiography with radionuclides (14.6%) and cardiac MRI (6.1%). The imaging data analysed were LVEF and reverse remodelling parameters such as left ventricular end systolic diameter (LVESD), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV), left ventricular mass and right ventricular systolic pressure (RVSP). These imaging data and laboratory parameters such as serum potassium and creatinine were evaluated before starting sacubitril/valsartan treatment and afterwards. The primary outcome was the variarion in LVEF and the secondary outcome was the variation in parameters indicative of reverse ventricular remodelling: LVESD, LVEDD, LVESV, LV mass and RVSP.

EF was assessed according to the dose of sacubitril/valsartan received. An increase in mean ejection fraction was observed regardless of whether the patient was receiving the medium/high dose or the low dose. However, the mean increase in EF tended to be slightly greater in the group receiving high doses than in the group treated with low doses, with a mean increase of 5.09% (± 1.36) and 4.03% (± 3.17), respectively ($p = 0.184$). With regard to the primary outcome, i.e. improvement in LVEF after sacubitril/valsartan therapy, a significant increase was observed, from a mean baseline value of 25.33% to a value of 30.14% ($p < 0.001$) with a mean treatment duration of 3 months. The response rate was not statistically different between patients with and without ischaemic heart disease (68.2 % and 76.0 %; $p = 0.550$, respectively). Furthermore, the response did not differ between patients with comorbidities such as diabetes, hypertension or atrial fibrillation. There were significant improvements in the indicator parameters of left ventricular remodelling, such as reductions in LVESD (3.36 ± 1.6 mm), LVEDD (2.64 ± 1.1 mm) and LV mass index (14.4 ± 3.9 g/m2), (all p values < 0.05). There were non-statistically significant reductions in LVESV and LVEDV. All patients in the study received optimal medical therapy for at least one year; patients with a recent diagnosis of HF (i.e. less than one year) were excluded from

the analysis. The fact that the benefits observed in this study were really attributable to the drug was supported by the assessment of the LVEF performed at three times, which showed that the LVEF remained unchanged at baseline compared with the 8 months prior to the start of sacubitril/valsartan, in which the patients were on OMT with ACEi/ARB, BB and MRA, and that it improved significantly after the start of therapy. This was the first study to describe in the so-called 'real world', outside the context of clinical studies, an inverse remodelling effect of sacubitril/valsartan. A limitation of this study is the variability between the methods used for the assessment of ventricular function.

The aim of the 2018 single-centre prospective study[24] by Martens et al. was to evaluate the effects of sacubitril/valsartan therapy in terms of reverse remodelling in patients with HFrEF with a class I indication for treatment (NYHA class II-IV, LVEF<35%, optimised medical therapy with anti-RAAS drugs). The drug dosage was optimized according to the individual tolerance of each patient. A total of 125 patients (66 ± 10 years) were prospectively included. The echocardiographic parameters considered were: LVEDV, LVESV, LVEF assessed by Simpson biplane method, SV assessed as the difference between volumes, E-wave and A-wave, E/A ratio, deceleration time (DT), (considering as restrictive pattern the one with E/A>2 or with E/A>1 and DT<140 msec.), diastolic filling time (interval between the beginning of the E wave and the end of the A wave), severity of mitral and tricuspid valve insufficiency assessed by colour Doppler and RVSP. At the time of follow-up, 44 (35%) patients were on 24/26 mg sacubitril/valsartan, 46 (37%) on 49/51 mg and 35 (28%) on 97/103 mg. A total of 39 (32.5%) patients reported an improvement in NYHA class, while 75 (62.5%) patients reported no change and 6 (5.0%) reported a worsening of their functional status. Systolic blood pressure had fallen by an average of 7.4 mmHg. After the start of sacubitril/valsartan, patients showed a significant decrease in ventricular volumes, predominantly LVESV (LVESV; 147 ± 57 mL vs 129 ± 55 mL; P < .001 and LVEDV; 206 ± 71 mL vs 197 ± 72 mL; P = .027), with a subsequent increase in LVEF (29.6 ± 6% vs 34.8 ± 6%; P < .001) and SV. This improvement in systolic function and volume remodelling was also associated with a reduction in the extent of mitral valve insufficiency and an improvement in diastolic function parameters (reduction in E/A ratio: 1.75 ± 1.13 vs 1.38 ± 0.88; P = .002, increase in diastolic filling time: 48 ± 9% vs 52 ± 1%; P = 0.005 and a reduction in the percentage of patients with a restrictive filling pattern: from 47% to 23%; P = .004) and a downward trend in RVSP. In addition, a dose-dependent effect was observed for changes in LVEF (P < .001) and LVESV (P = .031), and higher doses of the drug were significantly associated with higher degrees of left ventricular reverse remodelling. Patients treated with the highest dose (97/103 mg) tended to be more often women and more often had a non-ischaemic aetiology of

heart failure. The main findings of the study indicated that switching to sacubitril/valsartan in patients with HFrEF, already treated with maximum tolerated dose of ACEIs or ARBs, induced incremental, dose-dependent reverse remodelling, positively influencing both systolic and diastolic function parameters. The drugs that have always been the cornerstone of HF medical therapy, including ACE-I, ARBs, beta-blockers and MRAs, have been shown to induce a positive effect on reverse remodelling:[25] ACE-Is and ARBs improve LVEF between 1%-4%,[(26-28)] beta-blockers between 4%-12%[(29-31)] and MRAs generally improve LVEF by a further 4%.[32] In this study, a 5% incremental improvement in LVEF was noted after switching from ACE-I or ARB therapy to another sacubitril/valsartan therapy, again with a class I indication. Increasing the likelihood that sacubitril/valsartan is responsible for the demonstrated reverse remodelling is the described dose-dependent effect and the observed relationship between treatment with longer duration and a tendency towards a greater degree of reverse remodelling (P = 0.053). In addition, patients before the start of sacubitril/valsartan were not treated with lower doses of RAAS blockers, and given the long duration of heart failure before the drug was started, the therapies already in place were necessarily to be considered optimised. Indeed, the dose of valsartan after initiation of sacubitril/valsartan was equipotential to the dose of ACE-I or ARB taken before. This study demonstrated the potential of the new drug to induce left ventricular reverse remodelling in addition to standard medical therapy of heart failure. The limitations of the study were mostly related to the lack of analysis of some echocardiographic parameters, in fact while an impact on changes in LVEF and LVESV, which are the parameters also preferentially used in previous studies to assess the role of pharmacotherapy on reverse remodelling, was clearly demonstrated, it is also true that many more echocardiographic assessments can be performed such as measurement of atrial volumes, analysis of myocardial deformation parameters and tissue Doppler parameters. In addition, for volumetric analysis, a 3D echocardiogram or MRI is now recommended, whereas in this study, FE was assessed in 2D. The PRIME study[33] evaluated the use of the sacubitril/valsartan combination in patients with functional mitral insufficiency (MI), on the hypothesis that dual blockade of the renin-angiotensin system and neprilysin may give better results than the use of sartan alone. This study was conducted in a double-blind manner in 118 patients with heart failure and functional MI secondary to left ventricular dysfunction, who were randomised to receive sacubitril/valsartan or valsartan alone, in addition to standard treatment for the underlying condition. Primary endpoint of the study was the change in valvular area affected by regurgitation at 12 months after baseline assessment. Secondary endpoints included changes in valve regurgitation volume, end systolic and end diastolic volume of left ventricle, and area of incomplete valve leaflet closure. The

results at 12 months showed a significantly greater reduction in valvular regurgitant area in the group treated with the sacubitril/valsartan combination (-0.058±0.095 vs -0.018±0.105 cm2; p=0.032). In addition, a significantly greater reduction in the volume of valvular regurgitation was also observed in this subgroup than in patients treated with valsartan alone (mean difference -7.3 ml, 95% CI -12.6 to 1.9; p=0.009). No significant differences were found between the two groups with regard to the change in the area of incomplete valve leaflet closure, the volumes of the left ventricle and the change in pressure values. Thus, in patients with functional MI, sacubitril/valsartan appears to reduce valve insufficiency to a greater extent than valsartan alone. The combination of a sartan and a neprilysin inhibitor could therefore be considered in the context of the optimal medical therapy of these patients, for whom treatment options are currently very limited. The PROVE-HF study[34] shows that patients with HFrEF achieve the greatest survival benefit by avoiding hospitalization when NT- proBNP rapidly reduced with sacubitril/valsartan. The results extend to patients with new-onset heart failure, and suggest that even a suboptimal dose of the angiotensin-neprilysin receptor inhibitor is still effective. Reductions in NT-proBNP concentration in patients treated with sacubitril/valsartan were weakly but significantly related to improvements in markers of cardiac volume and function. The PROVE-HF study[34] enrolled 794 patients at 78 US sites. All subjects had HFrEF and were taking beta-blockers and ACE inhibitors or angiotensin receptor blockers and were eligible for treatment with an ARNI. Three subgroups of patients were included in PROVE-HF that have not been previously evaluated in other studies: patients who had new-onset HF and/or were naïve to renin-angiotensin system inhibitors, those with natriuretic peptide concentrations below the inclusion criteria for the PARADIGM-HF[27] study, and patients who were unable to reach the maximum dose of sacubitril/valsartan (97 mg/103 mg twice daily) at titration. The latter group, instead of going out from the study, continued with the dosage they had been able to achieve. The median NT-proBNP concentration at baseline was 816 pg/mL. Over 12 months, the demonstrated change in NT-proBNP concentrations correlated with several measures of cardiac remodelling, including progressive improvements in left ventricular ejection fraction, LVEDVi, LVESVi, LAVi, and E/E' ratio ($P < 0.001$ for all changes) within the overall cohort and subgroups of interest. LVEF increases averaged 5.2% within 6 months and 9.4% within 12 months. In post hoc analyses, LV mass index decreased from 124.77 g/m^2 at baseline to 107.82 g/m^2 at 12 months ($P < 0.001$). Reverse cardiac remodelling in each of the three specified subgroups was comparable to the overall cohort. However, in the new-onset group in particular an average increases in LVEF of about 13% over 12 months of treatment was observed, which was higher than the average for the rest of the group. Patients with the most important reductions in NT-proBNP and

left ventricular volume had the lowest rates of death and hospitalization for heart failure, while those with suboptimal reductions in both measures had the highest event rates. A major limitation of PROVE-HF[34] is the lack of a control group, which leaves open the possibility that drugs other than sacubitril/valsartan alone or in combination with sacubitril/valsartan played a role in reverse remodelling.

Bibliography

1 "2021 *ESC Guidelines for the diagnosis and treatment of Acute and Chronic Heart Failure"* European Heart Journal (2021)

2 Gheorghiade M, Bohm M, Greene SJ, Fonarow GC, Lewis EF, Zannad F, Solomon SD, Baschiera F, Botha J, Hua TA, Gimpelewicz CR, Jaumont X, Lesogor A, Maggioni AP, *"ASTRONAUT Investigators and Coordinators. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial."*JAMA 2013;309:1125–1135.

3 Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. *"2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC)."* Eur Heart J 2015;36:2793-867.

4 Wolff G, Dimitrios D, Andreotti F, et al. *"Survival benefits of invasive versus conservative strategies in heart failure in patients with reduced ejection fraction and coronary artery disease: a meta-analysis."* Circ Heart Fail 2017;10:e003255.

5 Tavazzi L, Senni M, Metra M, et al.; IN-HF (Italian Network on Heart Failure) Outcome Investigators. *"Multicenter pro- spective observational study on acute and chronic heart failure: one-year follow-up results of IN-HF (Italian Network on Heart Failure) Outcome registry."* Circ Heart Fail 2013;6:473-81.

6 Swedberg K, Komajda M, Bohm M, et al.; SHIFT Investigators. *"Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. "*Lancet 2010;376:875-85.

7 McMurray JJ, Packer M, Desai AS, et al.; *"PARADIGM-HF Investigators and Com- mittees. Angiotensin-neprilysin inhibition versus enalapril in heart failure."* N Engl J Med 2014;371:993-1004.

8 Volpe M, Carnovali M, Mastromarino V. *"The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment."* Clin Sci (Lond) 2016;130:57-77.

9 Anand IS, et al. (1992) *"Pathogenesis of the congestive state in chronic obstructive pulmonary disease: studies of body water and sociium, renal function, hemo- dynamics, and plasma hormones during edema and after recovery."* Circulation 86(1):12–21

10 Packer M.*"Pathophysiology of chronic heart failure"*Lancet (London, England).1992;340:88-92

11 Potter L*"Natriuretic peptide metabolism, clearance and degradation"*FEBS J 2011;278:1808-17

12 Bayes-Genis A, Barallat J, Richards AM (2016) *"A test in context: Neprylisin. Function, inhibition, and biomarker"* 2016 J Am Coll Cardiol 68(6):639–653.

13 Smith MW, Espiner EA, Yandle TG, Charles CJ, Richards AM (2000) *"Delayed metabolism of human brain natriuretic pep- tide reflects resistance to neutral endopeptidase."* J Endocrinol 167(2):239–246

14 Ferrari R (2014) *"Coronary artery disease: use of ACE inhibi- tors in stable CAD—what is the truth?"* Nature Rev Cardiol 11(6):315–316

15 Ferrari R, Ceconi C (2012) "Landmark Trials: PERTINENT" Cardiovasc Res 96(2):204–207

16 Mulderry PK, Ghatei MA, Rodrigo J, Allen JM, Rosenfeld MG, Polak JM, Bloom SR (1985) *"Calcitonin gene-related peptide in cardiovascular tissues of the rat"* Neuroscience 14(3):947–954

17 Hanko J, Hardebo JE, Kahrstrom J, Owman C, Sandler F (1985) "Calcitonin gene-related peptide is present in mammalian cerebro-vascular nerve fibers and dilates pial and peripheral arteries" Neurosci Lett 57(1):91–95

18 Agnoletti G, Cornacchiari A, Panzali AF, Ghielmi S, De Giuli F, Ferrari R (1990) *"Effect of congestive heart failure on rate of atrial natriuretic factor release in response to stretch and isoprenaline."* Cardiovasc Res 24(11):938–945

19 Nadel JA, Borson DB (1991) *"Modulation of neurogenic inflammation by neutral endopeptidase."*Am Rev Respir Dis 143(3 Pt 2):S33–36

20. Spillantini MG, Sicuteri F, Salmon S, Malfroy B (1990*) "Characterization of endopeptidase 3.4.24.11 ("enkephalinase") activity in human plasma and cerebrospinal fluid."* Biochem Pharmacol 39(8):1353–1356

21 Roques BP, Noble F, Daugé V, Fournié-Zaluski MC, Beaumont A (1993) *"Neutral endopeptidase 24.11: structure, inhibition, and experimental and clinical pharmacology."* Pharmacol Rev 45(1):87–146

22 Miners JS et al *"Aβ degrading ezymes: potential for treatment of alzheimer disease"* J Neuropathol Exp Neurol 2011; 70: 944-59

23 Almufleh A[1,2]et al. **"***Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients."* Am J Cardiovascular Disease 2017 Dec 20;7(6):108-113. eCollection 2017.

24 Martens P[1,2], Beliën H[1], Dupont M[1], Vandervoort P[1,3], Mullens W[1,3].
"The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction." Cardiovasc Ther. 2018 Aug;36(4):e12435. doi: 10.1111/1755-5922.12435. Epub 2018 Jun 7.

25 Nijst P, Martens P, Mullens W. *"Heart failure with Myocardial Recovery - the patient whose heart failure has improved: what Next?"* Prog Cardiovasc Dis. 2017;60:226-236.

26 Gotzsche CO, Sogaard P, Ravkilde J, Thygesen K. *"Effects of captopril on left ventricular systolic and diastolic function after acute myocardial infarction."* Am J Cardiol. 1992;70:156-160.

27 Greenberg B, Quinones MA, Koilpillai C, et al. *"Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD*

echocardiography substudy." Circulation. 1995;91:2573-2581.

28 Wong M, Staszewsky L, Latini R, et al. *"Valsartan benefits left ventricular structure and function in heart failure: Val-HeFT echocardiographic study."* J Am Coll Cardiol. 2002;40:970-975.

29 Colucci WS et al. *"Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group."* Circulation. 1996;94:2800-2806.

30 Doughty RN, Whalley GA, Gamble G, MacMahon S, Sharpe N. "*Left ventricular remodeling with carvedilol in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. "*J Am Coll Cardiol. 1997;29:1060-1066.

31 Groenning BA, Nilsson JC, Sondergaard L, Fritz-Hansen T, Larsson HB, Hildebrandt PR. *"Antiremodeling effects on the left ventricle during beta-blockade with metoprolol in the treatment of chronic heart failure."* J Am Coll Cardiol. 2000;36:2072-2080.

32 Chan AK et al. *"Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure."*J Am Coll Cardiol. 2007;50:591-596.

33 Kang DH et al. *"Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation: PRIME Study."* Circulation 2019;139:1354–1365. doi: 10.1161/CIRCULATIONAHA.118.037077

34 Januzzi JL et al. *"Rationale and methods of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF)."* Am Heart J. 2018 May;199:130-136. 2017.12.021. Epub 2018 Feb 13.

3. Study

3.1 Introduction and purpose of the study

The pharmacological therapy of heart failure has undergone considerable updates in recent years, thanks to the introduction of numerous new molecules. Among these, the class of drugs called ARNI (angiotensin receptor neprilysin inhibitor), of which sacubitril/valsartan is the progenitor, represents an original and innovative therapeutic potential, thanks to its joint action of neprilysin inhibition and angiotensin II antagonism. Its integrated neuromodulation activity allows not only an antagonism towards RAAS and CNS hyperactivation, but also a modulating activity in favour of the natriuretic peptide system with vasodilator, natriuretic, antiproliferative and antifibrotic effects.

PARADIGM-HF,[1] the largest trial ever conducted in patients with HFrEF, aimed to clinically validate the pathophysiological hypothesis of the importance of enhancing the action of natriuretic peptides. This study was discontinued prematurely, after an average follow-up of 27 months, due to evidence of a significant benefit in the sacubitril/valsartan-treated group of patients compared to the enalapril-treated group, in terms of cardiovascular death, hospitalization for heart failure and all-cause mortality. Further studies were conducted subsequently, with the aim of expanding the information on the safety and efficacy of sacubitril/valsartan in different clinical settings and at different dosages than those considered in PARADIGM-HF.[1] TITRATION[2] showed that reaching the target levels of the drug more slowly, with more gradual titration, does not compromise clinical benefit. The TRANSITION[3] study and the subsequent PIONEER-HF[4] study showed that sacubitril/valsartan, started during hospitalization after the hemodynamic stabilization, is effective and has a favourable safety profile, even in patients with first-diagnosis HFrEF.

While the pathophysiological processes involved in the mechanism of action and the clinical efficacy of sacubitril/valsartan have been described extensively in numerous studies, there is still much to be investigated regarding the drug's impact on reverse remodeling and other echocardiographic parameters.

Almufleh et al.[5] described for the first time in 2017 significant improvements in some of the parameters indicative of reverse remodelling in patients treated with sacubitril/valsartan, observing a reduction in ventricular diameters, indexed myocardial mass and ventricular volumes, without any difference in response rate between ischaemic and non-ischemic patients, as also described in PARADIGM-HF.[1]

Martens et al.[6] in their study in 2018 demonstrated how sacubitril/valsartan promoted

an improvement in systolic and diastolic function and a reduction in ventricular volumes and the degree of mitral valve insufficiency, inducing a dose-dependent reverse remodelling, which mainly occurred in women and non-ischemic patients, i.e. in those patients who, unlike the others, reached the target dose.
With regard to the correlation with plasma levels of atrial natriuretic peptides, the PROVE-HF[7] study demonstrated a reduction in NT- proBNP concentrations correlated with an improvement in several cardiac remodelling parameters, showing this result also in three specific subgroups of patients: those with a new diagnosys of HFrEF, who have never received ACEi or ARB therapy, those unable to reach the maximum dose of sacubitril/valsartan, and those with natriuretic peptide concentrations below the inclusion criteria for the PARADIGM-HF[1] study.
Finally, the PRIME study,[8] as well as demonstrating a reduction in regurgitant volume and EROA in functional ischaemic mitral insufficiency, that was the primary endpoint of the study, showed a reduction in telediastolic volume after 12 months of sacubitril/valsartan therapy.
The 2017 study of Almufleh et al.[5] has as a specific limitation: the variability between the methods used to assess ventricular function. Limitations common to all the studies described are the failure to assess volumes and EF through 3D echocardiography, currently considered the diagnostic gold standard method, and the failure to use the analysis of myocardial deformation parameters of Speckle Tracking echocardiography, which allows a more precise assessment of myocardial function in a practical and non-invasive manner.
The aim of the present study was to assess reverse remodelling in patients with HFrEF after six months of treatment with sacubitril/valsartan. Innovative and accurate diagnostic methods were used, such as 3D echocardiography and two-dimensional Speckle Tracking echocardiography, which are known to allow automatic and reproducible assessment of ventricular volumes, ejection fraction, left atrium volume and global longitudinal strain of the left ventricle and left atrium.
Additional echocardiographic parameters such as ventricular diameters and thicknesses, indexed myocardial mass, indexed stroke volume, and ventricular filling pressures were also evaluated.

Regarding right heart, size and function were assessed, with PAPS, TAPSE and S'TDI estimated.
A further aim of the study was to analyse the clinical and echocardiographic baseline characteristics of the patients in order to identify the presence of factors predictive of significant reverse remodelling, and, thus, of response to sacubitril/valsartan therapy.
Finally, the variation in atrial natriuretic peptides plasmatic levels after sacubitril/valsartan therapy was also evaluated.

3.2 Materials and Methods

3.2.1 Patient selection

In this prospective longitudinal study, patients with heart failure with reduced ejection fraction were enrolled, with the aim of assessing the response to medical therapy with sacubitril/valsartan in terms of reverse remodelling, the impact of the drug on other echocardiographic parameters such as myocardial deformation, and to identify predictors of response to therapy. Finally, the variation in plasma atrial natriuretic peptide levels after sacubitril/valsartan therapy was evaluated.
Patients whose conditions met the following inclusion criteria were considered eligible for the study:

1) Patients over 18 years old;
2) Patients with heart failure with ejection fraction ≤35% symptomatic in NYHA class II-IV;
3) Patients already being treated with maximum tolerated dosage of ACEi or ARB;
4) Patients naïve to ACEi or ARB undergoing pre-treatment with either drug before starting sacubitril/valsartan;
5) Outpatients;
6) Patients recently discharged after an episode of acute heart failure.

The exclusion criteria were as follows:

1) Symptomatic hypotension;
2) Systolic blood pressure <100 mmHg;
3) eGFR <30 mL/min/1.73m^2;
4) Serum potassium levels >5.2 mmol/L;
5) History of angioedema;
6) Adverse reactions during ACEi/ARB therapy;
7) Concomitant initiation of therapy capable of inducing reverse remodelling, such as CRT implantation during follow-up or in the six months prior to screening.

In patients on ACE inhibitor therapy, the latter was discontinued at least 36 hours earlier to minimise the risk of angioedema, which can be caused by increased circulating bradykinin levels due to simultaneous ACE enzyme and neprilysin inhibition. In patients already on therapy with a dosage of ACEi or ARB corresponding to at least 50% of the target dose of sacubitril/valsartan, the drug was started with the intermediate dosage 49/51 mg twice daily, while the lowest dosage, i.e. 24/26 mg twice

daily, was used in patients in whom the dosage of ACEi or ARB was less than 50% of the target dose, and also in those who were older, or had a history of renal insufficiency or low baseline systemic tensor values (≤110 mmHg).
Patients enrolled after an episode of acute heart failure started sacubitril/valsartan in the period prior to discharge, in the case of patients already on ACEi or ARB therapy, or after discharge and following treatment for at least one month with ACEi or ARB, started during hospital stay, in the case of patients naïve to RAAS inhibitor drugs.
Titration of the drug, depending on individual patient tolerance, was performed approximately every fortnight, where possible.
Patients underwent a clinical examination, electrocardiogram, transthoracic color-Doppler echocardiogram and blood tests, including NT-proBNP, before starting sacubitril/valsartan and after six months of therapy.
Functional assessment was performed using the NYHA classification.

3.2.2 2D/3D echocardiographic parameters

All patients enrolled underwent a 2D and 3D echocardiogram using a standard commercial echocardiograph (GE Vivid E9 XD-Clear). Images were acquired in supine lateral decubitus, with simultaneous recording of the electrocardiographic trace. Regarding the morphology of the left ventricle, the end diastolic and end systolic ventricular diameters indexed by body surface area, the thicknesses of the interventricular septum and posterior wall, which were measured in the parasternal long axis projection, were evaluated; myocardial mass measurements and relative parietal thickness (RWT) were then derived, through which the ventricular geometry of each patient was classified.[9]

Left ventricular function parameters were assessed by processing the 3D dataset acquired with the HeartModel A.I. software, which allows a fully automated, valid and reproducible quantification of the ejection fraction and simultaneously an estimation of the volumes of the ventricle and left atrium. Stroke volume was estimated too, which was calculated as the product of the cross-sectional area (CSA in cm2) by the integral of the velocity-time curve of flow (VTI in cm) through that area. The diameter of the outflow tract was measured in a parasternal long axis projection, placing the probe parallel and immediately adjacent to the aortic valve in mesosystole, while the velocity curve was recorded in an apical viewing plane by placing the sample volume at the valve annulus. Using pulsed Doppler and placing the sample volume at the end of the mitral valve leaflets, early diastolic filling velocity (E), atrial filling velocity (A), and deceleration time (DT) were measured. Thrigh a small sample volume placed in the myocardium at the septal and lateral insertion sites of the mitral leaflets, the septal E' and lateral E' myocardial velocity were recorded; subsequently using the average of these two velocities, the E/E' ratio was calculated. The indexed atrial volume was measured in the apical 4- and 2-chamber views.[9] Finally, the peak velocity of tricuspid regurgitation was measured and, in accordance with the guidelines, the degree of diastolic dysfunction of each patient was defined.[11] Mitral and tricuspid valvular insufficiencies were assessed using traditional echocardiographic parameters.[9] Right ventricle size, PAPS and function parameters, such as TAPSE and S'TDI, were also assessed according to current guidelines.[12]

3.2.3 Imaging 2D-Speckle Tracking

To perform the 2D Speckle Tracking analysis, two-dimensional images were acquired, synchronised with the electrocardiographic trace, in the apical 4-, 3- and 2-chamber views, during apnoea to minimize the displacements related to breath acts, optimising the sector width and increasing the frame-rate to a value at least above 60 Hz, considering that the optimal range is between 60 and 110 Hz.[13]
The analysis of the acquired images was then performed offline using TomTec Imaging Systems' innovative AutoSTRAIN software, which allows, through an automated and reproducible tri-planar analysis, a rapid and valid measurement of the GLS (global longitudinal strain) of the left ventricle. Using the same software, 2D speckle tracking analysis was also performed to assess the function of the left atrium.[14] For this purpose, two-dimensional images were then acquired, with the same precautions as described above, in the apical 4- and 2-chamber views, obviously with complete visualization of the left atrial chamber.

3.2.4 Statistical analysis

Statistical analysis was performed using SPSS statistics software v 20. All continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as absolute value and percentage. Analysis of difference between groups was performed by Student's t-test or Mann Whytney test for continuous variables and by $\chi 2$ test for categorical variables. These analyses were performed both for independent samples (in the inter-group comparison) and for paired data (in the comparison of pre- and post-therapy data). The linear correlation between continuous variables was analysed by means of Pearson's test. A value of $p < 0.05$ was considered statistically significant.

3.3 Results

3.3.1 Study population

A total of 43 patients were prospectively included in the study between November 2021 and March 2023. Three patients discontinued the drug due to symptomatic hypotension and the appearance of skin rash, two patients died, and for a further six patients a complete echocardiographic analysis could not be performed due to the suboptimal acoustic window.

Thus, the final study population consisted of 32 patients presenting these main clinical features: age 69.8 ± 12.7 years; ischemic etiology of the cardiomyopathy in 18 cases (56%) and non-ischemic in 14 cases (44%); NYHA class III in 17 cases (53%) and NYHA class II in 15 cases (47%). EF of the total population was 29.5 ± 5.7%; eGFR 75.7 ± 30.7 ml/min; kalemia averaged 4.2 ± 0.6 mmol/L, systolic blood pressure 126.4 ± 12.1 mmHg, NT-proBNP value 2930.9 ± 550. All baseline characteristics are summarized in Table 1.

At the time of the 6-month follow-up: 10 patients (31%) were treated with the dosage 24/26 mg, 16 patients (50%) with the dosage 49/51 mg, 6 patients (19%) with the dosage 97/103 mg (Figure 1); in 27 patients (84%) an improvement of the NYHA class was documented, in 5 patients (16%) there was no change of the NYHA class. None of the patients reported a worsening of their clinical-functional status. No significant differences were found in creatinine, potassium, and systolic blood pressure values. There was, however, a clear decrease in the NT-proBNP value (1081.6 ± 950 pg/ml).

3.3.2 Echocardiographic parameters

After six months of medical therapy with sacubitril/valsartan several echocardiographic parameters improved significantly in the entire study population: DTD (64.6 ± 5.2 mm vs. 61.0 ± 5.7 mm, p = 0.001), DTS (51.6 ± 6.8 mm vs. 47.0 ± 7.5 mm, p = 0.001), index mass (196.0 ± 43.0 g/m^2 vs. 175.9 ± 50.4 g/m^2, p = 0.002), VTSi (70.4 ± 23.2 ml/m^2 vs. 55.4 ± 23,8 ml/m^2, p= 0.000), VTDi (99.2 ± 29.0 ml/m2 vs 87.5 ± 29.8 ml/m^2, p= 0.001), FE (29.5 ± 5.7% vs 38.0 ± 7.4%, p=0.000), GLS (-9.3 ± 3% vs -12.8 ± 4%, p=0.000), global LAS (13.6 ± 5.0 vs 18.0 ± 8.0%), PAPS (34.8 ± 9.9 mmHg vs 29.8 ± 5.7 mmHg, p=0.014), mean E/e'mean (13.5 ± 6.0 vs 10.0 ± 2.4, p= 0.002). These parameters are shown in Table 2.

No significant changes were found in right ventricular function parameters: TAPSE (18.6 ± 4.0 mm vs. 19.4 ± 3.0 mm, p = 0.17), S' TDI (10.4 ± 2.6 cm/s vs. 11.0 ± 2.4 cm/s, p = 0.18).

On the basis of previous studies in literature,[15-16] patients were classified as 'super responders' to sacubitril/valsartan therapy, who showed an improvement in EF greater than or equal to 5 percentage points over baseline after 6 months of therapy, and 'responders' those who did not show such this improvement. Using this criterion, 13 (41%) of the patients in the study population were classified 'responders' and 19 (59%) were 'super responders'.

The baseline characteristics of the two groups of patients were compared in order to identify factors predictive of reverse remodelling and thus of response to therapy. In the 'responders' group more severe left ventricular remodelling before treatment was documented, in particular higher VTDi values, as well as higher indexed atrial volumes. In contrast, no differences were observed in creatinine, kalemia, systemic blood pressure, ischaemic etiology of cardiomyopathy and the remaining echocardiographic parameters, such as those indicative of diastolic or right ventricular function. The comparison between the groups is shown in Table 3.

Although no improvement in EF greater than 5 points was observed in the 'responders' group at 6 months after the start of treatment, an improvement in global ventricular and atrial strain was also observed in this group, although less marked than the other group (Table 4).

Table 1. Clinical and echocardiographic characteristics of the population before treatment with sacubitril/valsartan.

Clinical features	**Study population (n=32)**
Age (years)	69.8 ± 12.7
Gender (% women)	5/32 (16%)
Hypertension	25/32 (78%)
Diabetes mellitus	1/32 (3%)
Dyslipidemia	18/32 (56%)
Smokers	13/32 (41%)
Ischemic heart disease	18/32 (56%)
NYHA class II	15/32 (47%)
NYHA class III	17/32 (53%)
Systolic pressure (mmHg)	126.4 ± 12.1
Diastolic pressure (mmHg)	78.3 ± 7.3
Heart rate (bpm)	70.5 ± 12.9
K+ (mEq/l)	4.2 ± 0.6
Creatinine (mg/dl)	1.16 ± 0.4
GFR (ml/min)	75.7 ± 30.7
Hemoglobin (gr/dl)	13.5 ± 1.9
NT-proBNP (pg/ml)	2930.9 ± 550
Echocardiographic parameters	**Study population (n=32)**
EDD (mm)	64.6 ± 5.2
ESD (mm)	51.6 ± 6.8
IVS (mm)	10.7 ± 1.8
PW (mm)	10.0 ± 1.2
LV mass i (g/m2)	196.0 ± 43.0
EDVi (ml/m2)	99.2 ± 29.0
ESVi (ml/m2)	70.4 ± 23.2
3D EF (%)	29.5 ± 5.7
SVi (ml/m2)	32.6 ± 10.4
Average E/e’	13.5 ± 6.0
LAVi (ml/m2)	53.1 ± 24.3
MR (≥II degree) (%)	14/32 (44%)
TTG (mmHg)	27.6 ± 9.2
PAPs (mmHg)	34.8 ± 9.9
TAPSE (mm)	18.6 ± 4.0
S' TDI (cm/s)	10.4 ± 2.6
TR (≥II grade) (%)	6/32 (19%)
Speckle tracking analysis	**Study population (n=32)**
GLS (%)	-9.3 ± 3.0
LAS (%)	13.6 ± 5.0

Figure 1. Sacubitril/valsartan dosage achieved at follow-up after six months of treatment.

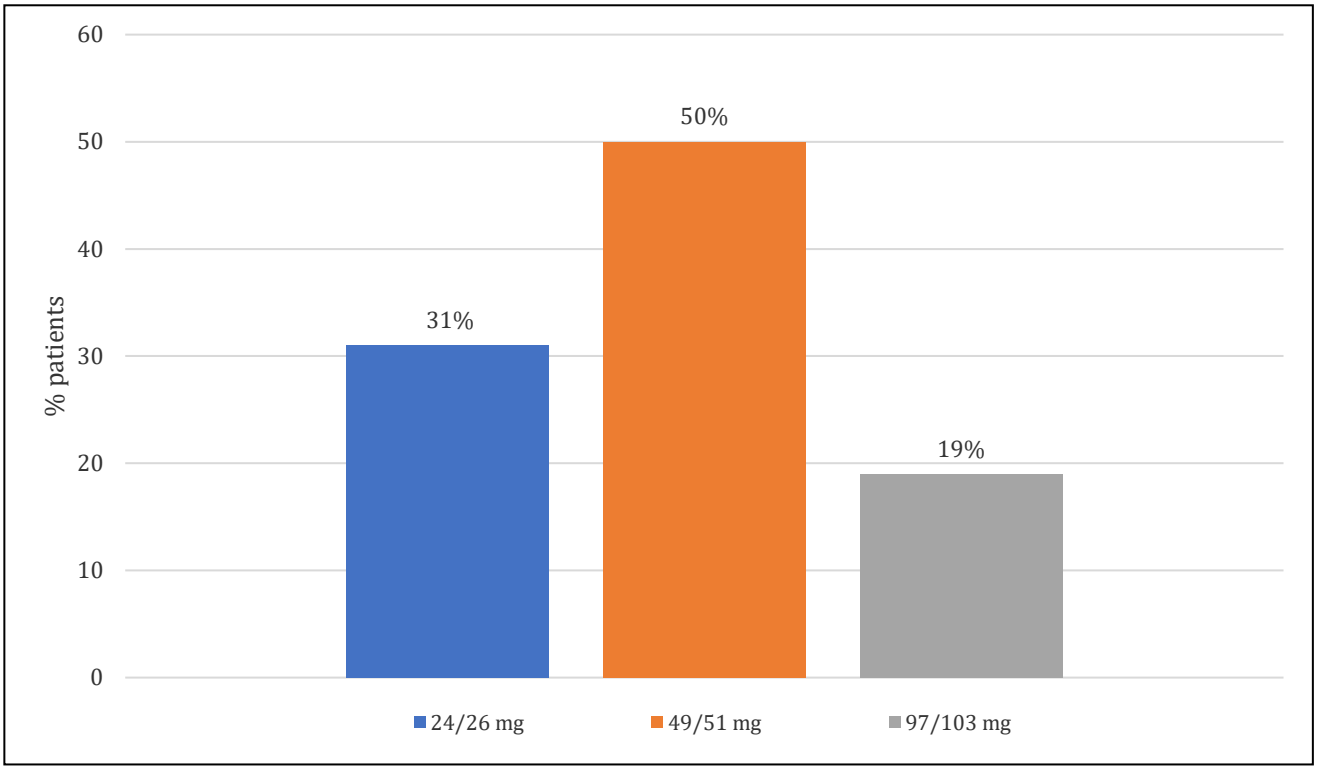

Table 2. Comparison of echocardiographic and clinical parameters before and after six months of treatment with sacubitril/valsartan.

Clinical features	**Before treatment**	**After 6 months of sacubitril/valsartan**	**P value**
Systolic pressure (mmHg)	126.4 ± 12.1	121.0 ± 15.0	0.09
Diastolic pressure (mmHg)	78.3 ± 7.3	72.0 ± 7.0	0.08
Heart rate (bpm)	70.5 ± 12.9	67.0 ± 8.0	0.07
K+ (mEq/l)	4.2 ± 0.6	4.4 ± 0.5	0.123
Creatinine (mg/dl)	1.16 ± 0.4	1.2 ± 0.5	0.66
GFR (ml/min)	75.7 ± 30.7	74.0 ± 29.6	0.42
NYHA	2.6 ± 0.5	1.5 ± 0.7	0.04
NT-proBNP (pg/ml)	2930.9 ± 950	1081.6 ± 950	0.05
Echocardiograpic parameters	**Before treatment**	**After 6 months of sacubitril/valsartan**	**P value**
EDD (mm)	64.6 ± 5.2	61.0 ± 5.7	0.001
ESD (mm)	51.6 ± 6.8	47.0 ± 7.5	0.001
LV mass i (g/m2)	196.0 ± 43.0	175.9 ± 50.4	0.002
EDVi (ml/m2)	99.2 ± 29.0	87.5 ± 29.8	0.001
ESVi (ml/m2)	70.4 ± 23.2	55.4 ± 23.8	0.000
3D EF (%)	29.5 ± 5.7	38.0 ± 7.4	0.000
SVi (ml/m2)	32.6 ± 10.4	34.5 ± 8.4	0.24
Average E/e’	13.5 ± 6.0	10.0 ± 2.4	0.002
LAVi (ml/m2)	53.1 ± 24.3	51.0 ± 25.7	0.27
MR (≥II degree) (%)	14/32 (44%)	9/32 (28%)	0.05
TTG (mmHg)	27.6 ± 9.2	23.6 ± 8.3	0.091
PAPs (mmHg)	34.8 ± 9.9	29.8 ± 5.7	0.014
TAPSE (mm)	18.6 ± 4.0	19.4 ± 3.0	0.17
S' TDI (cm/s)	10.4 ± 2.6	11.0 ± 2.4	0.18
TR (≥II grade) (%)	6/32 (19%)	4/32 (13%)	0.05
Speckle tracking analysis	**Before treatment**	**After 6 months of sacubitril/valsartan**	**P value**
GLS (%)	-9.3 ± 3.0	-12.8 ± 4.0	0.003
LAS (%)	13.6 ± 5.0	18.0 ± 8.0	0.005

Table 3. Comparison of clinical and echocardiographic characteristics between 'super responders' and 'responders' patients.

Clinical features	**Super responders (n=19, 59%)**	**Responders (n=13, 41%)**	**P value**
Age (years)	66.4 ± 13.5	70.0 ± 12.6	0.27
Gender (% women)	3 (16%)	2 (15%)	0,96
Arterial hypertension	18	7	0.001
Systolic pressure (mmHg)	127.9 ± 11.2	124.2 ± 13.0	0.23
Diastolic pressure (mmHg)	77.6 ± 6.3	79,2 ± 8.5	0.38
GFR (ml/min)	77.0 ± 28.2	73.6 ± 34.1	0.66
CAD	10	8	0.48
Diabetes mellitus	0	2	0.082
Dyslipidemia	11	7	0.74
NYHA	2.5 ± 0.6	2.6 ± 0.5	0.54
NT-proBNP (pg/ml)	1978.69 ± 350	467.74 ± 250	0.03
Echocardiograpic parameters	**Super responders (n=19, 59%)**	**Responders (n=13, 41%)**	**P value**
EDD (mm)	64.0 ± 5.2	65.5 ± 4.9	0.285
ESD (mm)	50.2 ± 6.3	53.8 ± 7.0	0.075
Indexed LV Mass (g/m2)	198.5 ± 39	192.8 ± 49	0.338
EDVi (ml/m2)	92.4 ± 25	109 ± 31	0.013
ESVi (ml/m2)	66.3 ± 21	76.4 ± 25	0.147
3D EF (%)	28.9 ± 6.3	30.4 ± 4.7	0.380
Average E/e’	12.6 ± 3.4	14.7 ± 8.6	0.22
LAVi (ml/m2)	46.0 ± 14	63.3 ± 31.4	0.004
PAPs (mmHg)	34.1 ± 9.4	35.8 ± 10.6	0.5
TAPSE (mm)	18.2 ± 4.2	19.1 ± 3.5	0.34
S' TDI (cm/s)	10.3 ± 2.5	10.6 ± 2.7	0.59
Speckle tracking analysis	**Super responders (n=19, 59%)**	**Responders (n=13, 41%)**	**P value**
GLS (%)	-9.8 ± 3.4	-8.5 ± 2.1	0.152
LAS (%)	13.1 ± 4.9	14.2 ± 5.7	0.430

Table 4. Comparison of atrial and ventricular strain between 'super responders' and 'responders' patients before and after treatment.

Speckle tracking analysis in super responders (n=19, 59%)			
	Before treatment	**After 6 months of sacubitril/valsartan**	**P value**
GLS (%)	-9.8 ± 3.4	-14.5 ± 4.0	0.02
LAS (%)	13.6 ± 5.1	19.5 ± 9.2	0.01

Speckle tracking analysis in responders (n=13, 41%)			
	Before treatment	**After 6 months of sacubitril/valsartan**	**P value**
GLS (%)	-8.5 ± 2.1	-10.5 ± 2.6	0.01
LAS (%)	14.1 ± 6.0	17.3 ± 8.4	0.02

3.4 Discussion

The main pharmacological classes representing the historical pillars in the treatment of patients with HFrEF (ACEi, ARB, beta-blockers, MRA) have been shown to prevent ventricular remodelling and, in some cases, to induce reverse remodelling, thus leading to a gradual improvement in cardiac function and consequently in patients' prognosis.[17] In a PARADIGM-HF analysis of a total of 2067 patients in the study was found that in patients with HFrEF, biomarkers associated with profibrotic signalling are altered and that sacubitril/valsartan significantly reduces many of these biomarkers (such as aldosterone, sST2, TIMP-1, MMP-9, PINP and PIIINP).[18] As well known, one of the histological signs of advanced heart failure is the progressive increase in the collagen content of the heart. Reactive fibrosis, which may present as perivascular or interstitial fibrosis, and 'replacement' fibrosis, which develops in response to cardiomyocyte cell necrosis represent two processes that contribute to the structural and functional cardiac changes[(19-21)] that in patients with HFrEF are associated with abnormalities in systolic and diastolic function, altered myocardial perfusion and a propensity to develop both atrial and ventricular arrhythmias, and thus an increased risk of sudden cardiac death.[22] The described characteristic of sacubitril/valsartan to exert an antiarrhythmic effect and potentially induce reverse remodelling may be attributable, at least in part, to its role in the profibrotic signalling pathway.[23]

The study subject of this thesis demonstrates that sacubitril/valsartan leads to a reduction in the size and volume of the left ventricle, an increase in the ejection fraction and in the ventricular and atrial GLS, thus confirming other data[(24-27)] already found in literature, which indicate the possibility of reverse remodelling. The described improvement in ventricular function occurred more in 'super responders' patients who had less left ventricular dilatation before the start of therapy. In contrast, a more severe degree of both ventricular and atrial cardiac remodelling at baseline assessment was observed in the group of 'responders' patients. It seems likely that the explanation for this finding lies in the consideration that 'responders' patients may be those most compromised, both clinically, so as to be in a NYHA class higher than II, and structurally in terms of greater myocardial dilatation and fibrosis, i.e. with significant ultrastructural remodelling. In fact, heart failure with reduced ejection fraction is a progressive pathology, with phases of apparent stability, alternating with worsening phases that may require hospitalization and contribute to accelerating structural deterioration, characterized precisely by myocardial fibrosis, remodelling, dysfunction and ventricular dilatation. Since less frequent hospitalization leads to longer survival, early treatment of patients in NYHA class II may help to slow down the progression of

decompensation to more severe forms. Thus, sacubitril/valsartan should be seen, not so much as a drug to be used in cases that do not respond to treatment with ACEi or ARB, but as a "disease modifying" therapy being able to act on the pathological pathway of heart failure from the very beginning.[28]

In addition to the favourable effect in terms of reverse remodelling, the results of this study demonstrate the ability of sacubitril/valsartan to improve symptoms. An improvement in NYHA class was found in almost all patients, which was partially attributable to the reduction in PAPS values and left ventricular filling pressure documented through echocardiography. Furthermore, we documented an improvement in atrial and ventricular strain values not only in 'super responders' but also in 'responders' group, although less marked than in the former. As well known, left ventricle is the fundamental determinant of left atrial afterload. In fact, the progressive increase in ventricular volume and pressure causes an increase in atrial wall stress and a progressive deterioration of its function, which can be assessed precisely through longitudinal strain. This parameter, which is mainly an expression of atrial reservoir function, has shown excellent sensitivity and specificity in predicting filling pressures; in fact, its strong correlation with PCWP values has been demonstrated both in patients with preserved EF and in those with reduced EF.[29] In the latter group of patients, the assessment of E/e' ratio does not always correlate well with ventricular filling pressures, as is more often the case in patients with preserved ejection fraction. Therefore, a reduction in longitudinal atrial strain values in patients with reduced EF may be a very useful index to consider, also because of its prognostic value, given its demonstrated correlation with NYHA class.[30]

3.5 Limitations of the study

The main limitation of the study is the limited sample size, so that it was not possible to describe whether 'responders' included more ischaemic patients or not and whether ventricular remodelling was dose-dependent. Regarding the latter point, the only possible observation is that of the entire study population, only six patients in the super-responder group were able to reach and maintain the target dosage of 97/103 mg twice daily.
Moreover, it was not possible to study the impact of the drug on the right ventricle due to the impossibility of performing an accurate early detection of morphofunctional RV parameters, a limitation linked to the right ventricle geometry, position and functional characteristics. It is not possible, in fact, to carry out an assessment of potential right ventricular dysfunction, a condition which very often manifests itself only when the right ventricle is already severely compromised.

3.6 Conclusions

Based on the findings of this study, it can be concluded that in patients with HFrEF sacubitril/valsartan significantly improves the parameters of reverse remodelling. This result tends to occur more significantly in patients with a lower degree of ventricular dilatation. In accordance with these considerations, the drug should be used early and independently of the apparent clinical "stability" in order to avoid further progression of ventricular remodelling.
These results and considerations are in line with the direction taken by the latest 2021 European Society of Cardiology heart failure guidelines, which have included ARNI as a therapeutic option also in mildly reduced ejection fraction, albeit with recommendation class IIb.
Further studies in support of these considerations may lead to an indication of sacubitril/valsartan since an earlier stage of the disease, such as in heart failure with preserved ejection fraction.

Bibliography

1 Packer M. et al *"Angiotensin receptor neprilysin inhibition compared with enalapril on the risk of clinical progression in surviving patients with heart failure"* Circulation 2015

2 Senni M, McMurray JJV et al *"Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens"*. Eur J Heart Fail. 2016; 18:111193-202

3 Wachter R, Senni M, Belohlavek J, Bu- tylin D, Noe A, Pascual-Figal D; *"Initiation of sacubitril/ valsartan in hospitalized patients with heart failure with reduced ejection fraction after hemodynamic stabilization: primary results of the TRANSITION study"*. Eur Heart J 2018;39:ehy564.P886

4 Velazquez EJ, Morrow DA, DeVore AD, et al. *"Rationale and design of the comparison of sacubitril/valsartan versus enalapril on effect on NT-proBNP in patients stabilized from an acute heart failure episode (PIONEER-HF). "*Am Heart J 2018;198:145- 51

5 Almufleh A. et al. **"***Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients."* Am J Cardiovascular Disease 2017 Dec 20;7(6):108-113. eCollection 2017

6 Martens P et al.*"The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction."* Cardiovasc Ther. 2018 Aug;36(4):e12435. doi: 10.1111/1755-5922.12435. Epub 2018 Jun 7

7 Januzzi JL et al. *"Rationale and methods of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF)."* Am Heart J. 2018 May;199:130-136. doi: 10.1016/j.ahj.2017.12.021. Epub 2018 Feb

8 Kang DH et al. *"Angiotensin receptor neprilysin inhibitro for functional mitral regurgitation PRIME study."* Circulation 2019; 139:1354-65

9 M. Galderisi, B. Cosyns, T. Edvardsen, N. Cardim, V. Delgado, G. Di Salvo, et al., *"Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging,"* Eur. Heart J. Cardiovasc. Imaging 12 (2018) 1301–1310.

10 G. Tamborini, C. Piazzese, R.M. Lang, M. Muratori, E. Chiorino, M. Mapelli, et al.*,"Feasibility and accuracy of automated software for transthoracic three-dimensional left ventricular volume and function analysis: comparisons with two-dimensional echocardiography, three-dimensional trans-thoracic manual method, and cardiac magnetic resonance imaging"* J. Am. Soc. Echocardiogr. 30 (2017) 1049–1058.

11 S.F.Nagueh, O.A. Smiseth, C.P. Appleton, B.F. Byrd, H. Dokainish, T. Edvardsen, 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"* J. Am. Soc. Echocardiogr. 29 (2016) 277–314.

12 L.G. Rudski, W.W. Lai, J. Afilalo, L. Hua, M.D. Handschumacher, K. Chandrasekaran, et al., *"Guidelines for the echocardiographic assessment of the right heart in adults:a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography,"* J. Am. Soc.Echocardiogr. 23 (2010) 685–713.

13 J.U. Voigt, G. Pedrizzetti, P. Lysyansky, T.H. Marwick, H. Houle, R. Bauman, et al., *"Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of EACVI/ASE/Industry Task Force to standardize deformation imaging,"* Eur. Heart J. Cardiovasc. Imaging 16 (2015) 1–11.

14 L.P. Badano 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 19 (2018) 591–600.

15 Cintron G[1], Johnson G, Francis G, Cobb F, Cohn JN. *"Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. The V-HeFT VA Cooperative Studies Group."* Circulation. 1993 Jun;87(6 Suppl):VI17-23

16 Wong M[1], Staszewsky L, Latini R, Barlera S, Glazer R, Aknay N, Hester A, Anand I, Cohn JN. *"Severity of left ventricular remodeling defines outcomes and response to therapy in heart failure: Valsartan heart failure trial (Val-HeFT) echocardiographic data."* J Am Coll Cardiol. 2004 Jun 2;43(11):2022-7

17 Filho J et al. *"Reverse cardiac remodeling: a marker of better prognosis in heart failure."*Arq Bras Cardiol 2015;104(6):502-6

18 Zile MR et al.*"Effects of sacubitril/valsartan on biomarkers of extracellular matrix regulation in patients with HFrEF."* J Am Coll Cardiol. 2019;73:795–806.

19 González A, Schelbert EB, Díez J, Butler J. *"Myocardial interstitial fibrosis in heart failure: biological and translational perspectives."* J Am Coll Cardiol 2018;71:1696–706.

20 Schelbert EB, Piehler KM, Zareba KM, et al. *"Myocardial fibrosis quantified by extracellular volume is associated with subsequent hospitalization for heart failure, death, or both across the spectrum of ejection fraction and heart failure stage."* J Am Heart Assoc 2015;4:e002613.

21 Bradshaw AD. *"The extracellular matrix."* In: Bradshaw RA, Stahl PD, editors-in-chief. Encyclopedia of Cell Biology. Vol. 2. Waltham, MA: Academic Press, 2016:694–703.

22 Gulati A, Jabbour A, Ismail TF, et al. *"Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy."* JAMA 2013;309:896–908.

23 De Diego C, González-Torres L, Núñez JM, Centurión Inda R, Martin-Langerwerf DA, Sangio AD, Chochowski P, Casasnovas P, Blazquéz JC, Almendral J. *"Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices."* Hear Rhythm. 2018;15:395–402.

24 Almufleh A. et al. **"***Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients."* Am J Cardiovascular Disease 2017 Dec 20;7(6):108-113. eCollection 2017.

25 Martens P et al.*"The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction."* Cardiovasc Ther. 2018 Aug;36(4):e12435. doi: 10.1111/1755-5922.12435. Epub 2018 Jun 7.

26 Januzzi JL et al. *"Rationale and methods of the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure (PROVE-HF)."* Am Heart J. 2018 May;199:130-136. doi: 10.1016/j.ahj.2017.12.021. Epub 2018 Feb

27 Kang DH et al. *"Angiotensin receptor neprilysin inhibitro for functional mitral regurgitation PRIME study."* Circulation 2019; 139:1354-65

28 E. Fabris et al.*"Sacubitril/valsartan:Updates and Clinical Evidence for a Disease-modifyng Approach"* Heart Fail Rev 21(1):65-76

29 Cameli et al. (2016) *"Left atrial strain: a new parameter for assessment of left ventricular filling pressure"* Heart Fail Rev 21(1):65-76

30 Rosca M. et al. (2010) *"Left atrial dysfunction as a correlate of heart failure symptoms in hypertrophic cardiomyopathy"* Drugs 2019 79: 1543-1556