SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Impact of Sacubitril/Valsartan Therapy on Left Ventricular Reverse Remodelling and Clinical Outcomes in Patients With CRT Nonresponders and HFrEF Patients Without CRT Indication

by Dr. Krisztina Mária Szabó

Supervisor: Prof. Dr. Zoltán Csanádi

UNIVERSITY OF DEBRECEN
KÁLMÁN LAKI DOCTORAL SCHOOL

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By Krisztina Mária Szabó, MD

Supervisor: Zoltán Csanádi, MD, PhD DSc

Kálmán Laki Doctoral School, cardiovascular diseases program
University of Debrecen

Head of the **Defense Committee**:	Prof. Dr. György Balla, Member of the Hungarian Academy of Sciences
Reviewers:	Dr. Annamária Kosztin, PhD Dr. Balázs Muk, PhD
Members of the Defense Committee:	Dr. Attila Kardos, PhD Dr. István Lőrincz, PhD

The PhD defense will take place at the Auguszta Lecture Hall, Faculty of Medicine, University of Debrecen, on February 13, 2026, at 1:00 PM.

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List of Abbreviations

ACC – American College of Cardiology

ACEi/ARB – Angiotensin-Converting Enzyme Inhibitors / Angiotensin Receptor Blockers

LBBB – Left Bundle Branch Block

CRT – Cardiac Resynchronization Therapy

CRT-D – Cardiac Resynchronization Therapy with Defibrillator

CRT-NR – Cardiac Resynchronization Therapy Non-Responder

CRT-P – Cardiac Resynchronization Therapy with Pacemaker

dP/dt – Rate of Left Ventricular Pressure Rise (echocardiographic parameter of contractility)

EF – Ejection Fraction

ESC – European Society of Cardiology

HFmrEF – Heart Failure with Mildly Reduced Ejection Fraction

HFpEF – Heart Failure with Preserved Ejection Fraction

HFrEF – Heart Failure with Reduced Ejection Fraction

HTx – Heart Transplantation

LVEDD – Left Ventricular End-Diastolic Diameter

LVESD – Left Ventricular End-Systolic Diameter

LVESV – Left Ventricular End-Systolic Volume

LVESVi – Left Ventricular End-Systolic Volume Index

LVAD – Left Ventricular Assist Device

MRA – Mineralocorticoid Receptor Antagonist

NT-proBNP – N-Terminal pro-B-Type Natriuretic Peptide

NYHA – New York Heart Association Functional Class

S/V – Sacubitril/Valsartan

SGLT2i – Sodium–Glucose Cotransporter-2 Inhibitor

SV – Stroke Volume

HF – Heart Failure

1. Introduction and Literature Review

1.1 Definition and Pathophysiology of Heart Failure

Heart failure (HF) represents a complex clinical syndrome with high global prevalence and major prognostic implications. According to the 2021 European Society of Cardiology (ESC) guidelines, HF is defined as a constellation of characteristic symptoms and signs caused by structural and/or functional cardiac abnormalities, resulting in impaired ventricular filling and/or ejection. The fundamental pathophysiological hallmark is the inability of the heart to maintain adequate cardiac output to meet the metabolic demands of peripheral tissues at normal filling pressures, or the requirement for elevated filling pressures to sustain such output.

The pathophysiology of HF is tightly interconnected with hemodynamic disturbances, neurohormonal activation, and molecular–cellular maladaptations. A reduction in forward stroke volume and cardiac output triggers compensatory upregulation of the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system (SNS). While initially adaptive, the chronic activation of these pathways induces vasoconstriction, sodium and water retention, increased myocardial oxygen demand, and ultimately adverse cardiac remodeling characterized by myocyte hypertrophy, fibrosis, and chamber dilatation. In contrast, natriuretic peptides—biomarkers of myocardial wall stress—counteract RAAS and SNS overactivation by promoting vasodilation, natriuresis, and antifibrotic effects. Their diagnostic and prognostic utility is now firmly established.

1.2 Epidemiology and Clinical Significance of Heart Failure

Heart failure constitutes a major global cardiovascular burden, affecting approximately 64 million individuals worldwide. In industrialized populations, its prevalence among adults is 1–2%, but exceeds 10% in persons over the age of 70. The exponential rise with advancing age reflects both the accumulation of cardiometabolic comorbidities (hypertension, diabetes mellitus, obesity, and coronary artery disease) and age-related myocardial and vascular structural changes.

Recent nationwide epidemiological analyses from Hungary substantiate a similarly concerning disease burden. According to comprehensive datasets from the National Health Insurance Fund, the number of patients living with HF has ranged between 163,723 and 247,095 in the past decade, corresponding to a population-level prevalence of 1.6–2.5%. The yearly number of incident HF cases is 44,000–65,000, demonstrating a higher incidence than previously estimated. Notably, the epidemiological trend is characterized by increasing prevalence but gradually declining incidence, consistent with international observations of improved acute cardiac care, but rising chronic disease load.

The clinical impact of HF is considerable due to its unfavorable prognosis. Five-year mortality approaches 50%, comparable to or worse than several oncological disorders. HF is among the leading causes of hospitalization in individuals ≥65 years and represents a major driver of healthcare utilization. Recurrent decompensation episodes reduced functional capacity and impaired health-related quality of life, further contributing to the substantial personal and socioeconomic burden associated with the disease.

1.3 Classification of Heart Failure

Heart failure can be categorized according to several clinically relevant dimensions:

1. Classification based on ejection fraction (EF)

Left ventricular ejection fraction represents the principal quantitative marker of left ventricular systolic performance and forms one of the key determinants of diagnostic and therapeutic pathways. According to the 2021 ESC Guidelines, the following categories are distinguished:

- HFrEF (Heart Failure with Reduced Ejection Fraction): EF ≤40%
- HFmrEF (Heart Failure with Mildly Reduced Ejection Fraction): EF 41–49%
- HFpEF (Heart Failure with Preserved Ejection Fraction): EF ≥50%

2. Classification based on symptoms and functional status

The New York Heart Association (NYHA) classification is widely used in routine clinical practice, stratifying patients into four groups based on symptom severity and exercise tolerance:

- NYHA I: asymptomatic, no limitations of ordinary physical activity
- NYHA II: mild symptoms; slight limitation during ordinary physical activity
- NYHA III: marked limitation of physical activity; symptoms occur with minimal exertion
- NYHA IV: symptoms present at rest; inability to perform any physical activity without discomfort

Due to its prognostic relevance and practicality, this system is widely used in clinical trials and everyday patient care.

3. Classification according to temporal presentation

- Acute heart failure: abrupt onset or rapid worsening of symptoms, typically requiring hospital admission and representing a potentially life-threatening condition.
- Chronic heart failure: long-standing, slowly progressive disease with intermittent episodes of decompensation.

4. Classification based on etiology

The underlying etiology of heart failure is heterogeneous. Major etiologic categories include:

- Ischaemic heart disease (the most common cause in developed countries)
- Hypertension
- Cardiomyopathies**,** categorized according to the 2023 ESC Cardiomyopathy Guidelines**:**
    - dilated cardiomyopathy (DCM)
    - hypertrophic cardiomyopathy (HCM)
    - restrictive cardiomyopathy (RCM)
    - left ventricular noncompaction cardiomyopathy (LVNC)
    - arrhythmogenic cardiomyopathy (ACM)
- Valvular heart diseases
- Less common etiologies**,** including:
    - myocarditis
    - infiltrative disorders (e.g., amyloidosis, sarcoidosis)
    - endocrine disorders
    - toxic exposures (e.g., alcohol, chemotherapeutic agents)
    - pregnancy-associated and postpartum cardiomyopathy

1.4 Evolution of first-line pharmacological therapy in HfrEF

1.4.1 ACEi/ARB, β-blockers, MRA (mineralocorticoid receptor antagonists), sodium–glucose cotransporter 2 inhibitors (SGLT2 inhibitors)

The foundations of pharmacological treatment for heart failure were established by large-scale, multicentre randomized clinical trials conducted in the 1980s, which first demonstrated that neurohormonal blockade can substantially improve patient prognosis. The CONSENSUS trial was the first to clearly show that the angiotensin-converting enzyme inhibitor (ACEi) enalapril confers a marked survival benefit in patients with severe (NYHA class IV) heart failure. Subsequently, the SOLVD trial confirmed these effects in a less advanced, symptomatic HFrEF population, demonstrating that ACE inhibitors not only reduce mortality but also decrease the rate of hospitalizations. These trials fundamentally changed the therapeutic approach and established ACE inhibitors as the cornerstone of heart failure management for many years. Later studies further showed that, in cases of ACE inhibitor intolerance – primarily due to cough or angioedema – angiotensin receptor blockers (ARBs) represent an effective alternative. The Val-HeFT trial demonstrated that valsartan significantly improves morbidity endpoints and, although it did not confer a significant advantage in terms of all-cause mortality, the reduction in hospitalization rates was clinically relevant.

The introduction of β-blockers into heart failure therapy brought another revolutionary change. Excessive activation of the sympathetic nervous system plays a key role in disease progression, and the suitability of β-blockers to counteract this has been confirmed by numerous studies. The MERIT-HF trial demonstrated the efficacy of metoprolol succinate, showing a substantial reduction in mortality. Similar findings were reported in the CIBIS-II trial, in which bisoprolol significantly reduced mortality. The effect of carvedilol was confirmed by the COPERNICUS trial, which showed that the benefits of treatment are preserved even in the most advanced patients with severe symptoms. Collectively, these studies unequivocally established β-blockers as a fundamental pillar in the treatment of HFrEF.

The need for further inhibition of the renin–angiotensin–aldosterone system was clearly highlighted by the introduction of mineralocorticoid receptor antagonists (MRAs). As early as the late 1990s, the RALES trial demonstrated that adding spironolactone to standard therapy significantly reduces mortality in patients with severe HFrEF. Later, the EMPHASIS-HF trial confirmed that eplerenone also confers a substantial survival benefit in a population with less severe disease and milder symptoms. Based on these two trials, MRAs have been incorporated routinely into standard heart failure therapy.

In the past decade, sodium–glucose cotransporter 2 (SGLT2) inhibitors have emerged as a new therapeutic option; these drugs were originally developed for the treatment of diabetes mellitus. The DAPA-HF trial was the first to show that dapagliflozin significantly reduces the risk of cardiovascular death and heart failure hospitalization in patients with HFrEF, irrespective of the presence of diabetes. This was corroborated by the EMPEROR-Reduced trial, which found similarly favourable effects with empagliflozin. These findings represented a paradigm shift, as for the first time, a drug class developed for a non-cardiovascular indication became one of the main pillars of heart failure therapy. Accordingly, the 2021 guidelines of the European Society of Cardiology, as well as the 2023 focused update, already list SGLT2 inhibitors among the core components of pharmacological treatment for HFrEF, on an equal footing with ACEi/ARB, β-blocker, and MRA therapy.

1.4.2 Introduction and effects of sacubitril/valsartan in HFrEF

Recognizing the importance of neprilysin inhibition represents another milestone in the history of pharmacological therapy. Neprilysin is an endopeptidase enzyme responsible for the degradation of natriuretic peptides. Its inhibition enhances the effects of these vasoactive peptides, promoting vasodilation, natriuresis, and a reduction in sympathetic activity. The combination of sacubitril and valsartan—an angiotensin receptor–neprilysin inhibitor (ARNI)—was the first therapeutic strategy designed to simultaneously target both the renin–angiotensin system and the natriuretic peptide system.

The results of the PARADIGM-HF trial were published in 2014. In this study, which enrolled more than 8,000 patients, sacubitril/valsartan reduced the composite primary endpoint—cardiovascular death or heart failure hospitalization—by 20% compared with enalapril. Moreover, the treatment also conferred a significant reduction in all-cause mortality. The study was terminated prematurely due to the clear superiority of sacubitril/valsartan, a rarity in the history of cardiovascular clinical research. The PIONEER-HF trial demonstrated that sacubitril/valsartan can be safely initiated during hospitalization following acute decompensation and that it significantly reduces NT-proBNP levels—an established biomarker of myocardial stress—within as little as 8 weeks. The TRANSITION trial similarly confirmed that in-hospital initiation of therapy is well tolerated, regardless of prior ACEi or ARB treatment.

Long-term effects were analysed in the PROVE-HF trial, a prospective, multicentre, single-arm study that followed more than 700 patients with HFrEF over 12 months. One of the key aims of the study was to assess the effects of sacubitril/valsartan on structural and functional parameters of the left ventricle. By the 6-month follow-up, a significant improvement was already evident in left ventricular ejection fraction, which increased by more than 5% on average, with further improvement by 12 months. In addition, left ventricular end-diastolic and end-systolic volumes decreased significantly, indicating favourable reverse remodelling. These structural changes were accompanied by improvements in biomarker profiles: NT-proBNP levels fell markedly early during therapy and showed a strong correlation with the degree of reverse remodelling.

The EVALUATE-HF trial was another important randomized, controlled clinical study comparing sacubitril/valsartan with enalapril in 464 patients with HFrEF. The primary endpoint consisted of changes in aortic stiffness, central hemodynamic parameters, and arterial elasticity. After 12 weeks, significant improvements were observed in echocardiographic measures in the sacubitril/valsartan group, including reductions in left atrial volume index (LAVi), left ventricular end-systolic and end-diastolic volume index, as well as favourable trends in ejection fraction, global longitudinal strain, and central blood pressure and pulse-wave analysis parameters. These findings indicate that ARNI therapy exerts beneficial effects not only on myocardial function but also on vascular properties, reducing left ventricular afterload and contributing to long-term cardiovascular protection. Thus, EVALUATE-HF complemented the findings of PARADIGM-HF and PROVE-HF by demonstrating that the effects of sacubitril/valsartan extend beyond myocardial function alone, reflecting a broad, system-level cardiovascular benefit.

The cumulative evidence from these trials was sufficiently compelling that the 2021 heart failure guidelines of the European Society of Cardiology placed sacubitril/valsartan alongside ACE inhibitors—under the designation “ACEi/ARNI”—as a first-line therapy for heart failure with reduced ejection fraction. Although this terminology formally denotes an alternative, it clearly reflects that ARNI therapy is supported by stronger evidence than conventional ACE inhibitor treatment. This shift marked a fundamental change in therapeutic strategy, as sacubitril/valsartan replaced ACE inhibitors and angiotensin receptor blockers as first-line therapy in appropriate patient groups. The 2023 ESC focused update reinforced this direction, confirming the central role of combined neprilysin inhibition and angiotensin receptor blockade in contemporary heart failure management.

A parallel shift occurred in the United States, though with an even stronger emphasis on sacubitril/valsartan. The 2022 joint guideline issued by the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA) no longer presents ARNI therapy as an alternative to ACE inhibitors, but rather designates it as the preferred first-line agent for the treatment of HFrEF. This difference highlights that, while European guidelines maintain a more cautious and equivalence-based formulation, the American guidance unequivocally places ARNI therapy at the top of the therapeutic hierarchy.

1.5 Device-based therapy: the history and mechanism of CRT

The development of cardiac resynchronization therapy (CRT) is primarily attributed to French electrophysiologists (Daubert, Cazeau), and its introduction represents one of the most significant advances in the treatment of heart failure over the past two decades. CRT aims to reduce left ventricular dyssynchrony—frequently associated with heart failure with reduced ejection fraction—by coordinating ventricular activation. Conduction abnormalities, particularly left bundle branch block, lead to asynchronous contraction of different myocardial regions, increasing mechanical stress, reducing left ventricular efficiency, and contributing to progressive remodelling. Through targeted pacing, CRT restores synchrony of ventricular contraction, reduces wall stress, alleviates mitral regurgitation, and promotes long-term reverse remodelling.

The first landmark study was the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial, published by Abraham and colleagues in 2002. In this study, more than 450 patients with severe heart failure (NYHA class III–IV) were randomized into two groups: one received CRT in addition to optimal medical therapy. In contrast, the control group received optimal medical therapy alone, with biventricular pacing either deactivated or not provided. The results demonstrated that patients treated with CRT exhibited significant improvements in the 6-minute walk test, reductions in heart failure symptoms, and enhanced quality of life. This study was the first large-scale randomized trial to show that CRT provides clinically meaningful symptomatic and functional benefits.

The next major milestone was the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, published by Bristow and colleagues in 2004. This study enrolled more than 1500 patients with advanced heart failure (NYHA class III–IV), who were randomized into three groups: optimal medical therapy alone; optimal medical therapy plus CRT; or optimal medical therapy plus CRT combined with an implantable cardioverter–defibrillator (CRT-D). The results showed that CRT—particularly in the CRT-D group—significantly reduced the composite endpoint of all-cause mortality or hospitalization due to heart failure. This trial clearly demonstrated that CRT not only improves symptoms but also confers a measurable survival benefit.

The long-term impact of CRT on mortality and prognosis was confirmed by the CARE-HF (Cardiac Resynchronization–Heart Failure) trial, published by Cleland and colleagues in 2005. More than 800 patients with severe heart failure (NYHA class III–IV), all receiving optimal medical therapy, were enrolled. One group received CRT, while the control group continued with medical therapy alone. During a mean follow-up of 29 months, CRT significantly reduced all-cause mortality as well as cardiovascular hospitalizations.

1.5.1 Indications for CRT

Since the introduction of CRT, patient selection criteria have gradually become more refined. This process has been shaped primarily by the results of large-scale clinical trials and the international guidelines derived from them. The early studies—including MIRACLE, COMPANION, and CARE-HF—clearly demonstrated that CRT provides significant clinical benefit in patients with severe, symptomatic heart failure with reduced ejection fraction and a wide QRS complex, even when they are already receiving optimal medical therapy. These benefits were evident both in symptom improvement and survival.

In the first guidelines, the indication for CRT was mainly restricted to patients with advanced heart failure (NYHA class III–IV) and a QRS duration of at least 120–130 ms. Later studies, however, showed that the greatest benefit is observed in patients with left bundle branch block (LBBB) morphology and a QRS duration ≥150 ms. Consequently, subsequent guidelines increasingly emphasized this subgroup. Based on the results of the REVERSE and MADIT-CRT trials, it also became evident that CRT may provide benefit in patients with milder symptoms (NYHA class II), as it can slow the process of left ventricular remodelling and reduce the rate of heart failure hospitalization. These findings contributed to the expansion of CRT indications, making the therapy recommended not only for the most severe cases but also for moderately symptomatic patients.

During the refinement of indications, QRS morphology became a key determinant. In conduction abnormalities without LBBB morphology (e.g., right bundle branch block or nonspecific intraventricular conduction delay), the effect of CRT proved to be substantially weaker. In these patients, the benefit of implantation is more uncertain, and guideline recommendations are correspondingly weaker. Patients with atrial fibrillation constitute a special category. In this group, CRT is effective only if near-complete (≈100%) biventricular pacing can be ensured, which often requires atrioventricular (AV) node ablation.

The 2021 ESC heart failure guideline gives a Class I, Level A recommendation for CRT in patients who are in sinus rhythm, have LVEF ≤35%, NYHA class II–IV symptoms, and a QRS duration ≥150 ms with LBBB morphology. In patients with QRS duration 130–149 ms, CRT may be considered but carries a weaker recommendation. In the absence of LBBB morphology, indications fall into Class IIa or IIb depending on QRS width.

The 2022 ACC/AHA/HFSA guideline provides broadly similar criteria but places even greater emphasis on the pivotal role of LBBB morphology. In the U.S. guidelines, CRT is recommended as a primary therapeutic option for patients with LBBB and a wide QRS complex, whereas in non-LBBB patterns, the indication is weaker and typically considered only selectively.

1.5.2 Definition, prevalence, and prognosis of non-response

One of the most important limitations of CRT therapy is non-response, defined as the failure of a patient to derive adequate clinical or structural benefit from treatment despite technically successful device implantation. However, the definition of non-response is not uniform in the literature. Some studies use clinical criteria (e.g., lack of improvement in NYHA functional class or absence of change in the 6-minute walk test), others rely on structural parameters (e.g., failure to achieve ≥15% reduction in left ventricular end-systolic volume), while several investigations apply combined criteria.

As a result, the reported prevalence of non-response varies, but large clinical trials and meta-analyses estimate that 20–40% of patients do not respond adequately to CRT. This substantial proportion represents a major clinical challenge, as many patients with heart failure fail to realize the symptomatic, structural, and prognostic benefits associated with CRT.

Multiple factors may contribute to non-response, including limitations in patient selection (non-LBBB morphology, shorter QRS duration, atrial fibrillation), suboptimal lead positioning, and the presence of comorbidities such as myocardial scar tissue or significant pulmonary or renal disease. Recent consensus statements emphasize that improving patient selection, incorporating advanced imaging modalities, and optimizing implantation techniques are key strategies to reduce the proportion of non-responders.

From a prognostic perspective, non-responders clearly have worse outcomes. Numerous studies have shown that patients who do not exhibit reverse remodelling maintain higher risks of mortality and rehospitalization, and do not experience the long-term survival advantages conferred by CRT. Overall, non-response remains one of the greatest clinical challenges in CRT therapy and continues to be a major focus of ongoing research. Current efforts aim to increase responder rates through personalized selection strategies, advanced imaging, and greater procedural precision during implantation.

1.5.3 New pharmacotherapeutic options in patients undergoing CRT

In a subset of patients who undergo CRT implantation—particularly among non-responders—prognosis remains unfavourable, and adequate clinical improvement cannot be achieved despite optimal pharmacological and device-based therapy. Data from the ADVANCE CRT registry indicate that a substantial proportion of non-responder patients in routine clinical practice are managed passively, without full utilization of the available therapeutic options. This highlights the particular importance of introducing new therapeutic strategies for this patient population.

The emergence of sacubitril/valsartan (ARNI) has brought a transformative change to heart failure pharmacotherapy. Nevertheless, evidence regarding the efficacy of sacubitril/valsartan specifically in patients who have undergone CRT—especially non-responders—remains limited and is derived mainly from smaller observational studies. These studies suggest that ARNI therapy may improve left ventricular remodelling, slow functional deterioration, and reduce the frequency of hospitalizations, although the evidence supporting these benefits is still restricted.

2. Objectives and Rationale

Both cardiac resynchronization therapy (CRT) and angiotensin receptor–neprilysin inhibition (ARNI) have independently been shown to improve prognosis in patients with heart failure. However, therapeutic options remain limited for patients who undergo CRT implantation but fail to respond adequately, and evidence regarding the efficacy of ARNI in this specific population is scarce. Our study aimed to evaluate the extent to which treatment with sacubitril/valsartan can induce reverse remodelling and improve long-term clinical outcomes in heart failure patients who have undergone CRT but are classified as non-responders. To address this question, we compared CRT non-responder patients who continued ACE inhibitor or ARB therapy after the identification of non-response with those whose treatment regimen was switched to sacubitril/valsartan. Additionally, we established a further control group consisting of patients with HFrEF who received sacubitril/valsartan but did not undergo CRT due to the absence of guideline-based indications.

3. Materials and Methods

3.1 Study population and inclusion criteria

In this retrospective, observational study, we analysed the clinical database of the University of Debrecen. The database included patients treated between January 2018 and June 2021 for heart failure with reduced ejection fraction (HFrEF), defined according to contemporaneous guideline criteria as a left ventricular ejection fraction (LVEF) <40%. Patients were included if they had received either outpatient or inpatient care and were treated with guideline-directed medical therapy for heart failure (ACE inhibitor/ARB or sacubitril/valsartan, β-blocker, and MRA). Additionally, we included patients in whom cardiac resynchronization therapy (CRT-P or CRT-D) was implanted during the study period based on standard guideline indications. CRT-treated patients were categorized as responders or non-responders. Responder status was determined by comparing LVEF measured before CRT implantation with LVEF measured at least 6 months after implantation. Patients who did not demonstrate an improvement of ≥10% in left ventricular function were classified as non-responders. All echocardiographic measurements were performed using two-dimensional echocardiography with the Simpson biplane method. Echocardiographic assessments were carried out as part of routine clinical practice, in accordance with institutional protocols, by one or more experienced echocardiographers. For quantitative parameters, the average of multiple cardiac cycles was used when relevant; in the presence of atrial fibrillation, for stroke volume and LVOT VTI measurements, the mean of at least five consecutive beats was applied. Volume and functional parameters were obtained following standardized measurement techniques consistent with current international recommendations. Patients were excluded if the percentage of biventricular pacing was <95%, as well as those classified as CRT responders.

We divided the patients into three groups:

- **Group I (70 patients):** CRT-implanted non-responders in whom ACEi/ARB therapy was replaced by sacubitril/valsartan, with echocardiographic and NT-proBNP measurements available both prior to therapy initiation and after at least 6 months of treatment.
- **Group II (70 patients):** CRT-implanted non-responders who continued ACEi/ARB therapy, with two echocardiographic and NT-proBNP assessments available at least 6 months apart.

- **Group III (135 patients):** Patients with HFrEF who did not meet indications for CRT but were initiated on sacubitril/valsartan, with echocardiographic and NT-proBNP measurements available before therapy initiation and after a minimum of 6 months.

All patients received β-blocker, mineralocorticoid receptor antagonist, and diuretic therapy as clinically indicated. Sacubitril/valsartan therapy was initiated following ACEi/ARB discontinuation, starting at 100 mg (24/26 mg/day) or 200 mg (49/51 mg/day), and subsequently titrated to the maximum target dose of 400 mg (97/103 mg/day) depending on individual tolerance.

The effects of sacubitril/valsartan were evaluated over two distinct time horizons, according to the nature of the endpoints assessed. To analyse left ventricular reverse remodelling, we examined changes in echocardiographic parameters (LVEF, LVEDD, LVESD, LVOT VTI, stroke volume, and dP/dt as an index of contractility) and plasma NT-proBNP concentrations during a 6–9 month follow-up after therapy initiation. Long-term prognostic effects were assessed over a median follow-up of 22–24 months, during which the incidence of a composite clinical endpoint was analysed. This endpoint included all-cause mortality, heart transplantation, implantation of a left ventricular assist device (LVAD), and hospitalization for heart failure.

3.1 Endpoints

Primary endpoint:
The primary endpoints of the study focused on assessing changes in left ventricular function and neurohormonal activity. Accordingly, the primary outcomes were defined as the change in left ventricular ejection fraction (LVEF) and the change in plasma NT-proBNP concentration relative to baseline.

Secondary endpoints:
Secondary endpoints included additional echocardiographic parameters of reverse remodelling: left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left ventricular outflow tract velocity–time integral (LVOT VTI), stroke volume (SV), and the contractile function index dP/dt. The safety profile of the therapy was evaluated based on changes in systolic and diastolic blood pressure, estimated glomerular filtration rate (eGFR), and serum potassium levels.

Clinical endpoints:

Long-term prognosis was assessed using a composite clinical endpoint that included all-cause mortality, the need for heart transplantation (HTx), implantation of a left ventricular assist device (LVAD), and hospitalization for heart failure. As a secondary clinical outcome analysis, we separately evaluated the frequency of heart failure–related hospitalizations and the combined occurrence of mortality, HTx, or LVAD implantation.

4. Results

4.1 Baseline patient characteristics and medical therapy

A total of 275 patients were included in the study and assigned to three groups: Group I consisted of 70 patients (CRT-implanted non-responders who were switched from ACEi/ARB to sacubitril/valsartan [S/V]), Group II included 70 patients (CRT-implanted non-responders who continued ACEi/ARB therapy), and Group III included 135 patients (patients with HFrEF without CRT indication who received S/V therapy). Patients in the CRT-treated non-responder groups were older and had a higher burden of comorbidities compared with those who received S/V solely for HFrEF. There was no significant difference in the underlying aetiology of heart failure among the three groups. Most patients across all groups were classified as NYHA functional class III. Baseline left ventricular ejection fraction was significantly higher in Group II (CRT-NR + ACEi/ARB) compared with Group I (CRT-NR + S/V) and Group III (HFrEF + S/V). Median NT-proBNP levels were comparable among the groups: 2058 pg/mL (IQR 1041–4502) in Group I, 1474 pg/mL (IQR 655–5274) in Group II, and 2223 pg/mL (IQR 1233–4795) in Group III. At the time of inclusion, all patients were receiving guideline-directed medical therapy. Dose titration of S/V was performed using a unified protocol throughout the study, with baseline systolic blood pressure determining the initial dose. When systolic blood pressure was ≥110 mmHg, therapy was initiated at 49/51 mg; when systolic blood pressure was <100 mmHg, a starting dose of 24/26 mg was used. Dose escalation was attempted as early as possible, typically during subsequent regular follow-up visits, with most titration occurring at the 3–6 month controls. Among patients treated with S/V (Groups I and III), doses were titrated to the maximally tolerated level in accordance with guideline recommendations. In Group I, 22.8% (n=16) achieved a target dose of 100 mg/day (24/26 mg), 50% (n=35) reached 200 mg/day (49/51 mg), and 27.1% (n=19) achieved 400 mg/day (97/103 mg). In Group III, the distribution of maximally tolerated doses was: 28.8% (n=39) at 100 mg/day, 37.1% (n=50) at 200 mg/day, and 34.1% (n=46) at 400 mg/day. No significant difference was found between the two S/V groups regarding the distribution of maximally tolerated doses (p=0.587). Dose titration during follow-up was not limited to S/V, but also extended to other standard heart failure medications. The MRA dose was increased in 21 patients (30%) in Group I, in 12 patients (17%) in Group II, and in 28 patients (40%) in Group III. Similarly, β-blocker dose up-titration was achieved in 25 patients (35.7%), 28 patients (40%), and 49 patients (36.2%) in Groups I, II, and III, respectively. In Group II, the ACEi dose was increased to the maximally tolerated level in 13 patients (18.5%). Overall, all patients received guideline-directed optimal medical therapy throughout the study, with titration of each major drug class (S/V or ACEi/ARB, β-blocker, MRA) toward the maximally tolerated dose.

4.2 Effect of S/V on left ventricular remodelling

Changes in echocardiographic parameters were evaluated over a 6–9-month interval following enrolment (7.54 ± 1.8 months in the total cohort; 7.45 ± 1.6 months in Group I; 7.75 ± 2.2 months in Group II; and 7.51 ± 1.5 months in Group III). Left ventricular ejection fraction showed a significant improvement among patients receiving sacubitril/valsartan therapy. In Group I, LVEF increased from 25.2 ± 5.7% to 29.4 ± 6.7% ($p<0.001$), while in Group III it increased from 26.6 ± 6.4% to 29.9 ± 6.7% ($p<0.001$). A multivariable regression model—adjusted for age, sex, baseline EF, underlying aetiology, and comorbidities (hypertension, diabetes mellitus, atrial fibrillation, hyperlipidaemia, chronic kidney disease)—confirmed that S/V therapy was an independent predictor of LVEF improvement in both Group I (Coeff = 2.57; $p = 0.010$) and Group III (Coeff = 2.19; $p = 0.014$). In contrast, no significant change in LVEF was observed in Group II (CRT-NR + ACEi/ARB) (28.3 ± 5.9% vs. 29.0 ± 6.8%; $p = 0.106$). Plasma NT-proBNP levels also decreased significantly in patients treated with S/V. In Group I, levels declined from 2058.89 pg/mL [1041.07–4502.51] to 1121.55 pg/mL [545–2541] ($p<0.001$), and in Group III from 2223.35 pg/mL [1233.03–4795.96] to 1123.09 pg/mL [500.38–2651.27] ($p<0.001$). A robust multivariable regression model similarly confirmed that S/V therapy was an independent predictor of NT-proBNP reduction in both Group I (Coeff = –763.66; $p = 0.004$) and Group III (Coeff = –812.38; $p = 0.001$). In contrast, no significant change was observed in Group II (1474.57 pg/mL [655.8–5273] vs. 1986.3 pg/mL [1025.3–3359.1]; $p = 0.807$). There was no difference between Groups I and III in the magnitude of improvement in either LVEF ($p = 0.161$) or NT-proBNP levels ($p = 0.850$). Among secondary echocardiographic parameters, left ventricular end-systolic diameter showed a significant reduction in patients receiving S/V: from 56.6 ± 8.9 mm to 54.3 ± 8.7 mm in Group I ($p = 0.004$), and from 55.9 ± 9.9 mm to 54.3 ± 11.2 mm in Group III ($p = 0.021$). No significant changes were observed in other echocardiographic parameters (e.g., LVEDD, stroke volume, dP/dt). Safety analyses showed significant reductions in systolic and diastolic blood pressure in the S/V-treated groups. eGFR demonstrated a mild decline in Group I, whereas serum potassium levels increased in Group III. Importantly, discontinuation of S/V therapy was not required in any patient during the study period.

4.3 Effect of S/V on functional status

Changes in functional status were assessed using the New York Heart Association (NYHA) classification during the follow-up period. Based on the 6–9-month follow-up evaluations, patients receiving S/V therapy (Group I: CRT-NR + ARNI; Group III: HFrEF + ARNI) demonstrated a significant and clinically meaningful improvement. In both groups, the majority of patients improved from baseline NYHA class III to NYHA class II ($p < 0.001$), indicating a marked and early improvement in symptomatic status. In contrast, patients in Group II (CRT-NR + ACEi/ARB) did not show a statistically significant change in functional class ($p = 0.05$), although a trend toward mild improvement was observed.

4.4 Effect of S/V on clinical endpoints

During the full follow-up period, the primary composite endpoint (all-cause mortality, hospitalization for heart failure, heart transplantation [HTx], or implantation of a left ventricular assist device [LVAD]) occurred in 27/70 patients in Group I (38.57%; including 2 HTx and 1 LVAD), in 43/70 patients in Group II (61.42%), and in 60/135 patients in Group III (44.42%; including 2 HTx). The differences between Groups I and II, as well as between Groups II and III, were statistically significant, whereas outcomes were comparable between the two S/V-treated groups (Groups I and III; $p = 0.465$). Hospitalization for heart failure was significantly more frequent in Group II than in either Group I or Group III, while the two groups receiving S/V therapy exhibited similarly favourable outcomes in this regard. For the aggregated secondary endpoint (mortality + HTx + LVAD), no significant differences were observed among the three groups. We further analysed the occurrence of recurrent hospitalizations for heart failure. The incidence of ≥2 rehospitalizations was 12.8% in Group I (CRT-NR + S/V), 20% in Group II (CRT-NR + ACEi/ARB), and 10.3% in Group III (HFrEF + S/V). These findings align with the observation that Group II—receiving no S/V therapy—experienced more frequent heart failure hospitalizations, whereas the two S/V-treated groups showed similar clinical outcomes. Multivariable Cox regression analysis—adjusted for age, sex, and the presence of atrial fibrillation, diabetes mellitus, chronic kidney disease, and hypertension—demonstrated that CRT non-responder patients treated with S/V had a 64% relative risk reduction for the composite endpoint compared with those who remained on ACEi/ARB therapy (HR = 0.36; 95% CI 0.21–0.60; $p < 0.001$). Similarly, in Group I, the risk of heart failure hospitalization was lower compared with Group II (HR = 0.61; 95% CI 0.34–0.86; $p = 0.045$). However, for the mortality + HTx + LVAD endpoint, no statistically significant difference was observed between the two groups (HR = 0.69; 95% CI 0.36–1.70; $p = 0.247$). In Group I, we additionally examined LVEF and NT-proBNP values measured at initiation of S/V therapy and at 6–9-month follow-up, stratified by the occurrence of long-term composite events. Both LVEF and NT-proBNP improved significantly in patients who remained event-free. Among patients who experienced an event, NT-proBNP showed a moderate but significant reduction, whereas LVEF did not exhibit meaningful improvement. The clinical relevance of functional improvement is illustrated by the finding that a ≥5% increase in LVEF was observed in 39/70 patients (55.7%), of whom 33 patients (91.7%) remained free of composite events throughout follow-up. In contrast, among those without improvement (≤5% increase, n = 31), 15 patients (48.4%) experienced a composite endpoint event. NT-proBNP levels decreased to <1000 pg/mL in 27/70 patients (38.6%), of whom 24 (88.9%) remained free of composite events.

5. Discussion

In our study, we evaluated the effect of sacubitril/valsartan therapy on left ventricular reverse remodelling and long-term clinical outcomes in patients with heart failure who had undergone cardiac resynchronization therapy but failed to achieve an adequate therapeutic response. Our findings indicate that S/V treatment resulted in significant improvement in both left ventricular ejection fraction and NT-proBNP levels, and also showed favourable trends in selected echocardiographic markers of reverse remodelling. These results suggest that the pharmacological mechanism of S/V may partially counteract the unfavourable prognosis associated with CRT non-response. The improvement in LVEF and the significant reduction in NT-proBNP are consistent with the pathophysiological model whereby the dual mechanism of ARNI therapy—RAAS inhibition combined with neprilysin inhibition leading to increased natriuretic peptide availability and cGMP–PKG pathway activation—results in neurohormonal unloading and afterload reduction. Together with reduced arterial stiffness and antifibrotic effects, this creates a haemodynamic environment that may promote reverse remodelling even in the context of CRT non-response. NT-proBNP, as an early marker of therapeutic efficacy, reflects not only statistical improvement but also clinically meaningful prognostic benefit. With regard to clinical endpoints, the reduction in the incidence of the composite outcome (mortality, heart failure hospitalization, heart transplantation, LVAD implantation) over long-term follow-up further supports the benefit of S/V in this population. Although the observational nature of the study precludes establishing definitive causal relationships, the consistency of the findings strongly suggests that S/V therapy provides a meaningful clinical advantage in CRT non-responders. The clinical relevance of these results is strengthened by the observation that the magnitude of benefit was similar to that seen in HFrEF patients not treated with CRT. This implies that the mechanisms of action of S/V are independent of CRT responsiveness, and that non-responder status does not preclude the favourable physiological and clinical effects of ARNI therapy.

5.1 Our findings in the context of the existing literature

The effects of sacubitril/valsartan (S/V) in systolic heart failure have been extensively evaluated in numerous large-scale randomized clinical trials and registry analyses; however, the CRT-nonresponder (CRT-NR) subgroup has received limited dedicated attention. The PARADIGM-HF trial remains a landmark in HFrEF therapy: in more than 8,400 patients, S/V reduced the combined risk of cardiovascular death or heart-failure hospitalization by 20% compared with enalapril, and also demonstrated a significant reduction in all-cause mortality. Although no specific subgroup analysis was published for patients receiving CRT, the trial provides robust evidence for the efficacy of S/V across a broad HFrEF population. In this context, it is particularly relevant that in our study, similarly favourable effects were observed even in the CRT-NR subgroup. The PROVE-HF trial prospectively demonstrated that S/V induces significant reverse remodelling within as little as 6 months, with improvements in LVEF, reductions in LV volumes, and sustained decreases in NT-proBNP. These findings are consistent with our observations and suggest that the beneficial remodelling effects of S/V may occur independently of CRT response. Acute-heart-failure studies, including PIONEER-HF and TRANSITION, showed that S/V can be safely initiated during hospitalization and leads to rapid and substantial reductions in NT-proBNP. Although these studies did not focus on CRT populations, their message is clinically important: the therapeutic effect of S/V emerges early, which may be especially beneficial for CRT nonresponders, a group characterized by frequent hospitalizations. The EVALUATE-HF trial examined hemodynamic and vascular effects, demonstrating that S/V significantly improved aortic stiffness and central hemodynamics within 12 weeks and reduced left atrial and ventricular volumes. In our study, the reduction in LV end-systolic diameter and improvement in LVEF may be viewed as clinical manifestations of these complex physiological effects. In recent years, several publications have specifically addressed CRT-nonresponder populations. Chun et al. (2020) reported in a retrospective analysis that CRT-NR patients treated with S/V had lower all-cause mortality and a favourable trend toward reduced heart-failure rehospitalizations. Similar findings were observed in our study: increases in LVEF, reductions in LVESD, and significant decreases in NT-proBNP in

CRT-NR patients receiving S/V, with effect sizes comparable to those observed in HFrEF patients not treated with CRT. In another study, Chen et al. demonstrated that S/V treatment in nonresponders significantly reduced cardiac mortality (log-rank p = 0.029) and showed favourable trends in reducing HF-related hospitalizations. A recently published 2023 European analysis also indicated that hospitalization and survival outcomes in CRT-nonresponders treated with S/V were comparable to those of standard HFrEF populations, suggesting that the efficacy of S/V is independent of CRT response status. Real-world registry data further support these findings. The CHAMP-HF registry and the ARIADNE study both confirmed that S/V therapy is associated with better symptom control, lower rehospitalization rates, and improved functional status across diverse European cohorts. Among the most recent evidence, the STRONG-HF trial deserves special attention. This randomized, prospective study demonstrated that rapid therapy titration and intensive follow-up—including S/V use—significantly reduced 180-day mortality and rehospitalization after acute decompensation. Although not specific to CRT-NR patients, these results strongly imply that high-risk subgroups, including nonresponders, may derive particular benefit from early and aggressive S/V optimization. Taken together, these findings form a consistent picture: CRT-nonresponder status does not preclude the favourable effects of sacubitril/valsartan. On the contrary, available evidence suggests that this therapy may be especially valuable in this high-risk population, whose prognosis is otherwise poor. Nonetheless, methodological limitations—particularly retrospective designs and heterogeneous definitions of nonresponse—highlight the need for prospective, multicentre studies specifically targeting this subgroup.

5.2 Clinical significance of our findings

Our findings hold substantial implications for everyday clinical practice. Sacubitril/valsartan therapy demonstrated clinically meaningful benefits in patients with heart failure who exhibited nonresponse to CRT, a subgroup traditionally characterized by particularly poor prognosis. CRT nonresponse affects approximately 20–40% of implanted patients and is associated with higher mortality, increased rates of rehospitalization, and reduced quality of life compared with responders. The improvements observed during S/V therapy—including increases in left ventricular ejection fraction, reductions in NT-proBNP concentrations, and early indicators of reverse remodelling—suggest that this pharmacological intervention may enhance survival prospects and reduce the burden of hospital admissions within this high-risk population. From a therapeutic standpoint, S/V may offer particular value by delaying the need for advanced heart failure interventions such as LVAD implantation or heart transplantation. This could translate into longer periods of improved quality of life for patients while simultaneously reducing the strain on healthcare systems. Although current ESC and ACC/AHA/HFSA guidelines recommend ARNI therapy as a first-line option in HFrEF, specific directives for the management of CRT nonresponders are not yet available. The favourable effects observed in our study—together with registry-based and real-world evidence—provide a strong rationale for considering S/V as a targeted therapeutic option in this exceptionally high-risk cohort. Should these findings be confirmed in prospective multicentre trials, they may serve as a foundation for dedicated guideline recommendations addressing the management of CRT nonresponders.

5.3 Limitations of the study

A comprehensive interpretation of our findings necessitates a detailed consideration of the study's limitations, as these factors influence both the generalizability and the evidential strength of the conclusions drawn. The first limitation pertains to sample size. The number of patients included in the analysis was relatively modest, thereby reducing statistical power—particularly in subgroup analyses. Although several primary endpoints still demonstrated statistically significant differences, the limited sample increases vulnerability to random variation and potential confounders. Furthermore, heterogeneity in sex distribution, underlying aetiology, and age may also affect the extent to which the results can be extrapolated to broader populations. The study period (2018–2021) coincided with restricted access to ARNI therapy in Hungary, which represents an important methodological constraint. Until January 2019, sacubitril/valsartan could only be initiated following individual reimbursement approval from the National Health Insurance Fund (NEAK), substantially limiting the ability to start therapy and reducing the number of potentially eligible patients. From January 2019 onwards, the medication became reimbursable under specific indications; however, initiation remained contingent upon stringent clinical and administrative criteria (NYHA II–III symptomatic HFrEF, LVEF <35%, at least two prior rehospitalizations, documented clinical deterioration despite 12 months of optimal guideline-directed medical therapy, systolic blood pressure >100 mmHg, eGFR >30 mL/min, adequate serum potassium, elevated NT-proBNP, and restricted prescriber eligibility). These reimbursement and administrative constraints likely influenced the timing of therapy initiation, dose-titration kinetics, and the size of the treated cohort. Consequently, interpretation of outcomes must take into account the limited accessibility of ARNI therapy during the study period. A further limitation is the single-centre design. Patient characteristics, CRT implantation practices, device selection, and titration strategies for guideline-directed medical therapy reflect specific institutional patterns that may not be generalizable to other centres or healthcare systems. Results, therefore, cannot be directly extrapolated to populations in regions where therapeutic access, healthcare infrastructure, or financing mechanisms differ. Additionally, the retrospective, observational nature of the study imposes inherent methodological restrictions. Such a design does not permit causal inference; rather, the findings should be viewed primarily as hypothesis-generating. In contrast, prospective randomized trials—such as STRONG-HF—yield more robust, causally interpretable evidence, underscoring the need for similar targeted trials in the CRT-nonresponder population. The limited duration of follow-up represents another constraint. Although short- and mid-term improvements were observed in LVEF and NT-proBNP, long-term survival data are lacking, and it remains uncertain whether the observed reverse remodelling persists over several years. Longer-term follow-up studies will be essential to clarify these issues. Methodological limitations of echocardiographic assessment must also be acknowledged. Image quality, operator experience, and intra- and interobserver variability may influence measurement accuracy. Advanced imaging modalities—such as three-dimensional echocardiography and strain analysis—provide more precise insights into reverse remodelling but were not routinely available during the study period. Therapeutic adherence and dose optimization represent additional limitations. Not all patients achieved the target dose of sacubitril/valsartan, which may have influenced the effect size. Moreover, due to the retrospective design, precise assessment of adherence was not feasible, despite its potential impact on clinical outcomes. The pharmacological background during the study also differed from contemporary guideline-directed therapy. SGLT2 inhibitors, now considered a foundational component of HFrEF management, were at that time available only for diabetic indications. Therefore, the benefits observed with S/V monotherapy may differ from outcomes in modern multi-drug regimens.

Finally, generalizability is restricted by the predominantly European composition of the study cohort. Outcomes may not be fully reproducible in populations with different ethnic, genetic, or socioeconomic characteristics. The ARIADNE registry, for example, demonstrated significant regional variation in the use and effectiveness of sacubitril/valsartan across Europe, highlighting the influence of local healthcare practices on therapeutic outcomes.

6. Novel Scientific Findings

- We provide the first evidence that sacubitril/valsartan (S/V) therapy induces meaningful structural and functional improvement in the CRT-nonresponder (CRT-NR) HFrEF population.

- Reverse remodelling was detectable after 6–9 months of therapy, demonstrated by improvement in left ventricular ejection fraction, reduction in LV end-systolic diameter, and a significant decrease in NT-proBNP levels.
- Prognostic relevance of reverse remodelling:
  - ≥5% increase in LVEF → 91.7% 2-year event-free survival
  - NT-proBNP <1000 pg/mL → 88.9% 2-year event-free survival
- Improvement in clinical endpoints following switch to S/V in CRT-NR patients:
  - Composite outcome (death, HTx, LVAD implantation, HF hospitalization) reduced by 64%
  - Risk of HF hospitalization reduced by 39% compared with patients remaining on ACEi/ARB therapy
- The magnitude of clinical benefit is comparable to results from PARADIGM-HF, despite the considerably less favourable clinical profile of CRT-NR patients (older age, more severe LV dysfunction, higher NT-proBNP levels, greater comorbidity burden).
- New therapeutic perspective: Our findings highlight that even in CRT-nonresponders, rapid and comprehensive implementation of guideline-directed, contemporary medical therapy—including S/V—should be prioritised.
- Importance of therapy optimisation: S/V should not be regarded as a "last-line option," but rather as a cornerstone of modern HFrEF management, with demonstrable outcome benefits even in CRT-NR patients.
- Biomarker-based and personalised treatment: Dynamic monitoring of NT-proBNP and reverse remodelling parameters enables early assessment of therapeutic efficacy and supports personalised treatment strategies.
- At the guideline level, our results reinforce the concept that early and routine initiation of S/V therapy in CRT-NR patients confers clinically meaningful benefits.

7. Summary

Background: Cardiac resynchronization therapy (CRT) is an established therapeutic modality in patients with heart failure with reduced ejection fraction (HFrEF). Nevertheless, 20–40% of CRT-treated individuals fail to demonstrate meaningful clinical or structural improvement and are classified as CRT non-responders (CRT-NR). These patients have a significantly worse prognosis, characterized by higher mortality, increased rates of heart failure (HF) hospitalization, and impaired quality of life. Although sacubitril/valsartan (S/V) has been shown to improve cardiac function and clinical outcomes in HFrEF, evidence regarding its efficacy in CRT-NR patients remains limited. The present study evaluated the impact of S/V therapy on reverse remodelling, neurohormonal activity, and long-term clinical outcomes in CRT-NR patients.

Methods: A retrospective, observational analysis was conducted using the clinical database of the University of Debrecen. A total of 275 patients with HFrEF were included and allocated into three groups: I) CRT-NR patients treated with S/V after discontinuation of ACEi/ARB (n=70); II) CRT-NR patients who continued ACEi/ARB therapy (n=70); III) HFrEF patients without CRT indication but treated with S/V (n=135). CRT non-response was defined as <10% improvement in left ventricular ejection fraction (LVEF) ≥6 months post-implantation. Echocardiographic and biomarker parameters were assessed at baseline and after 6–9 months of therapy (overall mean: 7.54 ± 1.8 months). Clinical outcomes were evaluated over a median follow-up of 22–24 months. The primary endpoints were changes in LVEF and NT-proBNP; secondary endpoints included LV dimensions, LVOT VTI, stroke volume, dP/dt, safety parameters, and a composite clinical endpoint (all-cause mortality, HF hospitalization, heart transplantation [HTx], or LVAD implantation).

Results: S/V therapy resulted in significant reverse remodelling in CRT-NR patients. In Group I, LVEF increased from 25.2 ± 5.7% to 29.4 ± 6.7% (p<0.001), and NT-proBNP decreased from 2058 pg/mL [1041–4503] to 1122 pg/mL [545–2541] (p<0.001). Group III showed similar improvement: LVEF 26.6 ± 6.4% → 29.9 ± 6.7% (p<0.001); NT-proBNP 2223 pg/mL [1233–4796] → 1123 pg/mL [500–2651] (p<0.001). No significant changes were observed in Group II. LV end-systolic diameter significantly decreased in Group I (56.6 ± 8.9 mm → 54.3 ± 8.7 mm; p=0.004) and Group III (55.9 ± 9.9 mm → 54.3 ± 11.2 mm; p=0.021). The composite clinical endpoint occurred in 27/70 (38.6%) patients in Group I, 43/70 (61.4%) in Group II, and 60/135 (44.4%) in Group III. Cox regression analysis demonstrated a 64% relative risk reduction for the composite endpoint in S/V-treated CRT-NR patients compared with ACEi/ARB-treated CRT-NR patients (HR=0.36; 95% CI 0.21–0.60; p<0.001). HF hospitalization risk was also significantly lower (HR=0.61; 95% CI 0.34–0.86; p=0.045). Changes in mortality+HTx+LVAD rates did not differ across groups.

Discussion: S/V therapy produced clinically meaningful structural, functional, and biomarker improvements in CRT non-responders, despite their traditionally poor prognosis. The magnitude of improvement was comparable to that observed in HFrEF patients without CRT, suggesting that the therapeutic effect of S/V is independent of CRT response status. Early NT-proBNP reduction and LVEF improvement were strongly associated with long-term event-free survival (≥5% LVEF increase: 91.7% 2-year event-free survival; NT-proBNP <1000 pg/mL:

88.9%). These results emphasize the physiological plausibility and clinical relevance of ARNI-mediated dual RAAS and neprilysin inhibition in reversing adverse cardiac remodelling, even in the context of CRT non-response.

Conclusion: Sacubitril/valsartan therapy is effective in improving left ventricular function, reducing neurohormonal activation, and lowering HF hospitalization rates in CRT non-responders. Although mortality outcomes were unchanged, the favourable remodelling and biomarker responses—mirroring those seen in conventional HFrEF populations—highlight S/V as a key therapeutic component in the management of CRT-NR patients. Prospective, multicentre studies are warranted to validate these findings and inform guideline recommendations for this high-risk population.

8. List of Own Publications

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Registry number: DEENK/519/2025.PL
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Candidate: Krisztina Mária Szabó
Doctoral School: Kálmán Laki Doctoral School

List of publications related to the dissertation

1. **Szabó, K. M.**, Tóth, A., Nagy, L., Nagy, L. T., Sándorfi, G., Clemens, M., Nagy, A. C., Ráduly, A. P., Borbély, A., Barta, J., Csanádi, Z.: Comparable Benefits in Heart Failure Hospitalization and Survival with Sacubitril/Valsartan Therapy in CRT Nonresponders and HFrEF Patients Without CRT Indication.
   J Clin Med. 14, 1-12, 2025.
   DOI: http://dx.doi.org/10.3390/jcm14176098
   IF: 2.9 (2024)
2. **Szabó, K. M.**, Tóth, A., Nagy, L., Rácz, V., Pólik, Z., Hódosi, K., Nagy, A. C., Barta, J., Borbély, A., Csanádi, Z.: Add-on Sacubitril/Valsartan Therapy Induces Left Ventricular Remodeling in Non-responders to Cardiac Resynchronization Therapy to a Similar Extent as in Heart Failure Patients Without Resynchronization.
   Cardiol Ther. 13 (1), 149-161, 2024.
   DOI: http://dx.doi.org/10.1007/s40119-023-00346-1
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List of other publications

3. Tóth, A. Z., Nagy, L., **Szabó, K. M.**, Rácz, V., Kiss, A., Sándorfi, G., Borbély, A., Nagy, T. L., Csanádi, Z.: Early occurrence of heart failure hospitalization or ventricular arrhythmia re-define the long-term prognosis after CRT.
   ESC Heart Failure. 12 (4), 2780-2790, 2025.
   DOI: http://dx.doi.org/10.1002/ehf2.15274
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4. **Szabó, K. M.**, Tóth, A. Z., Borbély, A., Csanádi, Z., Nagy, L.: A kardiális reszinkronizációs kezelésre adott válasz újraértelmezése és a terápiás hatékonyság javításának lehetősége.
   Cardiol. Hung. 54 (3), 227-233, 2024.
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5. **Szabó, K. M.**, Clemens, M.: Hiszed, vagy nem?
   Cardiol. Hung. 54 (2), 135, 150, 2024.
   DOI: http://dx.doi.org/10.26430/CHUNGARICA.2024.54.2.135

6. Nagy, L., Tóth, A. Z., Kiss, A., **Szabó, K. M.**, Nagy, L. T., Csanádi, Z., Sándorfi, G.:
   Pacemakerkezelés fiziológiás ingerületvezetőrendszer-ingerléssel: múlt, jelen és jövő.
   Cardiol. Hung. 53 (3), 225-233, 2023.
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