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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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Содержание:

EFFICACY OF PERINDOPRIL IN PATIENTS WITH HEART FAILURE AND REDUCED EJECTION FRACTION (HFREF)

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Abstract.

Background / Introduction

Heart failure with reduced ejection fraction (HFrEF) represents a major global health burden, accounting for approximately half of all heart failure cases and characterized by high mortality, frequent hospitalizations, and progressive cardiac remodeling. Angiotensin-converting enzyme (ACE) inhibitors constitute a foundational cornerstone in the therapeutic management of HFrEF. Perindopril is a long-acting ACE inhibitor with a highly favorable safety profile; however, robust clinical data evaluating its specific efficacy in HFrEF cohorts remain scarce.

Aims

To evaluate the therapeutic efficacy, reverse cardiac remodeling, and clinical outcomes of perindopril versus sacubitril/valsartan in patients with HFrEF in routine clinical practice.

Methods

This retrospective cohort study included 214 HFrEF patients (LVEF < 40%, mean age 64.8 ± 11.0 years) treated at Tbilisi Heart Center between 2018 and 2025. Patients received GDMT and were divided into two groups: Perindopril (n = 118) and Sacubitril/Valsartan (n = 96). Clinical, echocardiographic, and biochemical metrics were assessed at baseline (Visit 1), 2–3 weeks (Visit 2), and 3–6 months (Visit 3). Primary endpoints included changes in LVEF and NYHA functional class.

Results

- Both treatment strategies significantly improved LVEF, reduced left ventricular dimensions (LVEDD, LVESD), and decreased pulmonary artery systolic pressure (ANOVA $p < 0.01$), with major reverse remodeling occurring between Visits 1 and 2.
- LVEF increased from 34.3 ± 3.9% to 41.3 ± 7.4% in the perindopril group and from 30.8 ± 5.2% to 33.8 ± 8.1% in the sacubitril/valsartan group.
- In multivariable linear regression analysis, treatment group (B = -3.170, p = 0.004), baseline LVEF (B = 0.381, p = 0.005), and de novo heart failure (B = 2.966, p = 0.005) were independent predictors of follow-up LVEF.
- Both cohorts showed significant longitudinal optimization in NYHA functional class ($p < 0.001$). No significant changes in serum potassium or renal function were observed. One-year all-cause mortality did not differ significantly between groups (33.1% vs. 22.9%, p = 0.103).

Conclusion

Perindopril therapy is associated with significant clinical improvement, LVEF recovery, and positive reverse cardiac remodeling in patients with HFrEF. Both perindopril and sacubitril/valsartan demonstrate comparable efficacy in reducing cardiac dimensions and optimizing NYHA functional status. Furthermore, perindopril maintains a favorable safety profile with low nephrotoxicity, confirming its potential as an effective therapeutic option in HFrEF management.

Key words. Perindopril, heart failure, reduced ejection fraction (HFrEF).

Introduction.

Heart failure (HF) is a structural and/or functional disorder of the heart that results in an increase in intracardiac pressure and/or a decrease in cardiac capacity, which leads to inadequate blood supply to tissues during rest or physical activity [1]. HF is a growing global problem; it is the second most frequent among cardiovascular diseases and the first in terms of hospitalization. Properly selected drug treatment for patients is the cornerstone of the management of this nosology.

According to the classification, heart failure is distinguished by the ejection fraction:

- **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%).

Worldwide, the burden of heart failure has risen to about 23 million people, 50% of whom are patients with HFrEF [2].

Heart failure presenting with a reduced ejection fraction is characterized by frequent episodes of worsening heart failure and high mortality. The primary targets of treatment (clinical endpoints) are: reducing mortality, reducing hospitalization, and improving the quality of life. According to the current therapeutic standard, first-line medications and recommended [3] treatments [4,5] for HfrEF include: angiotensin-converting enzyme (ACE) inhibitors, sacubitril-valsartan, beta-blocker, spironolactone, SGLT2 inhibitors, and diuretics.

Perindopril is an ACE inhibitor, characterized by a long half-life and a relatively low incidence of side effects (e.g., dry cough). It has clinically proven efficacy across various cardiovascular nosology, as demonstrated in major clinical trials including ASCOT, EUROPA, PROGRESS, PREAMI, and ADVANCE.

Perindopril is currently widely used for the treatment of hypertension [6], but data on its use in patients with a reduced ejection fraction for the treatment of heart failure are scarce [7].

An analysis of existing data suggests its potential efficacy within this specific cohort as well; however, strict adherence to the tenets of evidence-based medicine dictates that targeted clinical trials remain imperative to definitively substantiate these findings.

The primary objective of our study is to evaluate the therapeutic efficacy of perindopril versus sacubitril-valsartan (Uperio) in the management of heart failure among patients presenting with a reduced ejection fraction.

The objective of this retrospective observational cohort study was to compare clinical, echocardiographic, and biochemical outcomes among patients with HFrEF treated with either perindopril or sacubitril/valsartan in routine clinical practice.

Materials and Methods.

The study cohort comprised 214 patients with heart failure and reduced ejection fraction (HFrEF), aged 23 to 89 years (mean age: 64.77 ± 11.03 years), who underwent treatment at the 'Tbilisi Heart Center' clinic in Tbilisi between 2018 and 2025. The sample included 35 female and 179 male patients.

A retrospective, observational, non-randomized cohort study design was applied. Patients with missing baseline or follow-up data for the primary endpoint were excluded from the corresponding analysis. No imputation methods were applied

Inclusion Criteria:

- Age 18 years and older
- Left ventricular ejection fraction (LVEF) < 40%
- Estimated glomerular filtration rate (eGFR) > 30 mL/min, Renal function was assessed using serum creatinine and eGFR calculated by the CKD-EPI equation
- Systolic blood pressure > 100 mmHg
- Serum potassium level < 5.2 mmol/L

Exclusion Criteria:

- Intolerance to ACE inhibitors or ARBs due to adverse effects, particularly a documented history of angioedema
- Symptomatic hypotension, or asymptomatic systolic blood pressure < 100 mmHg
- eGFR < 30 mL/min, or a dynamic decrease of < 35% between study visits
- Baseline serum potassium level > 5.2 mmol/L at enrollment, or > 5.4 mmol/L during subsequent follow-up visits
- Implantable cardioverter-defibrillator (ICD) placement within 3 months prior to the initial visit
- Peripartum or chemotherapy-induced cardiomyopathy
- Hemodynamically significant aortic valve stenosis
- Presence of any comorbid condition limiting life expectancy to less than 1 year.

Therapeutic Intervention: Background therapy included beta-blockers, mineralocorticoid receptor antagonists, SGLT2 inhibitors, loop diuretics, and other medications according to contemporary heart failure guidelines-GDMT.

The study population was allocated into two parallel cohorts: the first cohort (n = 118) received perindopril at titrated doses of 2.5 mg, 5 mg, or 10 mg daily, whereas the second cohort (n = 96) was administered sacubitril/valsartan (Uperio) at doses of 24/26 mg, 49/51 mg, or 97/103 mg twice daily. Dose escalation was performed individually during follow-up visits, considering blood pressure, renal function, serum potassium levels, and overall tolerability. The objective was to achieve the maximally tolerated dose for each patient whenever clinically feasible. Both groups concurrently received comprehensive standard care as outlined by current guidelines. Throughout the follow-up period, clinical evaluations were conducted at a minimum of three distinct time points: an early assessment at 2–3 weeks post-baseline, followed by subsequent visits at 3 and 6 months after the initiation of therapeutic intervention. One-year mortality was assessed using hospital records and available follow-up data.

The parameters evaluated encompassed the severity of heart failure according to the New York Heart Association (NYHA) functional classification, alongside comprehensive clinical, echocardiographic, and biochemical characteristics.

Primary Endpoint:

Change in left ventricular ejection fraction (LVEF) from baseline to final follow-up, change in NYHA functional class.

Secondary Endpoints:

Changes in cardiac dimensions, PASP, creatinine, potassium, pleural effusion, mitral regurgitation severity, and all-cause mortality.

The study protocol was approved by the ethics committee of David Aghmashenebeli University of Georgia.

Statistical Analysis:

Continuous variables were expressed as mean % standard deviation, while categorical variables were presented as frequencies and percentages. Significant differences for independent continuous variables were determined using Student's t-test, whereas comparisons across different treatment stages were evaluated using Analysis of Variance (ANOVA); post hoc analysis was subsequently performed using the Tukey HSD test. Categorical characteristics were compared between the study groups using Pearson's chi-square and Fisher's exact tests. For longitudinal comparisons across timelines, Kendall's W test and the Wilcoxon signed-rank test were applied, respectively. A p-value of < 0.05 was considered statistically significant. All statistical analyses were executed utilizing IBM SPSS Statistics software, version 23.

Results.

The baseline clinical characteristics of the study population are summarized in Table 1.

The majority of the study population was male; acute myocardial infarction (MI) was observed in 68 (31.78%) patients, prior MI in 96 (44.86%), and atrial fibrillation (AF) in 66 (30.84%). Among the documented comorbidities, chronic obstructive pulmonary disease (COPD) was prevalent in 13 (6.07%) patients, diabetes mellitus in 66 (30.84%), and chronic kidney disease CKD, in 42 (19.63%).

The corresponding distribution of patients according to NYHA classification is illustrated in Figure 1 (Figure 1).

Baseline patient characteristics were compared according to the assigned therapeutic intervention. Cohort I comprised patients treated with perindopril, whereas Cohort II included those who received sacubitril-valsartan (Uperio) (Table 2).

In the perindopril group was reliably higher compared to uperio: de novo heart failure - 55(46.61) vs 18(18.75), p<0.001; A/H - 97(82.20) vs 62(64.58), p=0.003 frequency. With other general characteristics, the groups did not differ reliably.

Table 3 presents the dynamics of patients' monitorizations, comparing the perindopril and uperio groups with each other according to the stage of treatment, as well as changes in patient characteristics within the groups.

Prior to the initiation of treatment, no statistically significant difference was observed between the groups regarding the

NYHA functional class of heart failure. Similarly, the groups did not differ significantly in terms of medical history (prior comorbidities) or baseline biochemical characteristics.

In the perindopril cohort, compared to the Uperio cohort, the frequency of grade 1 mitral regurgitation was significantly higher: 36 (30.51%) vs. 18 (18.75%), $p = 0.049$.

Furthermore, the perindopril group, compared to the Uperio cohort, demonstrated a significantly higher mean ejection fraction, Respectively: 34.31 +3.90% vs. 30.79 +5.23%, $p < 0.001$. Conversely, significantly smaller dimensions were noted in the perindopril group compared to the Uperio cohort, for the following parameters: LV end-diastolic size (5.86 +0.52 vs. 6.21 +.52 cm; $p < 0.001$), LV end-systolic size (4.80 +0.53 vs. 5.15 + 0.61 cm; $p < 0.001$), right ventricular size (3.30 +0.28 vs. 3.43 +0.33 cm; $p = 0.003$), left atrial size (4.32 +0.36 vs. 4.58 + 0.37 cm; $p < 0.001$), and right atrial size 3 (4.13 +0.36 vs. 4.35 +0.40 cm; $p < 0.001$).

Regarding biochemical characteristics, at the third stage of treatment, the mean creatinine value was significantly lower in the perindopril group compared to the Uperio group. Among the echocardiographic parameters, the perindopril group maintained a significantly higher ejection fraction across all stages compared to Uperio, while concurrently exhibiting significantly lower values for LV end-diastolic size, LV end-systolic size, right ventricular size, left atrial size, and right atrial size.

Longitudinal observation over time (Repeated Measures ANOVA) revealed that neither the perindopril nor the Uperio group showed any statistically significant changes during the treatment period regarding mean biochemical and anthropometric metrics (including creatinine, potassium, body weight, and BMI). Among the echocardiographic data, left atrial size did not change significantly in either group, and right atrial size showed no significant changes specifically within the Uperio group. Table 4 presents the results of the post hoc analysis.

Post hoc analyses were conducted separately within cohorts.

The post hoc analysis revealed that within the perindopril cohort, the mean ejection fraction increased significantly from visit 1 to visit 2, as well as from visit 1 to visit 3. Additionally, from visit 1 to visit 2, a statistically significant decrease was observed in the mean values of LV end-diastolic size, LV end-systolic size, right ventricular size, right atrial size, and pulmonary artery pressure (PASP), as well as from visit 1 to visit 3; however, these parameters showed no significant changes from visit 2 to visit 3. A significant decrease in right atrial size was observed only between the first and second stages of the study.

Within the Uperio cohort, the mean ejection fraction demonstrated a significant increase both from visit 1 to visit 2 and from visit 1 to visit 3 and statistically unchanged from visit 2 to visit 3. Furthermore, a statistically significant reduction occurred from visit 1 to visit 2 in the mean parameters of LV end-diastolic size, LV end-systolic size, right ventricular size, and pulmonary artery pressure (PASP); nonetheless, these characteristics remained statistically unchanged from visit 2 to visit 3 and from visit 1 to visit 3.

As demonstrated, the primary clinical and structural changes in both groups occur predominantly between the first and second visits, whereas no statistically significant differences are observed from the second to the third visit.

Table 5 presents a comparison of clinical characteristics between the perindopril and Uperio groups at different stages, as well as within-group dynamics.

The incidence of pleural effusion did not differ significantly Between the perindopril and Uperio groups at any visit, and decreased significantly within groups.

No statistically significant difference was observed between the groups regarding the NYHA functional class at baseline.

Regarding the intra-group comparison across treatment stages, NYHA class IV was no longer observed in either group at the second visit (post-treatment); however, at the third visit, it was documented exclusively within Cohort II (the Uperio group). In the perindopril cohort, the frequency of NYHA class II significantly increased at the second stage ($p < 0.001$) and remained statistically unchanged between the second and third stages ($p = 1.000$). Correspondingly, the frequency of NYHA class III significantly decreased at the second stage ($p < 0.001$) and showed no significant change at stage III ($p = 1.000$). In the Uperio cohort, the frequency of NYHA class II significantly increased at the second stage ($p = 0.004$) and did not change significantly between the second and third stages ($p = 0.223$). Concurrently, the frequency of NYHA class III significantly decreased at the second stage ($p < 0.001$) and remained statistically unchanged at stage III ($p = 0.690$). Consequently, both the perindopril and Uperio groups demonstrated a statistically significant longitudinal improvement according to the NYHA functional classification over time ($p < 0.001$), with no significant differences observed between the two therapeutic groups.

At baseline, the combined frequencies of mitral regurgitation (MR) grades 1, 2, and 3 were significantly higher in the perindopril cohort. At the second stage, however, the frequency of MR grade 2 was significantly higher in the Uperio cohort, whereas no statistically significant differences were detected between the groups at stage III.

Regarding the intra-group analysis across treatment timelines, the frequency of MR grade 1 in the perindopril cohort significantly increased at the second stage ($p = 0.004$) and remained statistically unchanged between the second and third stages ($p = 0.655$). Correspondingly, the frequency of MR grade 2 significantly decreased at the second stage ($p = 0.014$) and showed no significant change at stage III ($p = 0.655$). Since the frequency of MR grade 3 did not change significantly over time, further intra-group pairwise comparisons were not performed. Within the Uperio cohort, Kendall's W test did not yield a statistically significant difference; therefore, subsequent post hoc intra-group statistical analysis was not conducted.

Over the 1-year follow-up period, 61 (28.5%) cases of all-cause mortality were recorded. Among these, 39 (33.05%) occurred in Cohort I (the perindopril group) and 22 (22.92%) in Cohort II (the Uperio group) ($F = 2.68$, $p = 0.103$), indicating that the difference between the groups was not statistically significant.

To account for baseline differences between treatment groups, a multivariable linear regression analysis was performed with follow-up LVEF as the dependent variable. The model included

Table 1. *Baseline Patient Data.*

Factors	**n (%) or (Mean+SD)**
De novo heart failure - n (%)	73(34.11%)
Male - n (%)	179(83.64%)
Female - n (%)	35(16.36)
Age - years (Mean+SD)	64.77+11.03
Height - cm (Mean+SD)	173.76+7.97
Diabetes - n (%)	66(30.84%)
CKD - n (%)	42(19.63%)
A/H - n (%)	159(74.3%)
Acute M.I.- n (%)	68(31.78%)
Prior M.I.- n (%)	96(44.86%)
COPD- n (%)	13(6.07%)
AF - n (%)	66(30.84%)
M.I. - Myocardial Infarction, COPD - chronic obstructive pulmonary disease, AF - atrial fibrillation, CKD - chronic kidney disease,	

Table 2. *Baseline Distribution of Patient Characteristics Between Treatment Groups Prior to Intervention.*

	Perindopril, n=118	**Uperio, n= 96**	**F/t**	**p**
	N(%)	**N(%)**		
de novo heart failure	55(46.61)	18(18.75)	19.80	<0.001
Gender (male)	96(81.36)	83(86.46)	1	0.318
Diabetes mellitus	42(35.59)	24(25.00)	2.80	0.096
CKD	18(15.25)	24(25.00)	3.21	0.075
A/H	97(82.20)	62(64.58)	8.88	0.003
Acute M.I.	43(36.44)	25(26.04)	2.65	0.105
Prior M.I	49(41.53)	47(48.96)	1.18	0.279
COPD	5(4.24)	8(8.33)	1.55	0.214
AF	32(27.12)	34(35.42)	1.71	0.193
M.I. - Myocardial Infarction, COPD - chronic obstructive pulmonary disease, AF - atrial fibrillation, CKD - chronic kidney disease,				

Table 3. *Patient Characteristics Over Time During Treatment with Perindopril and Uperio.*

Factors			**Perindopril, N=118**		**Uperio, N=96**		**t**	**p**
			Mean	**SD**	**Mean**	**SD**		
Biochemical characteristics	Creatinine (μmol/L)	Visit 1	93.14	26.20	99.06	30.62	-1.50	0.136
		Visit 2	94.22	26.22	99.98	28.69	-1.52	0.131
		Visit 3	92.51	26.97	102.38	37.03	-2.25	0.025
	ANOVA (F, p)		F=0.13 p=0.882		F=0.57 p=0.564			
	Potassium(mmol/L)	Visit 1	4.07	0.39	4.12	0.43	-0.86	0.391
		Visit 2	4.11	0.36	4.20	0.38	-1.69	0.093
		Visit 3	4.11	0.38	4.14	0.35	-0.56	0.575
	ANOVA (F, p)		F=0.51 p=0.600		F=1.11 p=0.331			
Anthropometric characteristics	Weight(kg)	Visit 1	87.67	17.04	91.79	20.97	-1.55	0.122
		Visit 2	86.86	16.10	91.49	20.22	-1.82	0.070
		Visit 3	87.03	16.52	91.05	20.22	-1.57	0.118
	ANOVA (F, p)		F=0.08 p=0.923		F=0.03 p=0.969			
	BMI (kg/m$^{2)}$	Visit 1	29.03	5.31	30.24	6.12	-1.52	0.130
		Visit 2	28.75	5.07	30.16	5.94	-1.84	0.067
		Visit 3	28.83	5.08	29.95	5.87	-1.47	0.143
	ANOVA (F, p)		F=0.10 0.907		F=0.06 0.941			

Ultrasound data	Ejection Fraction (%)	Visit 1	34.31	3.90	30.79	5.23	5.64	<0.001
		Visit 2	40.03	6.32	34.30	6.98	6.23	<0.001
		Visit 3	41.31	7.39	33.79	8.13	7.00	<0.001
	ANOVA (F, p)		F=43.32 p<0.001		F=7.29 p<0.001			
	L/V diastolic size(cm)	Visit 1	5.86	0.52	6.21	0.52	-4.86	<0.001
		Visit 2	5.69	0.53	5.98	0.59	-3.81	<0.001
		Visit 3	5.61	0.56	6.02	0.64	-5.04	<0.001
	ANOVA (F, p)		F=6.82 p=0.001		F=3.98 p=0.020			
	L/V systolic size(cm)	Visit 1	4.80	0.53	5.15	0.61	-4.50	<0.001
		Visit 2	4.53	0.59	4.89	0.68	-4.10	<0.001
		Visit 3	4.41	0.67	4.93	0.72	-5.39	<0.001
	ANOVA (F, p)		F=13.14 p<0.001		F=4.12 p=0.017			
	Right ventricular size(cm)	Visit 1	3.30	0.28	3.43	0.33	-2.99	0.003
		Visit 2	3.20	0.23	3.28	0.33	-2.31	0.022
		Visit 3	3.22	0.28	3.36	0.41	-3.07	0.002
	ANOVA (F, p)		F=5.54 p=0.004		F=3.91 p=0.021			
	Left atrium size(cm)	Visit 1	4.32	0.36	4.58	0.37	-5.04	<0.001
		Visit 2	4.24	0.37	4.49	0.40	-4.70	<0.001
		Visit 3	4.29	0.35	4.55	0.51	-4.38	<0.001
	ANOVA (F, p)		F=1.54 p=0.215		F=1.01 p=0.364			
	Right atrial size(cm)	Visit 1	4.13	0.36	4.35	0.40	-4.25	<0.001
		Visit 2	4.01	0.31	4.21	0.44	-3.93	<0.001
		Visit 3	4.06	0.39	4.27	0.58	-3.27	0.001
	ANOVA (F, p)		F=3.65 p=0.027		F=2.15 p=0.119			
	PASP	Visit 1	33.89	12.10	34.96	10.89	-0.68	0.498
		Visit 2	27.76	10.22	29.27	10.91	-1.04	0.302
		Visit 3	29.74	11.45	32.97	12.32	-1.97	0.050
	ANOVA (F, p)		F=9.06 p<0.001		F=6.16 p=0.002			

Table 4. *Comparison of Quantitative Data by Visits to Groups.*

	Perindopril					**Uperio**				
Dependent Variable	**(I)**	**(J)**	**Mean Difference (I-J)**	**Std. Error**	**p**	**(I)**	**(J)**	**Mean Difference (I-J)**	**Std. Error**	**p**
Ejection fraction (%)	1	2	-5.72*	0.79	<0.001	1	2	-3.51*	0.99	0.001
		3	-6.32*	0.79	<0.001		3	-3.00*	0.99	0.008
	2	1	5.72*	0.79	<0.001	2	1	3.512*	0.99	0.001
		3	-1.27	0.79	0.245		3	0.51	0.99	0.865
	3	1	6.92*	0.79	<0.001	3	1	3.00*	0.99	0.008
		2	1.27	0.79	0.245		2	-0.51	0.99	0.865
L/V Diastolic size(cm)	1	2	0.17*	0.07	0.048	1	2	0.22*	0.08	0.023
		3	0.25*	0.07	0.001		3	0.18	0.08	0.077
	2	1	-.17*	0.07	0.048	2	1	-0.22*	0.08	0.023
		3	0.09	0.07	0.416		3	-0.04	0.08	0.886
	3	1	-0.25*	0.07	0.001	3	1	-0.18	0.08	0.077
		2	-0.09	0.07	0.416		2	0.04	0.08	0.886
L/V systolic size(cm)	1	2	0.27*	0.08	0.002	1	2	0.26*	0.10	0.023
		3	0.39*	0.08	<0.001		3	0.22	0.10	0.061
	2	1	-0.27*	0.08	0.002	2	1	-0.26*	0.10	0.023
		3	0.12	0.08	0.264		3	-0.04	0.10	0.926
	3	1	-0.39*	0.08	<0.001	3	1	-0.22	0.10	0.061
		2	-0.12	0.08	0.264		2	0.04	0.10	0.926

Right ventricular size	1	2	0.11*	0.03	0.005	1	2	0.15*	0.05	0.015
		3	0.09*	0.03	0.031		3	0.07	0.05	0.416
	2	1	-0.11*	0.03	0.005	2	1	-0.15*	0.05	0.015
		3	-0.02	0.03	0.825		3	-0.08	0.05	0.280
	3	1	-0.09*	0.03	0.031	3	1	-0.07	0.05	0.416
		2	0.02	0.03	0.055		2	0.08	0.05	0.280
Right atrial size	1	2	0.133*	0.05	0.021	-	-	-	-	-
		3	0.07	0.05	0.240	-	-	-	-	-
	2	1	-0.12*	0.05	0.021	-	-	-	-	-
		3	-0.05	0.05	0.536	-	-	-	-	-
	3	1	-0.07	0.05	0.240	-	-	-	-	-
		2	0.05	0.05	0.536	-	-	-	-	-
PASP	1	2	6.13*	1.47	<0.001	1	2	5.69*	1.64	0.002
		3	4.15*	1.47	0.014		3	1.99	1.64	0.448
	2	1	-6.13*	1.47	<0.001	2	1	-5.69*	1.64	0.002
		3	-1.97	1.47	0.372		3	-3.70	1.64	0.065
	3	1	-4.15*	1.47	0.014	3	1	-1.99	1.64	0.448
		2	1.97	1.47	0.372		2	3.70	1.64	0.065

Table 5. *Comparison of clinical characteristics between the perindopril and Uperio groups.*

Factors		**Perindopril, N=118**		**Uperio, N= 96**		**F**	**p**
		n	**%**	**n**	**%**		
Pleural Effusion	Visit 1	33	27.97	26	27.08	0.02	0.886
	Visit 2	15	12.71	11	11.46	0.08	0.781
	Visit 3	14	11.86	12	12.50	0.02	0.888
Kendall's W Test		**c^2**=15.2 p<0.001		**c^2**=11.4 p=0.003			
NYHA2	Visit 1	26	22.03	26	27.08	0.73	0.394
	Visit 2	80	67.80	68	70.83	0.23	0.634
	Visit 3	79	66.95	64	66.67	0.00	0.965
Kendall's W Test		**c^2=75.3**, p<0.001		**c^2**=54.6 p<0.001			
NYHA3	Visit 1	92	77.97	68	70.83	1.42	0.234
	Visit 2	38	32.20	28	29.17	0.23	0.634
	Visit 3	39	33.05	31	32.29	0.01	0.907
Kendall's W Test		**c^2=75.3**, p<0.001		**c^2=48.0**, p<0.001		-	-
NYHA4	Visit 1	0	0.00	2	2.08	2.49	0.116
	Visit 2	0	0.00	0	0.00	-	-
	Visit 3	0	0.00	1	1.04	1.23	0.269
Kendall's W Test			-		-		
MR grade 1	Visit 1	36	30.51	18	18.75	3.91	0.049
	Visit 2	52	44.07	24	25.00	8.67	0.004
	Visit 3	50	42.37	27	28.13	4.72	0.031
Kendall's W Test		**c^2**=9.1 p=0.010		**c^2**=4.06 p=0.131			
MR grade 2	Visit 1	78	66.10	72	75.00	2.00	0.159
	Visit 2	63	53.39	68	70.83	6.94	0.009
	Visit 3	65	55.08	61	63.54	1.56	0.213
Kendall's W Test		**c^2**=7.8 p=0.200		**c^2**=4.65 p=0.098			
MR grade 3	Visit 1	4	3.39	6	6.25	0.97	0.326
	Visit 2	3	2.54	4	4.17	0.44	0.509
	Visit 3	3	2.54	7	7.29	2.69	0.103
Kendall's W Test		**c^2=0.333,** p=0.846		**c^2**=1.56, p=0.459		-	-

Table 6. *To account for baseline differences between treatment groups, a multivariable linear regression analysis was performed with follow-up LVEF as the dependent variable.*

Model		Unstandardized Coefficients		Standardized Coefficients	t	p
		B	Std. Error	Beta		
1	(Constant)	55.307	11.466		4.824	<0.001
	de novo HF	2.966	1.038	0.164	2.856	0.005
	Gender (male)	.355	1.333	0.015	0.266	0.790
	age	-.057	.045	-0.073	-1.246	0.214
	A/H	.119	1.117	0.006	0.106	0.915
	AF	-1.227	1.131	-0.066	-1.085	0.279
	Uperio	-3.170	1.090	-0.184	-2.908	0.004
	NYHA1	1.426	1.083	0.074	1.317	0.189
	Ejection fraction (%) - 1	0.381	0.135	0.216	2.828	0.005
	L/V Diastolic size(cm)-1	-2.915	2.189	-0.186	-1.332	0.185
	L/V systolic size(cm) - 1	-2.354	2.188	-0.163	-1.076	0.283
	Right ventricular size - 1	2.173	2.278	0.078	0.954	0.341
	Left atrial size - 1	0.706	1.950	0.032	0.362	0.718
	Right atrial size - 1	-2.583	2.257	-0.118	-1.144	0.254

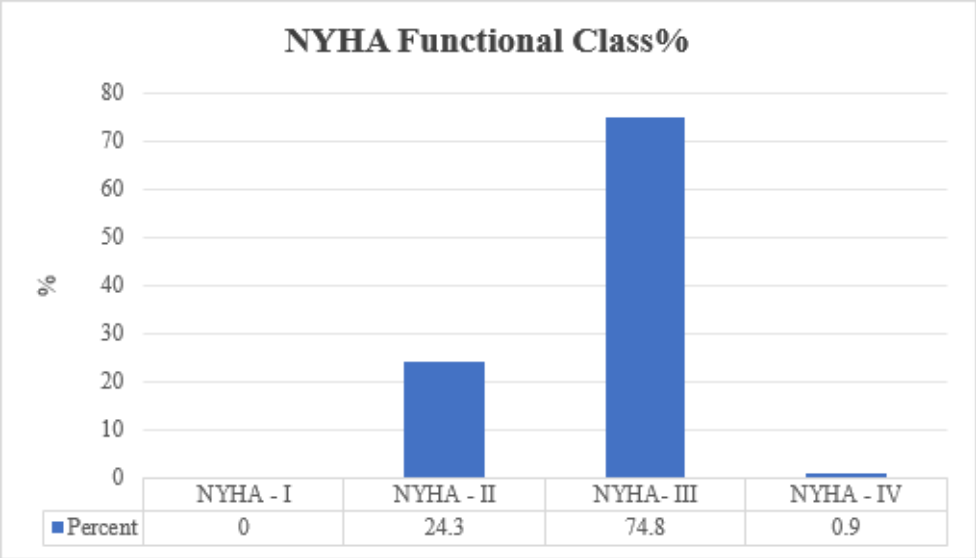

Figure 1. *The highest frequency among patients was NYHA-III class, NYHA-1 was not observed.*

treatment group, age, sex, de novo heart failure, arterial hypertension, atrial fibrillation, NYHA class, baseline LVEF, and baseline echocardiographic parameters (Table 6).

Dependent Variable: Ejection fraction (%) 3.

The overall regression model was statistically significant ($F(13,200)=11.523$, $p<0.001$), explaining 42.8% of the variance in follow-up LVEF ($R^2=0.428$; adjusted $R^2=0.391$).

After adjustment for baseline covariates, treatment group remained independently associated with follow-up LVEF. Patients receiving sacubitril/valsartan demonstrated a mean follow-up LVEF that was 3.17 percentage points lower than that observed in the perindopril group (B=-3.170, p=0.004). Baseline LVEF (B=0.381, p=0.005) and de novo heart failure (B=2.966, p=0.005) were also independent predictors of follow-up LVEF.

Discussion.

The contemporary management concept of HFrEF is fundamentally based on the inhibition of neurohormonal activation, given that the chronic activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system drives progressive myocardial remodeling, hemodynamic destabilization, and increased mortality. Consequently, evaluating the real-world clinical efficacy of perindopril represents a matter of significant practical interest [8].

The present retrospective cohort study evaluated the therapeutic efficacy of perindopril versus sacubitril/valsartan in patients with heart failure and reduced ejection fraction (HFrEF) against the background of contemporary guideline-directed medical therapy (GDMT) [1]. Although ARNI-class drugs are recommended over ACE inhibitors in predominantly symptomatic HFrEF in ACC/AHA guidelines, ACE inhibitors remain a fundamental component of treatment. The results obtained demonstrated that both therapeutic strategies were associated with significant improvements in clinical, functional, and echocardiographic parameters; the perindopril cohort exhibited a tendency of more positive trajectory across several specific metrics. However, direct comparisons between

treatment groups should be interpreted cautiously because important baseline differences existed between the cohorts.

Sacubitril-valsartan is the first approved agent in the class of angiotensin receptor-neprilysin inhibitors (ARNIs). The medication is approved by the United States Food and Drug Administration (FDA) for the treatment of chronic heart failure with reduced ejection fraction in New York Heart Association classes II, III, or IV [9].

Studies demonstrate that at the 1-year follow-up, patients with HFrEF exhibit significant improvements in echocardiographic parameters, including left ventricular ejection fraction (LVEF), systolic pulmonary artery pressure (PAPsys), and cardiac valvular regurgitation [10].

Meta-analysis confirms that sacubitril/valsartan significantly reduces the risk of all-cause and cardiovascular mortality in heart failure patients compared to conventional ACE inhibitors or ARBs. However, the therapeutic benefit is accompanied by a substantially higher incidence of symptomatic and worsening hypotension. Aside from hypotension, sacubitril/valsartan demonstrates a favorable safety profile, showing a lower risk of renal impairment, hyperkalemia, and cough than standard therapy. The study also highlights that the occurrence of these adverse events can be significantly influenced by baseline factors such as study duration, patient race, and specific underlying comorbidities. Ultimately, the authors conclude that while sacubitril/valsartan is highly effective, clinicians must carefully monitor blood pressure and individual patient profiles to optimize safety and treatment adherence [11].

There is a divergence of opinion regarding the impact on renal function; according to Barboza JJ et al., in adults with heart failure, sacubitril/valsartan likely reduced the doubling of serum creatinine compared to ACE inhibitors or ARBs but may have little to no effect on hyperkalemia [12]. In conclusion, sacubitril/valsartan has shown a protective effect on the kidneys, effectively reducing the risk of kidney deterioration [13]. The PARADIGM-HF trial demonstrated that sacubitril/valsartan may induce a minor increase in serum creatinine levels; however, this elevation is frequently not clinically significant [14]. According to our findings, no statistically significant differences in serum creatinine levels were observed between the groups at the baseline and intermediate stages (visits 1 and 2, $p > 0.05$). However, at the final evaluation stage, a statistically significantly higher creatinine level was recorded in the Uperio group ($p = 0.025$). Regarding serum potassium levels, no statistically significant differences were detected either between the groups or across the follow-up timelines ($p > 0.05$). This indicates that both therapeutic regimens are relatively safe from a renal function perspective, although the minor elevation of creatinine within the Uperio cohort aligns with existing literature. Furthermore, no significant differences in body weight or BMI were observed between the groups ($p > 0.05$) or within intra-group dynamics over time (ANOVA, $p > 0.05$).

In contrast, profound changes were identified among the echocardiographic parameters. One of the primary findings of our study was a statistically significant improvement in left ventricular ejection fraction (LVEF) within both treatment arms. Specifically, LVEF increased from 34.31 ± 3.90% to 41.31 ± 7.39% in the perindopril cohort, and from 30.79 ± 5.23% to 33.79 ± 8.13% in the sacubitril/valsartan cohort. Post hoc analysis further revealed that the most substantial improvement occurred predominantly between the first and second clinical visits, which is highly consistent with the established effects of early GDMT titration documented in contemporary HFrEF trials [15], while changes were relatively stable in the subsequent period. This observed trajectory aligns with the contemporary concept of HFrEF management and the well-documented phenomenon of reverse remodeling according to which the early initiation of GDMT exerts its most substantial hemodynamic and anti-remodeling effects during the initial months of treatment [2].

Intriguingly, despite the established evidentiary superiority of sacubitril/valsartan demonstrated in the landmark PARADIGM-HF and PROVE-HF trials [16], the perindopril cohort showed a tendency toward greater improvement in several echocardiographic parameters. Given the baseline differences between groups and the non-randomized study design, these findings should be considered hypothesis-generating rather than conclusive. Patients in the sacubitril/valsartan arm presented with inherently more severe baseline structural impairment, characterized by a lower baseline LVEF, larger left ventricular end-diastolic and end-systolic dimensions, as well as greater atrial and right ventricular volumes. Consequently, the study cohorts were not entirely homogeneous, suggesting a selection bias where clinically more advanced or high-risk patients were preferentially allocated to the ARNI group—a confounding trend that accurately reflects real-world clinical practice. Furthermore, it is crucial to highlight that the perindopril cohort comprised a substantially higher proportion of de novo heart failure patients compared to the sacubitril/valsartan group (46.61% vs. 18.75%, $p < 0.001$). In clinical practice, treatment-naive patients routinely exhibit a more dramatic initial myocardial response and pronounced functional recovery upon the introduction of guideline-directed medical therapy (GDMT). This systemic baseline disparity provides a highly plausible pathophysiological explanation for the more prominent early increase in LVEF (+5.72%) observed within our perindopril arm, rather than indicating a superior molecular efficacy of the ACE inhibitor over the Uperio regimen.

Crucially, the clinical efficacy of perindopril in the acute phase of myocardial infarction and ischemic heart disease has been extensively validated in landmark clinical trials, most notably the EUROPA and PREAMI studies, which demonstrated substantial reductions in cardiovascular mortality and recurrent ischemic events through potent neurohormonal inhibition and endothelial protection. Our findings are generally consistent with previous studies demonstrating the beneficial effects of perindopril in patients with cardiovascular disease. The therapeutic benefit of perindopril remains remarkably robust even within the high-risk sub-population of patients presenting with reduced ejection fraction (HFrEF) of ischemic etiology. In this vulnerable cohort, guideline-directed medical therapy with perindopril successfully driven significant positive reverse remodeling and dynamic functional recovery, thereby confirming that its secondary preventive and anti-remodeling properties are fully preserved in the presence of advanced systolic dysfunction.

Notably, both therapeutic strategies were associated with

definitive signs of reverse remodeling [17]. In the perindopril cohort, both left ventricular end-diastolic and end-systolic dimensions were significantly reduced, indicating a favorable shift in myocardial structural remodeling. A similar trajectory was observed within the sacubitril/valsartan cohort, albeit less pronounced. It is well established that ACE inhibitors facilitate afterload reduction, inhibit the deleterious effects of angiotensin II, and attenuate the progression of myocardial fibrosis [18]. Which ultimately leads to the long-term improvement of left ventricular function. These pathophysiological mechanisms are particularly critical in HFrEF of ischemic etiology, which was present in a significant proportion of our study cohort.

A longitudinal improvement in left ventricular ejection fraction (LVEF) was observed over time in both groups (ANOVA $p < 0.001$); however, LVEF remained significantly higher in the perindopril cohort across all evaluation stages ($p < 0.001$), a finding that may be attributed to their superior baseline values.

In the PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for HF) study, after 12 months of therapy with sacubitril/valsartan, the median LVEF increased from 28.2% to 37.8% (difference: 9.4%; 95% CI: 8.8%–9.9%; $p < 0.001$) [17].

In our study, during perindopril treatment, the mean left ventricular ejection fraction (LVEF) at the second stage increased by 5.72% compared to the baseline ($p < 0.001$), whereas a 3.51% increase was recorded in the Uperio group ($p = 0.001$). Between the second and third stages, LVEF further increased by 1.27% in the perindopril cohort ($p = 0.245$), while it decreased by 0.51% in the Uperio cohort ($p = 0.865$). Notably, the longitudinal changes between stages 2 and 3 did not reach statistical significance in either group. Left ventricular dimensions—both end-diastolic and end-systolic—were significantly smaller in the perindopril cohort across all evaluation stages ($p < 0.001$).

Similarly, atrial and right ventricular dimensions were consistently smaller in the perindopril group at all timelines ($p < 0.001$), with the intra-group changes demonstrating partial statistical significance. The larger cardiac dimensions observed in the ARNI cohort likely reflect a more severe baseline clinical status. Regarding pulmonary artery systolic pressure, no statistically significant differences were detected between the treatment arms ($p > 0.05$); however, a statistically significant longitudinal improvement was observed in both groups over time (ANOVA $p < 0.01$). This indicates that both therapeutic strategies are equally effective in mitigating pulmonary hypertension. Conversely, the improvement in mitral regurgitation severity was significantly more pronounced in the perindopril cohort. This finding should be interpreted cautiously because baseline differences between treatment groups may have influenced the observed results.

An important observation of the present study is that the clinical and echocardiographic outcomes achieved with perindopril were generally comparable to those observed with sacubitril/valsartan, a treatment supported by extensive evidence from large-scale randomized trials and currently recommended as a foundational therapy for HFrEF. Although this study was not designed to assess superiority or non-inferiority between treatment strategies, several echocardiographic parameters showed a numerically more favorable direction of change in the perindopril cohort during follow-up. Given the non-randomized design and baseline differences between groups, these findings should be interpreted with caution and considered hypothesis-generating, warranting further evaluation in prospective randomized studies.

Consequently, both pharmacological agents demonstrate robust clinical efficacy in the management of chronic heart failure. This therapeutic response is characterized by an increase in LVEF, a reduction in cardiac chamber dimensions, and a decrease in pulmonary artery pressure. Furthermore, the analysis of NYHA functional class revealed a statistically significant chronological improvement in both the perindopril and Uperio groups ($p < 0.001$), primarily driven by the favorable shifting of patients from NYHA class III to class II. No statistically significant differences were observed between the cohorts ($p > 0.05$), underscores the comparable efficacy of both regimens regarding symptomatic control. Both outcomes closely align with contemporary clinical guidelines, which establish that both ACE inhibitors and ARNI class agents effectively optimize the functional status of patients living with heart failure [3].

Study Limitations.

When interpreting these outcomes, it is imperative to account for baseline clinical discrepancies, as the sacubitril/valsartan arm inherently comprised patients with more advanced structural impairment and severe baseline status.

The non-randomized, observational design of the study.

A single-center study.

Conclusion.

- Perindopril was associated with significant clinical and echocardiographic improvement in patients with HFrEF within this observational cohort.
- Guideline-directed medical therapy with perindopril is associated with a statistically significant longitudinal improvement in left ventricular ejection fraction (LVEF), a reduction in both left ventricular end-diastolic and end-systolic dimensions, a decrease in pulmonary artery systolic pressure, and a substantial optimization of clinical status according to the NYHA functional classification.
- Both therapeutic strategies—perindopril and sacubitril/valsartan—exhibit definitive signs of reverse cardiac remodeling and contribute to a meaningful reduction in symptomatic disease burden.
- Within this study cohort, the perindopril group demonstrated a more pronounced improvement across several key echocardiographic parameters; however, when interpreting these outcomes, it is imperative to account for baseline clinical discrepancies, as the sacubitril/valsartan arm inherently comprised patients with more advanced structural impairment and severe baseline status.
- Perindopril maintains a highly favorable safety and tolerability profile, demonstrated by the absence of any clinically significant elevations in serum potassium or acute deteriorations of renal function throughout the treatment course.
- No statistically significant difference was detected between

the two groups regarding 1-year all-cause mortality, an outcome that may be fundamentally attributed to the limited sample size and the non-randomized, observational design of the study.

Conflict of Interest.

The authors declare no conflict of interest.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, et al. 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2023;44:3627-39.
2. Murphy SP, Ibrahim NE, Januzzi Jr JL. Heart failure with reduced ejection fraction: a review. Jama. 2020;324:488-504.
3. Maddox TM, Januzzi Jr JL, Allen LA, et al. 2024 ACC expert consensus decision pathway for treatment of heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. Journal of the American College of Cardiology. 2024;83:1444-88.
4. Writing Committee, Hollenberg SM, Stevenson LW, et al. 2024 ACC expert consensus decision pathway on clinical assessment, management, and trajectory of patients hospitalized with heart failure focused update: a report of the American College of Cardiology Solution Set Oversight Committee. Journal of the American College of Cardiology. 2024;84:1241-67.
5. Kozhevnikova MV, Emelianov AV, Zheleznykh EA, et al. Impact of Digital Remote Monitoring on the Optimization of Guideline-Directed Medical Therapy Titration in Heart Failure with Reduced Ejection Fraction. Cardiology. 2026;66:21-30.
6. Lababidi JM, Kabil MF, Azzazy HM. Perindopril: A comprehensive profile. Profiles of drug substances, excipients, and related methodology. 2026;51:211-52.
7. Joubert A. The development, validation, and evaluation of quantitative assays for determining adherence of heart failure patients to carvedilol, enalapril and perindopril. 2023.
8. Li Y, Li J, Fu MR, et al. Effectiveness of palliative care interventions on patient-reported outcomes and all-cause mortality in community-dwelling adults with heart failure: A systematic review and meta-analysis. International Journal of Nursing Studies. 2024;160:104887.
9. Patel P, Nicolas D, Reed M. Sacubitril-Valsartan. InStatPearls. 2025.
10. Abumayyaleh M, Demmer J, Krack C, et al. Hemodynamic effects of sacubitril/valsartan in patients with reduced left ventricular ejection fraction over 24 months: a retrospective study. American Journal of Cardiovascular Drugs. 2022;22:535-44.
11. Huang Y, Zhang Y, Ma L, et al. Adverse events of sacubitril/valsartan: a meta-analysis of randomized controlled trials. Journal of Cardiovascular Pharmacology. 2021;78:202-10.
12. Barboza JJ, León-Figueroa DA, Pasupuleti V, et al. Effects of sacubitril/Valsartan on renal function in adults with heart failure: a systematic review and meta-analysis of randomised controlled trials. Heart, Lung and Circulation. 2025;34:753-63.
13. Zhang J, Lv J, Fu H, et al. Meta-analysis of the impact of sacubitril/valsartan and ARB drugs on renal function. Journal of Chinese Pharmaceutical Sciences. 2025;34.
14. Mogensen UM, Køber L, Kristensen SL, et al. The effects of sacubitril/valsartan on coronary outcomes in PARADIGM-HF. American Heart Journal. 2017;188:35-41.
15. Yun H.R, Singh M.K, Han S, et al. Biomarkers of Cardiac Metabolic Flexibility in Health, HFrEF and HFpEF. International Journal of Molecular Sciences. 2026;27:879.
16. Meral S. Heart failure in elderly. Geriatr Emergencies. 2022;51.
17. Januzzi Jr JL, Prescott MF, Butler J, et al. Association of change in N-terminal pro–B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. Jama. 2019;322:1085-95.
18. Malahfji M, Saeed M, Nguyen DT, et al. Cardiac remodeling and outcomes of patients with combined aortic and mitral regurgitation. Cardiovascular Imaging. 2026;19:180-93.