HEART TIME:
Advancing Heart Failure Management with Sacubitril/Valsartan

Module 2

Contents

Introduction

Sacubitril/Valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNi) licensed for the treatment of heart failure. It contains the angiotensin receptor blocker (ARB) 'valsartan' and the neprilysin inhibitor sacubitril in a 1:1 molecule ratio. The combination is thus stated as a "Angiotensin Receptor-Neprilysin Inhibitor" [Fala, et al. 2015]. Sacubitril/valsartan has been shown to effectively reduce both systolic and diastolic blood pressure (BP) in patients with grade I to III hypertension (office BP ≥180/110mmHg) with or without CKD [Kario K, et al.2016]. The BP lowering effect lasts 24 hours, including nocturnal and morning periods. Previous studies show that using sacubitril/valsartan once day, ranging from 100 mg to 400 mg, reduces 24-hour ambulatory blood pressure, including nocturnal to morning BPs, in hypertensive individuals from Western and Asian backgrounds [Kario K, et al. 2015]. A study found that sacubitril/valsartan is more effective than ARB in lowering central aortic systolic blood pressure in elderly patients with systolic hypertension and wide pulse pressure [Williams B, et al. 2017]. Systolic hypertension becomes more common as people age, and it is a significant risk factor for HFpEF in the elderly. Thus, sacubitril/valsartan has the potential to slow the age-related cardiovascular progression from hypertension to heart failure.

Sacubitril/valsartan is currently approved for the treatment of chronic heart failure with reduced ejection fraction (HFrEF). It has demonstrated safety in patients with heart failure with preserved ejection fraction (HFpEF) and shown efficacy in those with hypertension, a major risk factor for HFpEF. The PARADIGM-HF trial offered strong evidence that sacubitril/valsartan provides significant cardiovascular and survival benefits over enalapril, an ACE inhibitor, in patients with heart failure with reduced ejection fraction (HFrEF).The PARAGON-HF trial, a Phase III randomized controlled study, is investigating the effects of sacubitril/valsartan compared to valsartan on outcomes such as cardiovascular death and heart failure hospitalization in HFpEF patients, with completion expected in 2019 [Novartis, 2017]. This trial will also assess secondary outcomes, including changes in functional class, Kansas City Cardiomyopathy Questionnaire scores, and renal function. Another study, PARALLAX, is a 24-week, double-blind, controlled trial comparing sacubitril/valsartan with standard treatments (like enalapril, valsartan, or placebo) to evaluate its

effect on NT-proBNP levels, symptoms, exercise capacity, and safety in HFpEF patients [Novartis, 2017]. Real-world data indicates that only 20%–40% of HFrEF patients meet the eligibility criteria for initiating sacubitril/valsartan under current guidelines. Discrepancies between FDA labeling and international consensus recommendations could lead to the drug being prescribed to a broader HFrEF population than originally studied or recommended, raising potential safety concerns. Addressing this gap in evidence is essential to avoid unnecessary risks for patients. Additionally, variations in different guideline recommendations must be resolved, as these can influence patient selection. Despite these concerns, sacubitril/valsartan remains a significant advancement in HFrEF treatment, offering reductions in both morbidity and mortality when used in carefully chosen patients.

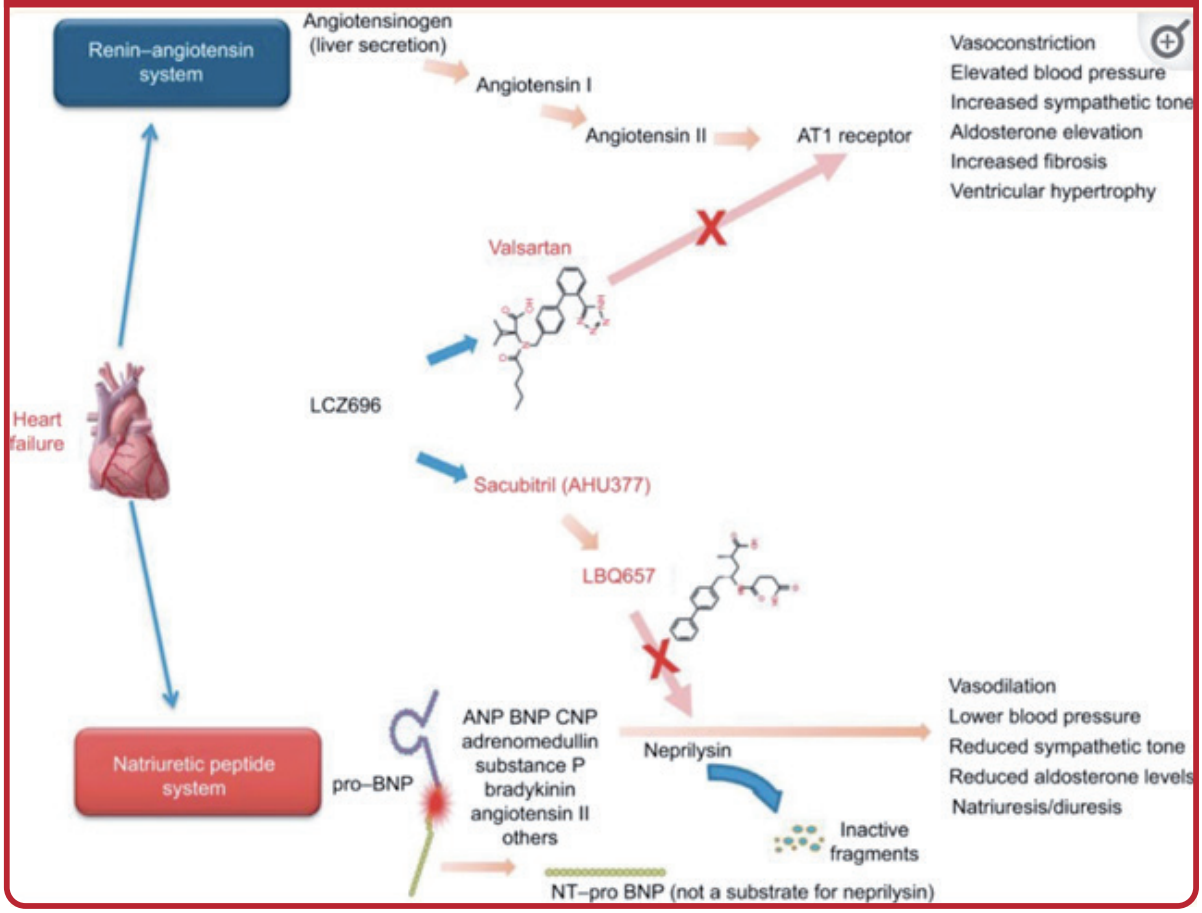
1.1 Mechanism of action

Heart failure pathophysiology involves a adaptive response where the renin-angiotensin-aldosterone system (RAAS) is activated. Mechanism of action of sacubitril/valsartan in heart failure is depicted in figure 1. This activation results in vasoconstriction, hypertension, increased aldosterone, heightened sympathetic activity, and eventually, cardiac remodeling, all of which worsen disease progression. ACE inhibitors or ARBs are crucial in reducing heart failure-related morbidity and mortality by inhibiting these harmful processes. At the same time, the natriuretic peptide system is triggered, resulting in elevated BNP and NT-proBNP during heart failure exacerbations. This compensatory mechanism promotes vasodilation, natriuresis, and diuresis, lowering blood pressure, reducing sympathetic tone, and decreasing aldosterone. The natriuretic peptide system opposes RAAS and positively impacts heart failure progression. Neprilysin breaks down natriuretic peptides [Du Ax, et al. 2019].

Sacubitril-valsartan is a combination therapy. Sacubitril, a pro-drug, inhibits neprilysin upon activation, preventing the breakdown of natriuretic peptides and extending their beneficial effects. Valsartan, an ARB, blocks the RAAS. Since neprilysin also degrades angiotensin II, neprilysin inhibitors must be paired with an ARB to counteract the accumulation of angiotensin II. Neprilysin also degrades bradykinin, so inhibiting neprilysin leads to bradykinin build-up. For this reason, sacubitril cannot be combined with ACE inhibitors, as the risk

of angioedema increases. A 36-hour washout is required when switching from an ACE inhibitor to sacubitril-valsartan to minimize this risk. Overall, RAAS inhibition is a cornerstone in the management of heart failure, significantly improving patient outcomes by targeting the maladaptive mechanisms driving disease progression [2021].

Figure1: Mechanism of action of sacubitril/valsartan in heart failure



Adapted from Vardeny O, et al. 2014

1.2 Pharmacokinetics of sacubitril/valsartan

Sacubitril-valsartan, after oral administration, breaks down into sacubitril and valsartan. Sacubitril is then metabolized into its active form, LBQ657. The bio-availability of sacubitril is over 60%. The time to peak plasma concentration (Cmax) is 0.5 hours for sacubitril, 2 hours for LBQ657, and 1.5 hours for val-sartan. Sacubitril and valsartan do not show significant accumulation at steady state (achieved within 3 days), though LBQ657 accumulates 1.6-fold. The presence of food does not affect the absorption of either component, so the drug can be administered with or without food.

In terms of distribution, valsartan and sacubitril have mean apparent volumes of distribution of 75 L and 103 L, respectively. All three molecules (sacubitril, LBQ657, and valsartan) are highly bound to plasma proteins (94% to 97%), with LBQ657 crossing the blood-brain barrier to a minimal extent (0.28%).

Metabolically, sacubitril is transformed into LBQ657 via esterases, while valsartan undergoes minimal metabolism (20%), with only a small fraction metabolized into a hydroxyl metabolite. After oral administration, 52% to 68% of sacubitril (as LBQ657) and about 13% of valsartan are excreted via urine. The remaining portion is excreted in feces. The half-lives of sacubitril, LBQ657, and valsartan are 1.4, 11.5, and 9.9 hours, respectively [Cada DJ, et al. 2015].

2. Indications for use of sacubitril/valsartan

Sacubitril/valsartan (LCZ696) is prescribed to lower the risk of cardiovascular death and hospitalization in patients with chronic heart failure (NYHA class II to IV) who have a reduced ejection fraction. It can be administered alongside other heart failure medications, serving as a substitute for an ACE inhibitor or an ARB. Additionally, sacubitril/valsartan has been researched for managing essential hypertension in adults. It is currently being compared with olmesartan in patients aged 60 and above to evaluate its effects on aortic stiffness and central aortic hemodynamics in the ongoing PARAMETER study. This 52-week trial aims to assess the impact on central aortic systolic pressure and pulse pressure, with results anticipated in 2015. Early studies are also underway to explore whether sacubitril/valsartan could help in cardiac remodeling following a myocardial infarction [Williams B, et al 2014].

Sacubitril-valsartan is the first drug in a new category known as angiotensin receptor neprilysin inhibitors (ARNI). It has received FDA approval for treating chronic heart failure with reduced ejection fraction (HFrEF) in patients classified as NYHA class II, III, or IV. This medication is recommended as a substitute for ACE inhibitors or angiotensin receptor blockers (ARBs) and is typically used alongside other standard heart failure therapies, such as beta-blockers and aldosterone antagonists. The 2016 guidelines from the American College of Cardiology/American Heart Association and the Heart Failure Society of America state that ACE inhibitors, ARBs, or ARNI should be used for managing chronic symptomatic HFrEF to lower morbidity and mortality rates (class I recommendation). Patients should be able to tolerate ACE inhibitors or ARBs

before starting sacubitril-valsartan. According to the 2022 AHA/ACC/HFSA guidelines, sacubitril-valsartan is also indicated for managing heart failure with preserved ejection fraction (HFpEF). Additionally, it is approved for use in pediatric patients with heart failure. The 2023 ACC Expert Consensus further supports the use of sacubitril in HFpEF, suggesting that SGLT2 inhibitors should be initiated before sacubitril. The drug is particularly recommended for male patients with left ventricular ejection fraction (LVEF) below 55% to 60%, and for female patients regardless of LVEF, as women typically have smaller left ventricular sizes, leading to higher LVEFs [Gregorietti, et al. 2020].

In a recent case study, four patients suffering from chemotherapy-related acute cardiac failure with significantly reduced ejection fractions were successfully treated with sacubitril-valsartan. This medication has also shown potential benefits in cases of anthracycline-related cardiac toxicity. Cancer therapy-related cardiac dysfunction (CTRCD) poses significant risks to both oncological and cardiovascular health, often hindering cancer treatment. A recent clinical trial indicated that sacubitril-valsartan could be an effective option for patients with refractory CTRCD. Although data is limited, earlier studies suggest promising results for sacubitril-valsartan in treating cardio-oncology patients; however, further clinical research is necessary to establish its efficacy and safety in CTRCD cases [Hubers SA, et al. 2016].

2.1 Sacubitril/Valsartan therapy

When managing heart failure with reduced ejection fraction (HFrEF), clinicians often question whether continuing treatment with ACE inhibitors (ACEi) or angiotensin receptor blockers (ARBs) is sufficient for patients who appear stable. Research and clinical studies have shown that sacubitril/valsartan, a combination drug, is superior to traditional RAAS inhibitors (ACEi/ARBs) in improving patient outcomes. This is true even in outpatient settings where the combination of sacubitril/valsartan consistently outperforms enalapril in terms of effectiveness, regardless of any other treatments patients may be receiving. The decompensation of heart failure, which signals worsening symptoms, is often the best clinical marker to determine if switching from ACEi/ARB to sacubitril/valsartan is necessary. Starting this combination therapy during hospitalization can offer an opportunity for better dose management and easier treatment of side effects [Mc causland FR, et al. 2020].

The therapeutic approach involving sacubitril/valsartan may also reduce the risk of hyperkalemia, particularly in patients already on mineralocorticoid receptor antagonists (MRA), and it provides enhanced renal protection compared to RAAS inhibitors. Recent data further suggest that adding sodium-glucose co-transporter 2 (SGLT2) inhibitors to HFrEF treatment regimens could offer additional benefits. However, it remains unclear whether these two drug classes should be used together from the outset or introduced sequentially. Trials such as DAPA-HF indicate significant benefits in patients receiving dapagliflozin while already on sacubitril/valsartan, which opens the possibility of combining ARNi, SGLT2i, MRA, and β-blockers for improved prognosis in HFrEF [Vaduganathan M, et al.].

In patients with heart failure and preserved ejection fraction (HFpEF), the use of sacubitril/valsartan is still debated. While the PARAGON-HF trial showed borderline improvements in reducing cardiovascular death and hospitalizations, those with a left ventricular ejection fraction (LVEF) between 40-55% may see more notable benefits. Conversely, HFpEF patients with LVEF greater than 55%, who typically have multiple comorbidities, do not currently benefit as significantly from this treatment [Bohm M, et al. 2020].

2.2 Sacubitril/valsartan: dosing and cautions

Sacubitril/valsartan is prescribed for the management of chronic heart failure with reduced ejection fraction (HFrEF), typically in patients within NYHA classes II to IV. The initial recommended dose is 49 mg of sacubitril and 51 mg of valsartan taken twice daily, regardless of food intake. After 2 to 4 weeks, if tolerated, the dose should be increased to the target maintenance dose of 97 mg sacubitril and 103 mg valsartan twice daily.For certain patients, a lower starting dose of 24/26 mg twice daily is recommended. This includes those who are either not on an ACE inhibitor or ARB, patients on low doses of these medications, or individuals with severe renal impairment (GFR < 30 mL/min/1.73m²), or moderate hepatic insufficiency. Dosage adjustments should be made as necessary over the next 2 to 4 weeks based on tolerance and clinical response [Cada DJ, et al. 2015].

Monitoring is essential, particularly for renal function and serum potassium levels, to avoid complications such as hyperkalemia. Sacubitril/valsartan is contraindicated for patients with systolic blood pressure lower than 100 mmHg

or potassium levels greater than 5.4 mmol/L. In cases of hypotension, hyperkalemia, or renal impairment, adjusting other medications (such as diuretics) is recommended.The treatment must be stopped if angioedema occurs, and a 36-hour gap is required between stopping an ACE inhibitor and starting sacubitril/valsartan to prevent adverse reactions. Additionally, the drug is contraindicated during pregnancy due to its potential to cause fetal harm.

If used concurrently with potassium-sparing diuretics, NSAIDs, or lithium, monitoring is necessary to manage increased risks of hyperkalemia, kidney failure, and lithium toxicity, respectively. Lastly, BNP levels should not be used to monitor heart failure severity in patients on sacubitril/valsartan, as the drug increases BNP levels by inhibiting neprilysin. Instead, NT-proBNP is preferred for accurate assessment of heart failure status [Mair J, et al.].

3. Clinical evidence supporting sacubitril/valsartan use

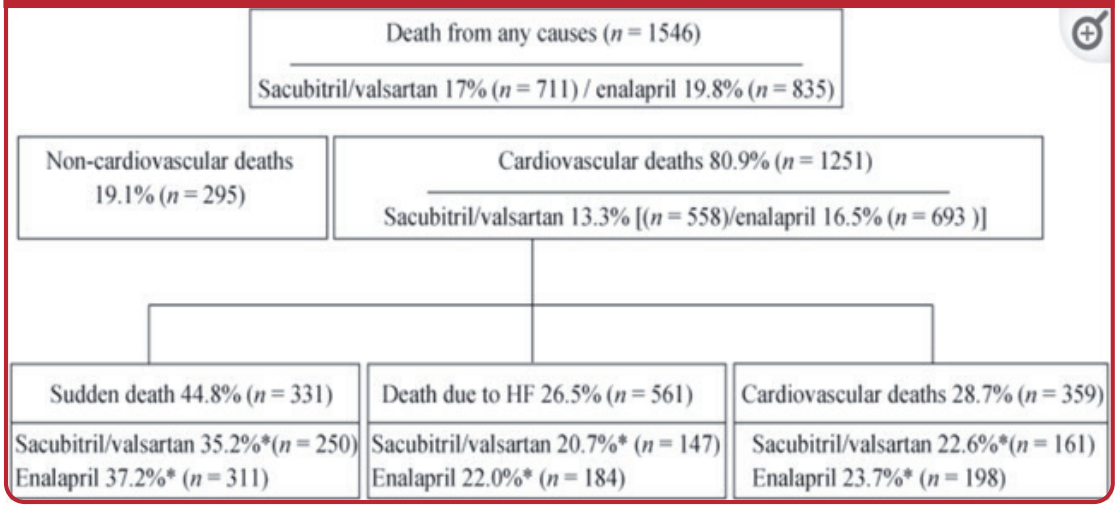
3.1 Heart failure with reduced ejection fraction: efficacy in and outside clinical trials

a. Efficacy of sacubitril/valsartan in the PARADIGM-HF trial

The PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) was a randomized controlled trial aimed at evaluating the effectiveness of sacubitril/valsartan (S/V) compared to enalapril in improving health outcomes in patients with heart failure with reduced ejection fraction (HFrEF). PARADIGM (HF) trial is depicted in figure 2. After an average follow-up of 27 months, results showed that S/V significantly reduced heart failure hospitalizations by 21%, cardiovascular mortality by 20%, and overall mortality by 16%. Further analyses indicated that S/V decreased the rate of sudden cardiac death in both patients with and without implantable cardioverter defibrillators (ICDs), and also contributed to longer estimated survival and event-free survival rates. S/V was found to enhance quality of life (QoL) and improve functional and social activities. Moreover, it led to fewer cases of diabetes requiring insulin, a slower decline in estimated glomerular filtration rate (eGFR), a reduced incidence of hyperkalemia, and a lower need for loop diuretics. Patients on S/V also exhibited decreased levels of clinical outcome predictors like NT-proBNP, troponin T, and soluble suppression of tumorigenesis-2 (sST2). Notably, significant benefits were observed within the first 30 days of treatment. The advantages of S/V

over ACE inhibitors were consistent across various patient demographics and conditions. As a result, both the 2021 European and American heart failure treatment guidelines recommend S/V as a first-line therapy for stable HFrEF patients [O' meara E, et al. 2018].

Figure2: PARADIGM (HF) trial



Adapted from O' meara E, et al. 2018.

b. Acute decompensated and severe heart failure

Initiating sacubitril/valsartan (S/V) therapy in patients hospitalized for acute decompensated heart failure (ADHF) shortly after achieving hemodynamic stabilization has been shown to be both feasible and safe. The PIONEER-HF trial compared S/V with enalapril in these patients and found that S/V led to more effective heart unloading, as evidenced by a more significant reduction in NT-proBNP levels. In addition to this, S/V was associated with fewer adverse outcomes, including reduced rates of heart failure re-hospitalizations, implantation of left ventricular assist devices, death, and heart transplants, without raising any notable safety concerns. Although the trial was not powered to detect clinical outcomes, it provided strong signals indicating risk reduction [Velazquezz EJ, et al. 2019].

A systematic review further validated these findings, showing that managing stabilized patients with ADHF using S/V significantly reduced the risk of serious clinical events and lowered NT-proBNP concentrations. For patients with heart failure with reduced ejection fraction (HFrEF) who have not previously taken ACE inhibitors, initiating S/V therapy is recommended (class IIb, level B evidence). In contrast, the LIFE trial, which focused on patients with advanced

HFrEF (NYHA class IV) and recent inotropic therapy, found no significant differences between S/V and valsartan in terms of NT-proBNP reduction or clinical outcomes. However, the study was prematurely terminated due to the COVID-19 pandemic, which limited its ability to detect these differences [Mann DL, et al. 2021].

c. Post-myocardial infarction

The PARADISE-MI trial compared the efficacy and safety of sacubitril/valsartan (S/V) with ramipril in patients following acute myocardial infarction (AMI), who had no previous history of heart failure but exhibited reduced left ventricular ejection fraction (LVEF) or transient pulmonary congestion. The primary endpoint, which included cardiovascular (CV) death, first heart failure (HF) hospitalization, or outpatient HF visits, did not show a significant reduction with S/V compared to ramipril. However, numerically lower event rates were observed in the S/V group.

Further analysis indicated a benefit for S/V when considering composite endpoints that included all HF events or investigator-reported HF events, not just the first occurrence. The study population, composed of high-risk post-AMI patients (76% with ST-elevation myocardial infarction or STEMI), was treated early (average 4.3 days post-hospitalization) without a run-in phase.

Both S/V and ramipril demonstrated similar safety and tolerability profiles. Rates of treatment discontinuation due to adverse events (AEs) or severe AEs (SAEs), along with serum monitoring for hyperkalemia, renal function, and liver enzyme abnormalities, were comparable. Hypotension was more common with S/V, while ramipril caused more cough and hepatotoxicity. There was no significant difference in rates of angioedema or cognitive impairment between the two treatment groups.

3.2 Efficacy and safety in patients with heart failure with preserved ejection fraction

The PARAGON-HF trial compared the effects of sacubitril/valsartan (S/V) against valsartan in patients with heart failure with preserved ejection fraction (HFpEF). The study found that S/V did not significantly lower the rate of hospitalizations due to heart failure or deaths from cardiovascular causes in patients with an ejection fraction (EF) of 45% or higher. Adverse events (AEs) and serious adverse events (SAEs) were similar between S/V and valsartan. However,

S/V was associated with higher rates of hypotension and angioedema, while the incidence of hyperkalemia and serum creatinine levels ≥2 mmol/L was lower. Additionally, the decline in estimated glomerular filtration rate (eGFR) was less pronounced with S/V than with valsartan, and the reduction in adverse renal outcomes occurred independently of baseline eGFR levels [Solomon SD, et al. 2019].

In the PARALLAX-HF trial, 2,572 patients with heart failure, EF above 40%, elevated NT-proBNP levels, and reduced quality of life were randomized to receive either S/V or standard medical therapy. While S/V resulted in a reduction of NT-proBNP, it did not improve 6-minute walk test distances, the Kansas City Cardiomyopathy Questionnaire—Clinical Summary Score (KCCQ-CSS), or New York Heart Association (NYHA) class. Although the proportion of SAEs was similar between groups, AEs and drug-related AEs occurred more frequently with S/V, primarily due to hypotension and albuminuria. Angioedema was rare and similar in both groups. Notably, patients on S/V experienced less decline in renal function over 24 weeks, as measured by eGFR. A pooled analysis of data from the PARAGON-HF and PARADIGM-HF trials examined the effects of S/V across different EF ranges. The analysis indicated that S/V had no measurable effect on patients with an EF above 55%. However, in patients with an EF between 40% and 50% (the "EF gap"), S/V significantly reduced hospitalization rates and mortality. Based on these findings, the 2021 European Heart Failure guidelines recommend considering S/V for patients with heart failure with mildly reduced ejection fraction (HFmrEF) to lower the risk of hospitalization and death [Solomon SD, et al. 2020].

3.3 Combination of sacubitril/valsartan with other heart failure drugs

The superiority of sacubitril/valsartan (S/V) over ACE inhibitors (ACEi) in the PARADIGM-HF trial was independent of other background treatments. Starting S/V, even when titrated to target doses, did not lead to more frequent discontinuation or dose reductions of other key guideline-recommended heart failure therapies and resulted in fewer withdrawals of mineralocorticoid receptor antagonists (MRAs). Additionally, MRA-treated patients with heart failure and reduced ejection fraction (HFrEF) were more likely to experience severe hyperkalemia with enalapril compared to S/V. The combination of S/V with

sodium-glucose co-transporter 2 inhibitors (SGLT2i) like dapagliflozin or empagliflozin has been shown to be effective, safe, and well-tolerated. In outcome trials, patients receiving S/V alongside SGLT2i experienced the same additional benefits as those not on S/V. Treatment discontinuations, adverse events (AEs), serious adverse events (SAEs), and issues like hyperkalemia or hypotension were similar between treatment groups.

The "fantastic four" treatment combination for HFrEF consists of S/V, beta-blockers, MRAs, and SGLT2i for maximum benefit in reducing mortality, heart failure hospitalizations, and improving symptoms. Observational data show that combining angiotensin receptor-neprilysin inhibitors (ARNI) and SGLT2i lowers the risk of heart failure hospitalizations and cardiovascular mortality compared to either treatment alone or ACEi/ARBs. Real-world studies also highlight echocardiographic improvements and reduced risk of hospitalization and death with combination therapy in diabetic patients with HFrEF, with good tolerability and slight reductions in kidney function but without increased hyperkalemia risk. Significant improvements in heart failure symptoms were also observed over six months in a Spanish registry study [Jiménez-Blanco Bravo M, et al. 2021].

4. Guidelines for management in HF patients

The 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure was developed to update and integrate prior guidelines, specifically the 2013 ACCF/AHA Heart Failure Guideline and the 2017 ACC/AHA/HFSA Focused Update (Table 1). Its main objective is to offer clinicians patient-focused recommendations for the prevention, diagnosis, and management of heart failure. The 2022 guideline not only refines and consolidates previous recommendations but also aligns with other relevant ACC/AHA guidelines. For instance, the 2019 guideline on the primary prevention of cardiovascular disease offers valuable strategies to prevent heart failure, while the 2021 valvular heart disease guideline provides specific guidance on mitral valve clipping for patients with mitral regurgitation. This comprehensive approach ensures that clinicians have access to the latest evidence-based practices in heart failure management, encompassing both prevention and therapeutic strategies across varying stages and presentations of the disease [ACCF/AHA 2020].

The 2013 ACCF/AHA Guideline for the Management of Heart Failure introduced the term "HFpEF-improved" to describe patients whose ejection fraction (EF) improved to over 40% from a previously lower level within the HFpEF category. Some experts have suggested using the term "HF-recovered EF" for those with an initial left ventricular ejection fraction (LVEF) of 40% or less, showing an increase of at least 10% and a subsequent LVEF measurement above 40%. Although a higher LVEF is linked to better outcomes, it doesn't necessarily indicate complete recovery of heart function, as structural heart issues, such as chamber enlargement and dysfunction, may remain. Additionally, LVEF changes aren't always consistent; EF may improve and later decline depending on factors like disease progression, medication adherence, or re-exposure to harmful conditions. Therefore, the guidelines prefer "HF with improved EF" (HFimpEF) to describe these patients rather than "recovered EF" or HFpEF, even if LVEF surpasses 50%. It's crucial to note that EF can drop again if treatment is stopped, and a sustained decline in LVEF often signals a poor prognosis.

Table 1: Guideline related to HF

Title	Organization
Guidelines	
2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery *Hillis et al., "2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery" is now replaced and retired by the "2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization"*[5]	ACCF/AHA
2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention *Levine et al., "2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention," is now replaced and retired by the "2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization"*[5]	ACCF/AHA/SCAI
2015 ACCF/AHA/SCAI Focused Update Guideline for Percutaneous Coronary Intervention	ACCF/AHA/SCAI
2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease	ACC/AHA
2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy	ACC/AHA
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease	ACC/AHA
2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation	AHA/ACC/HRS
2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults	ACC/AHA/AAPA/ABC/
2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure	ACC/AHA/HFSA
2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure	ACC/AHA/HFSA
2014 ACC/AHA/AATS/PCNA/SCAI/STS Focused Update of the Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease	ACC/AHA/AATS/PCN/
2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk	AHA/ACC
2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults	AHA/ACC/TOS
2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/AphA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol	AHA/ACC/AACVPR/A/
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults	ACC/AHA
2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk	ACC/AHA
2013 ACCF/AHA Guideline for the Management of Heart Failure	ACCF/AHA
2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction	ACCF/AHA
2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities	ACCF/AHA/HRS
2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease	ACCF/AHA/ACP/AATS

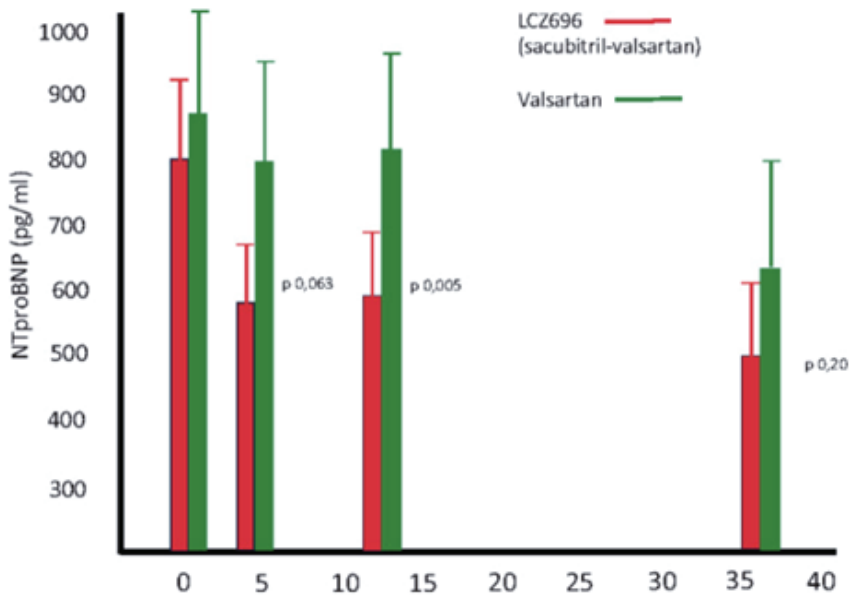
5. HF related trials

5.1. PARAGON-HF trials

The PARAGON-HF trial was designed to assess the effectiveness of sacubitril-valsartan in patients with heart failure with preserved ejection fraction (HFpEF). Results for PARGON-HF trial is depicted Sacubitril-valsartan is a combination drug that includes an angiotensin receptor blocker (valsartan) and a neprilysin inhibitor (sacubitril), targeting two pathways involved in the progression of heart failure. In this trial, patients with an ejection fraction of ≥45%, elevated natriuretic peptide levels, and structural heart disease were randomized to receive either sacubitril-valsartan or valsartan alone to determine if this combination would improve outcomes, particularly by reducing hospitalizations for heart failure and deaths from cardiovascular causes.

Although the trial did not meet its primary endpoint, meaning that the drug combination did not significantly reduce the overall rate of hospitalizations or cardiovascular death compared to valsartan alone, further analysis revealed important nuances. Subgroup analyses showed that patients with ejection fractions at the lower end of the HFpEF spectrum (closer to 45%) appeared to derive more benefit from sacubitril-valsartan. These findings suggested that while the drug may not be broadly effective for all HFpEF patients, it might offer a meaningful advantage for certain groups, especially those with borderline ejection fractions. This nuanced outcome echoes the challenge of treating HFpEF, a heterogeneous condition that does not respond uniformly to treatments. Current research and trials like PARAGON-HF underscore the need for personalized approaches in managing heart failure, especially among those with preserved ejection fractions, where therapies proven effective for reduced ejection fraction heart failure may not fully apply [Tridetti J, et al. 2020].

Figure 3: PARAGON-HF trial



Adapted from Tridetti J, et al. 2020

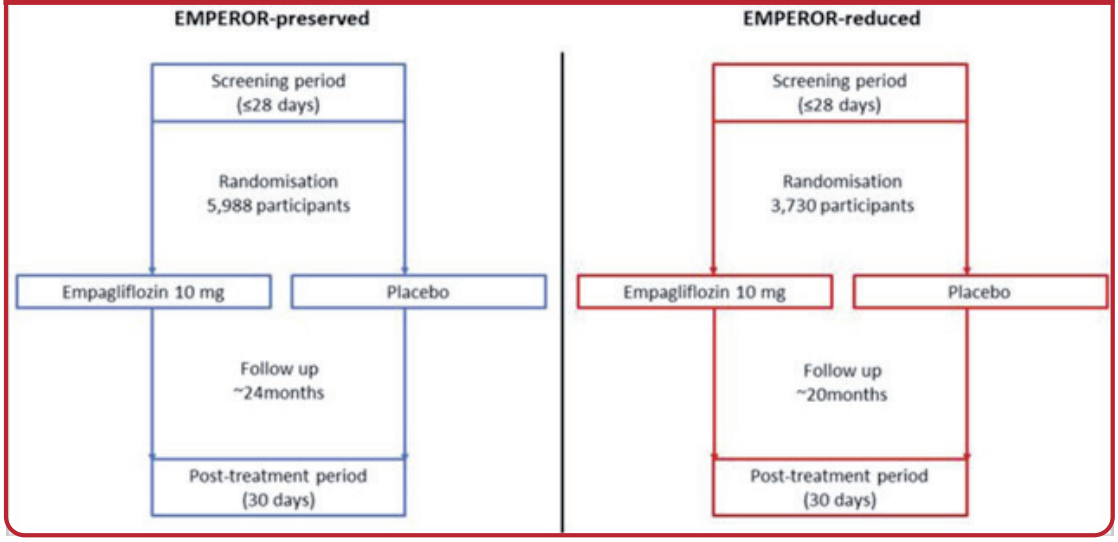
5.2. EMPEROR-HF trial

The EMPEROR trials, specifically the EMPEROR-reduced and EMPEROR-preserved studies, explore the effects of empagliflozin, an SGLT2 inhibitor, on different subtypes of heart failure (Figure 4). These trials are highly relevant because heart failure with reduced ejection fraction (HFrEF) has well-established treatment guidelines, while heart failure with preserved ejection fraction (HFpEF) presents a greater challenge due to limited therapeutic options that improve mortality.

Empagliflozin has already demonstrated significant cardiovascular benefits in patients with diabetes, particularly by reducing hospitalizations for heart failure. The EMPEROR-reduced trial showed that empagliflozin reduces the risk of cardiovascular death or hospitalization in patients with HFrEF, confirming its effectiveness as a disease-modifying agent across a range of heart failure conditions. The EMPEROR-preserved trial, on the other hand, brought new hope for HFpEF patients, showing that empagliflozin significantly reduces the risk of heart failure hospitalization in this group as well. This marks an important advancement, as no previous therapy had shown consistent benefits in reducing heart failure-related hospitalizations for HFpEF .By targeting both HFrEF and HFpEF, empagliflozin offers a broader approach to heart failure

management, addressing unmet needs in the HFpEF population and adding to existing treatments for HFrEF [Williams DM, et al. 2020].

Figure 4: EMPEROR-HF trial



Adapted from Williams DM, et al. 2020

5.3. PARALLAX-HF trial

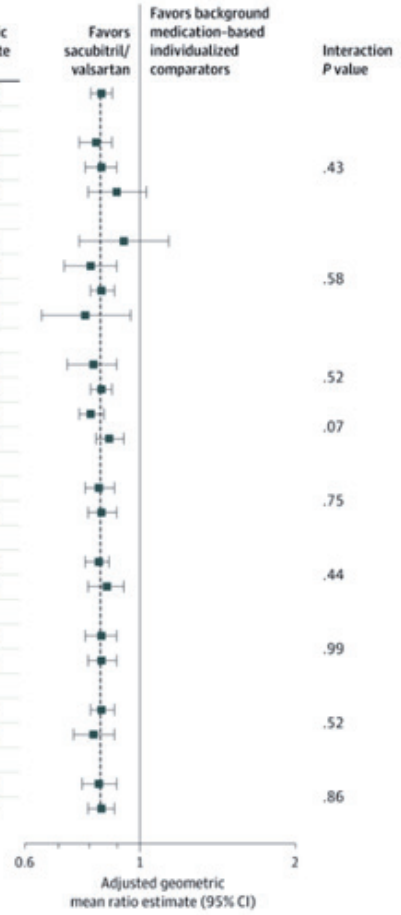
Sacubitril/valsartan, a combination of an angiotensin receptor blocker and neprilysin inhibitor, has shown significant benefits in managing heart failure, particularly in patients with reduced ejection fraction (HFrEF). In clinical studies, it has been associated with improved clinical outcomes compared to traditional therapies, such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).Sacubitril/valsartan has been demonstrated to reduce the risk of heart failure hospitalizations by approximately 20% and cardiovascular mortality by 14% compared to standard treatments. This indicates a meaningful impact on the overall prognosis of heart failure patients (Figure 5).

In direct comparisons, sacubitril/valsartan reduced all-cause mortality by 16% when compared to enalapril, one of the most commonly used ACEIs. This suggests that the combination therapy not only alleviates symptoms but also enhances long-term survival. Recent studies have highlighted potential cognitive benefits associated with sacubitril/valsartan, showing lower rates of neurocognitive disorders compared to traditional ACEI or ARB treatments in patients with HFrEF. Additionally, sacubitril/valsartan has been linked to renal protection, with studies indicating a significant increase in estimated glomerular

filtration rate (eGFR) compared to RAAS inhibitors. This dual effect of heart and kidney protection is crucial for managing heart failure patients, who often have concurrent renal issues. Clinical trials have also suggested improvements in quality of life measures among patients treated with sacubitril/valsartan, making it a comprehensive therapy for heart failure management. Overall, sacubitril/valsartan stands out as an effective therapy for heart failure, offering multifaceted benefits that extend beyond mere symptom relief, thus improving patient outcomes in various dimensions of health [Pieske B, et al. 2021].

Figure 5: PARALLAX-HF trial

Subgroup	No. of patients: Sacubitril/valsartan	No. of patients: Background medication-based individualized comparators	Adjusted geometric mean ratio estimate (95% CI)	Interaction *P* value
Overall	1203	1216	0.84 (0.80-0.88)	
Prior medication stratum				
ACE inhibitors	495	510	0.82 (0.76-0.88)	
ARB	552	558	0.84 (0.78-0.90)	.43
No RAS inhibitors	156	148	0.90 (0.79-1.03)	
Region				
North America	62	60	0.93 (0.76-1.14)	
Latin America	165	172	0.80 (0.71-0.90)	
Europe	911	921	0.84 (0.80-0.89)	.58
Asia, Pacific, and other	65	63	0.78 (0.64-0.96)	
Age group, y				
<65	183	209	0.81 (0.72-0.90)	
≥65	1020	1007	0.84 (0.80-0.88)	.52
<75	643	672	0.80 (0.76-0.85)	
≥75	560	544	0.87 (0.82-0.93)	.07
Sex				
Women	605	616	0.83 (0.78-0.89)	
Men	598	600	0.84 (0.79-0.90)	.75
Baseline NYHA class				
I or II	811	835	0.83 (0.78-0.87)	
III or IV	391	381	0.86 (0.79-0.93)	.44
Diabetes (history or HbA_{1c} ≥6.5%)				
Yes	530	558	0.84 (0.78-0.90)	
No	673	658	0.84 (0.79-0.90)	.99
LVEF, %				
≤60	899	922	0.84 (0.80-0.89)	
≥60	304	294	0.81 (0.74-0.89)	.52
Prior heart failure hospitalization				
Yes	414	429	0.83 (0.77-0.90)	
No	789	787	0.84 (0.79-0.89)	.86



Adapted from Pieske B, et al. 2021

5.4. PANORAMA-HF trials

The PANORAMA-HF trial is a pivotal study designed to investigate the efficacy and safety of sacubitril/valsartan (LCZ696) in pediatric patients with heart failure (HF) who suffer from reduced left ventricular systolic function. Sacubitril/valsartan has shown considerable success in adult patients with HF, but its effects on pediatric populations remain largely unexplored. Given the significant burden that pediatric heart failure places on patients and healthcare systems, this study aims to fill the gap by providing critical insights into the drug's effectiveness in younger populations (Figure 6).

The study is divided into two distinct parts to comprehensively assess both the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug, as well as its overall clinical efficacy. Pharmacokinetics refers to how the body interacts with and processes the drug, including absorption, distribution, metabolism, and excretion. Pharmacodynamics focuses on the effects of the drug on the body, such as molecular, biochemical, and physiological changes it induces.

In the first phase, pediatric patients are divided into three groups based on age: 6 to <18 years, 1 to <6 years, and 1 month to <1 year. This division ensures that sacubitril/valsartan's effects are evaluated in age-specific contexts. The ascending-dose study in this phase will explore how different doses of the drug affect children in each age group, helping to determine safe and effective dosing for these vulnerable populations. Importantly, this phase also assesses how the drug is processed differently in children compared to adults.

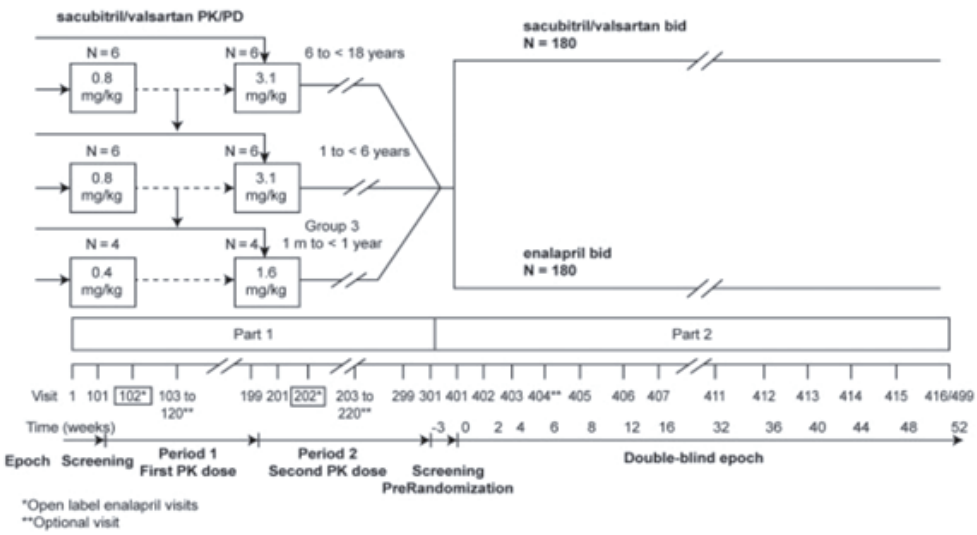
The second part of the study is a 52-week randomized trial where eligible patients will be split into two groups: one receiving sacubitril/valsartan and the other receiving enalapril, a widely used treatment for pediatric HF. By comparing sacubitril/valsartan to enalapril, researchers aim to establish whether sacubitril/valsartan provides superior outcomes in terms of reducing mortality, preventing worsening heart failure, and improving overall heart function.

A key feature of the trial is its global rank primary endpoint. This novel ranking system evaluates clinical events in a hierarchical manner, from the worst to the best outcomes. Events such as death, the need for mechanical life support, heart transplant listing, and worsening HF are among the critical factors ranked. Additionally, the study will consider functional capacity measures, such as New York Heart Association (NYHA) or Ross scores, and patient

reported symptoms to provide a more comprehensive view of heart failure management in these patients.

Ultimately, the PANORAMA-HF trial is groundbreaking in that it is the largest prospective pediatric HF trial ever conducted and the first to use a global rank primary endpoint. If sacubitril/valsartan proves superior to enalapril in this setting, it could significantly change the therapeutic landscape for pediatric HF, offering a more effective treatment option for this challenging condition [Brown Dm, et al. 2021].

Figure 6: PANORAMA-HF trial



Adapted from Shaddy R, et al. 2017

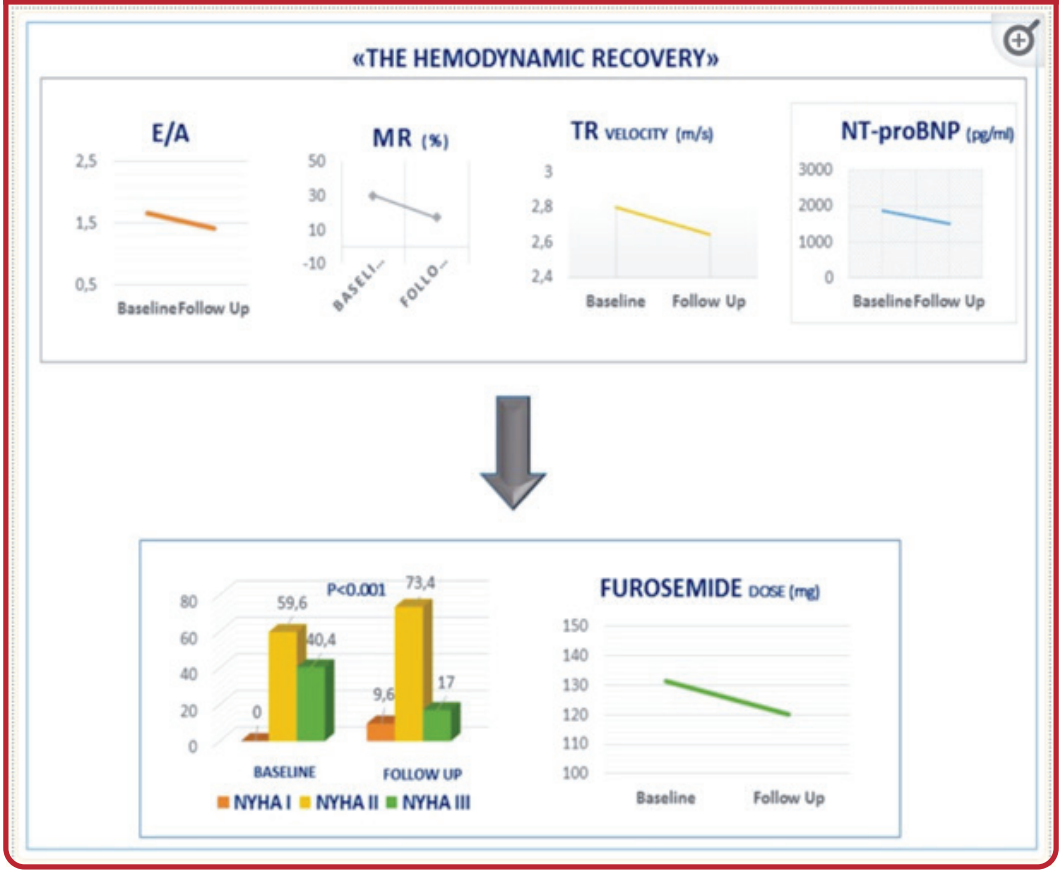
6. Hepatic impairment

Sacubitril/valsartan, a combination medication that includes an angiotensin receptor neprilysin inhibitor (ARNI), has demonstrated significant efficacy in managing patients with heart failure with reduced ejection fraction (HFrEF). Research has consistently shown that transitioning patients to sacubitril/valsartan can lead to considerable improvements in clinical outcomes. One of the key findings is the drug's ability to improve left ventricular ejection fraction (LVEF), indicating better heart function (Figure 7).

This medication works by enhancing hemodynamic status, which is crucial in reducing the symptoms associated with heart failure. Specifically, sacubitril/valsartan helps lower levels of NT-proBNP, a biomarker that reflects heart

failure severity, thus suggesting that the therapy effectively alleviates the cardiac stress and congestion typically experienced by these patients.Furthermore, studies indicate that initiating treatment with sacubitril/valsartan can lead to rapid reductions in NT-proBNP levels, observed as early as hospital discharge. Beyond merely improving LVEF, the use of sacubitril/valsartan has also been associated with reduced hospitalization rates due to heart failure exacerbations. This effect underscores the drug's role in enhancing patient quality of life and potentially reducing healthcare costs related to heart failure management In summary, the evidence suggests that sacubitril/valsartan not only facilitates hemodynamic recovery but also reverses detrimental cardiac remodeling processes, thereby offering substantial benefits to patients with HFrEF [Romano G, et al 2019].

Figure 7: Haemodynamic recovery



Adapted from Shaddy R, et al. 2017

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