Research and Development

Effects of sacubitril/valsartan dose on sociodemographic and clinical predictor variables: an Irish cross-sectional study

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Abstract

Background: The syndrome of heart failure is a recognised epidemic affecting between 1% and 2% of adults in the developed world. Several landmark clinical trials have led to improvements in heart-failure management over the past two decades. Aims: To examine the association between sociodemographic and clinical variables and change in ejection fraction, and whether age affected improvement in ejection fraction, New York Heart Association classification and estimated glomerular filtration rate following higher doses of sacubitril/valsartan. Methods: In this cross-sectional Irish study, descriptive and inferential statistical analyses were used. Results: Post sacubitril/valsartan ejection fraction measurements were taken on 162 people, as well as 198 measures for both New York Heart Association classification and estimated glomerular filtration rate post sacubitril/valsartan. With a dose of 97 mg/103 mg, twice daily, patients had 7.70 (2.812-21.078) times higher odds of improvement in ejection fraction than those who received the lower dose of 24 mg/26 mg twice daily. Irrespective of drug dose administered, patients aged under 65 years have a greater improvement in ejection fraction, relative to those aged over 65 years. Patients with myocardial infarction history had lower odds of ejection-fraction improvement than those with no myocardial infarction history. There was no association between age and improvement in New York Heart Association or estimated glomerular filtration rate. Conclusion: Sacubitril/valsartan is effective in improving ejection fraction. This improvement is greater among patients under 65 years of age. Higher dosages lead to higher odds of improvement, when adjusted for age and history of myocardial infarction.

Key words

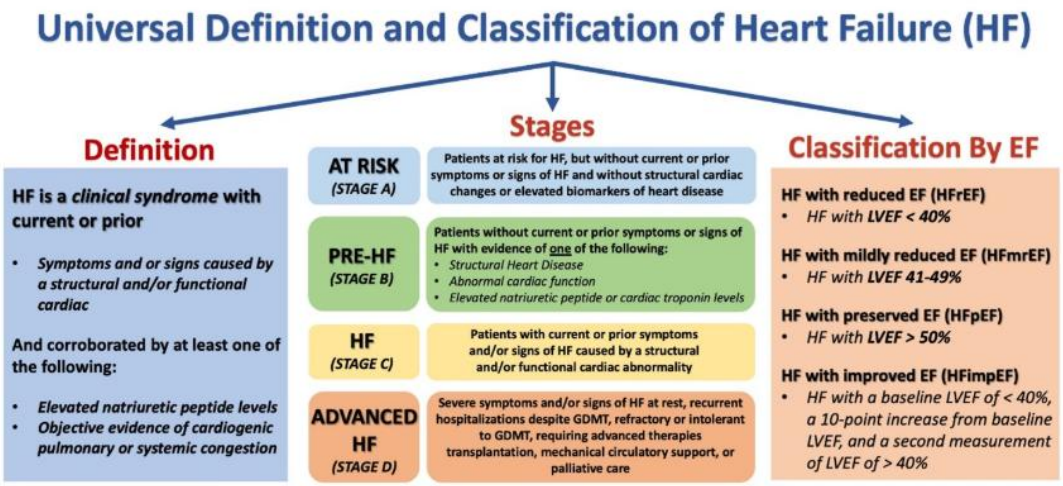
Ejection fraction, Glomerular filtration rate, Heart failure, New York Heart Association classification, Sacubitril/valsartan

Background

Heart failure is a chronic clinical syndrome. It is most often caused by a structural and/or functional cardiac abnormality, and is associated with elevated natriuretic peptide levels and/or evidence of pulmonary or systemic congestion (Savarese et al, 2023; Beghini et al, 2025). While the incidence of heart failure has declined over the years, the prevalence is increasing as a result of improved survival rates following myocardial infarction, an increase

in comorbidities, an ageing population with increased longevity and improvements in heart-failure management (McDonagh et al, 2021; Beghini et al, 2025). The classification of heart failure is dependent on left-ventricular ejection fraction. It includes heart failure with reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), preserved ejection fraction (HFpEF) and heart failure with improved ejection fraction (HFimpEF) (Bozkurt et al, 2021; McDonagh et al, 2023; Savarese et al, 2023) (*Figure 1*).

Figure 1. Definition and classification of heart failure (Gibson et al, 2021).



The management of HFrEF has seen significant scientific breakthrough in recent decades, and the ability to alter the natural history of the disease is very promising (Straw et al, 2021). The European Society of Cardiology (ESC) (McDonagh et al, 2023) and the American College of Cardiology/American Heart Association (Heidenreich et al, 2022) endorse the four pillars of pharmacological treatment for those with HFrEF or HFmrEF. These are drugs that target the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors, angiotensin II type-1 receptor blockers, angiotensin receptor–neprilysin inhibitors, beta blockers and mineralocorticoid receptor antagonists. Additionally, the use of SGLT2 inhibitors, vericiguat, and procedural therapies such as transcatheter mitral valve repair, have all contributed incrementally to improved prognosis beyond foundational neurohormonal therapies (Straw et al, 2021; Volterrani et al, 2024). Diuretics are considered a Class I recommendation for fluid retention and symptom management in both HFmrEF and HFpEF (McDonagh et al, 2023).

A decade ago, the PARADIGM-HF trial (McMurray et al, 2014) hailed the beginning of a dramatic alteration in the pharmacological management of patients with HFrEF. This randomised placebo-controlled trial (n=8442) compared an angiotensin receptor–neprilysin inhibitor, sacubitril, and an angiotensin II type-1 receptor blocker, valsartan (given to the study group) with enalapril (given to the control group) in patients with heart failure and reduced ejection fraction. The primary outcome was cardiovascular-related death or hospitalisation for heart failure. The trial was stopped prematurely because of the observed reduction in the primary outcomes among the study group (McMurray et al, 2014). This drug combination has since been recommended by the ESC for patients with HFrEF, pending satisfactory blood pressure and renal function (McDonagh et al, 2023).

The ESC recommends a start dose of 49 mg/51 mg of sacubitril/valsartan twice daily, pending satisfactory blood pressure and renal function, with a target dose of 97 mg/103 mg twice daily to reduce the risk of hospitalisation and death in patients with HFrEF (McDonagh et al, 2023). However, many eligible patients do not receive guideline-directed medical therapy, and the use and prescription of angiotensin receptor–neprilysin inhibitors remains suboptimal (Straw et al, 2021; Volterrani et al, 2024). Clinicians in heart failure are conscious of the important role of angiotensin receptor–neprilysin inhibitors, as one of the four pillars of heart-failure management. In this study, the authors examined whether there was an association between predictor sociodemographic and clinical variables and ejection fraction, with higher administered doses of sacubitril/valsartan. As heart failure is more prevalent with advancing age, the authors also investigated whether age affected changes in ejection fraction, New York Heart Association (NYHA) classification and estimated glomerular filtration rate (eGFR) with these higher doses.

Methods

Design and procedures

The present study was a collaboration between an advanced nurse practitioner in heart failure, clinical nurse specialists, cardiologists and academics linked to a higher education institution in Ireland. Ethical approval was granted for the study from the research ethics committee at the higher education institution (Research Ethics Administration Management System Number 2008). The data were taken from a hospital that runs a heart-efficiency service, alternatively known in some places as a heart failure service. The data set was retrieved from the Health Service Executive database and contained demographic and clinical variables including ejection fraction and pre and post administration of sacubitril/valsartan. All those included in the analysis had an ejection fraction of ≤35% at baseline.

As the data were collected in the course of daily work, and they were being fully anonymised before analysis, there was no ethical requirement for individual patient consent at the site. The authors were interested in identifying if, and how, sociodemographic variables (such as age, gender and smoking status), and clinical variables (such as history of hypertension and myocardial infarction, and ejection fraction pre sacubitril/valsartan readings) affected ejection fraction readings post sacubitril/valsartan. The study also aimed to understand if, and how, age affected ejection fraction, NYHA classification, and eGFR readings on receipt of the higher doses of 49 mg/51 mg or 97 mg/103 mg of sacubitril/valsartan. Patients on the low dose in the current study were those with hypotension or renal failure. The dataset, which contained information on 199 patients, was proofed and cleaned before analysis was undertaken using statistical software (SPSS v. 27).

Sample-size calculation

The required sample size estimated using G-power to perform multiple linear regression using eight predictors to achieve a power of 0.9 and a significance of 0.05 was 104, assuming an effect size of 0.2 (small effect size). In the authors' estimation of the required sample for logistic regression from G-Power, they needed to choose one main predictor. They selected myocardial infarction as the main predictor in this case. The probability to make a positive difference in the post sacubitril/valsartan ejection fraction readings with myocardial infarction (that is Pr(Y=1|X=1)H1) was calculated to be 0.66, and the probability to make a

positive difference in the ejection fraction sacubitril/valsartan readings without myocardial infarction (that is Pr(Y=1|X=1)H0) was calculated to be 0.90 from the sample. The significance was kept at 0.05 and power was set at 0.9. X parm or the proportion of participants with myocardial infarction was 0.438. The estimated sample size came out to be 140. From an event-per-variable (EPV) perspective, the EPV in this case is 14.75, which is also acceptable (Peduzzi et al, 1996).

As this study focused on changes in the output variables of ejection fraction, NYHA classification and eGFR, only those cases that had pre sacubitril/valsartan and post-sacubitril/valsartan readings for the three parameters were considered in the analysis. These output variables were analysed against the predictor variables of age, sex, hypertension history, myocardial infarction history, dose of sacubitril/valsartan (24 mg/26 mg, 49 mg/51 mg, or 97 mg/103 mg), smoking status and ejection fraction pre sacubitril/valsartan.

Of the 199 cases in the study, 37 patients did not have a recorded ejection fraction post sacubitril/valsartan, and in one case, there were missing data for NYHA classification and eGFR post sacubitril/valsartan. Thus, these cases were excluded from the study. The final sample size was 162 for ejection fraction, and 198 for both NYHA classification and eGFR. Additionally, post-sacubitril/valsartan data on ejection fraction, NYHA classification and eGFR with higher sacubitril/valsartan dosages of 49 mg/51 mg or 97 mg/103 mg were available for 133 participants. Thus, the remaining patients' data were excluded from the part of the analysis that looked at the effect of age on these three parameters for patients who were given higher dosages.

Statistical analyses

Descriptives statistics for predictor and output variables are shown in *Tables 1 and 2* respectively. Improvement in ejection fraction was determined by the difference between ejection fraction post and pre sacubitril/valsartan. A positive difference was classified as an improvement, while a negative difference was classified as a deterioration, and a 0 difference was classified as no change. Improvement in NYHA classification was recorded in terms of movement in NYHA class post-sacubitril/valsartan administration. Movement from a higher to a lower NYHA classification was deemed an improvement and the opposite was classified as a deterioration. Both pre- and post-sacubitril/valsartan eGFR were classified as $\leq$60 ml/minute/1.73m^2 and >60 ml/minute/1.73m^2. A movement from the former to the latter class was classified as an improvement, while the opposite was classified as a deterioration.

Table 1. Descriptives of predictor variables

Variable	**Variable categories**	**Mean, standard deviation, *n*=199**	***n*, Percentage, *n*=199**
Sex	Male	/	146, 73.4
	Female	/	53, 26.6
Hypertension history	Yes	/	96, 48.2
	No	/	103, 51.8
Myocardial infarction	Yes	/	88, 44.4
	No	/	110. 55.6
Maximum dosage	24/26	/	41, 20.7
	49/51	/	23, 11.6

	97/103	/	134, 67.7
Smoking status	Yes	/	25, 12.6
	No	/	174, 87.4
Age	Less than 65 years	/	66, 33.2
	65+ years	/	133, 66.8
Ejection fraction pre Entresto	/	28.21, 6.44	/

/: not applicable

Table 2. Descriptives of the output variables

Variable	**Number of patients included**	**Variable categories**	**Mean, standard deviation**	***n*, Percentage**
Improvement in ejection fraction	162	/	9.28, 10.74	/
Improvement in ejection fraction categorised	162	Deteriorated/no change	/	33, 20.4
		Improved	/	129, 79.6
Improvement in NYHA classification	198	Deteriorated/no change	/	102, 51.5
		Improved	/	96, 48.5
Improvement in eGFR	198	Deteriorated/no change	/	188, 94.9
		Improved	/	10, 5.1

/: not applicable; NYHA: New York Heart Association; eGFR: estimated glomerular filtration rate.

Different bivariate analyses were carried out between the output and predictor variables depending on the nature of variables involved. Associations between output variables in continuous form and the categorical predictor variables were identified using the Kruskal-Wallis and Mann-Whitney *U* tests, depending on whether the predictor had three or two categories respectively. The Smirnov-Kolmogorov and Shapiro-Wilk tests confirmed that none of the continuous variables were normally distributed. Chi-square test was used to find associations between categorical variables and Pearson's correlation coefficient was used when both predictor and outcome variables were continuous in nature.

P-values of less than 0.05 were used to identify significant associations. Wherever the *P*-value for the association was found to be between 0.05 and 1.0, the association was considered to be 'approaching significance.' Predictor variables that had significant associations or had associations that were approaching significance with the dependent variables in the bivariate analysis were fed into multivariate-regression models. A multivariate-logistic-regression model (with improvement in ejection fraction in categorical form as the dependent/outcome variable) was used to check whether predictors with significant associations in the bivariate analysis led to an improvement in ejection fraction when adjusted for the other predictors, whereas the multivariate linear regression model (with improvement in ejection fraction in continuous form as the dependent/outcome variable) was used to quantify the improvement where an improvement in ejection fraction was found.

Results

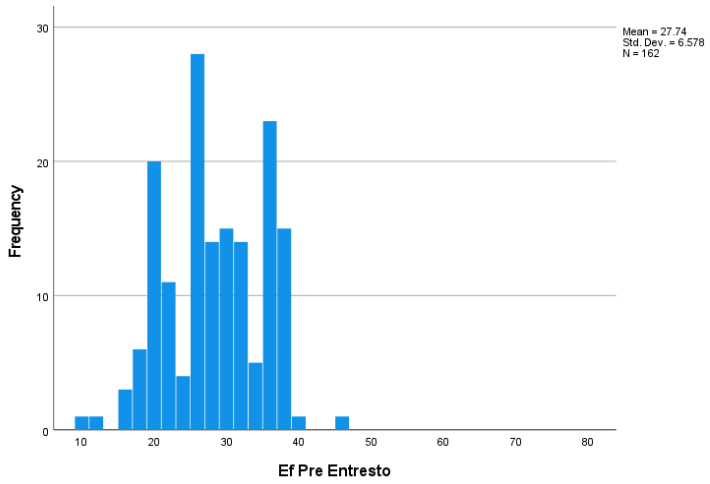
Demographic predictors and improvement in ejection fraction

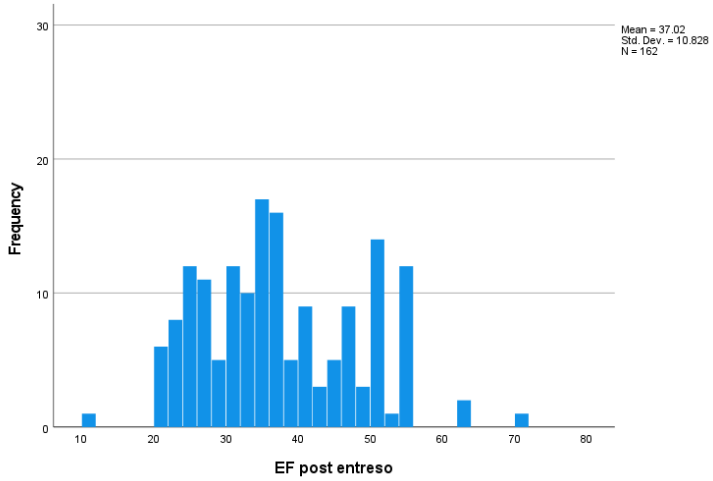
The Shapiro-Wilk test (*P*-value < 0.001) and Kolmogorov-Smirnov test (*P*-value < 0.001) confirmed that improvement in ejection fraction readings were not normally distributed, and the Wilcoxon signed rank test (*P*-value < 0.001) was used to establish that as paired observations, ejection fraction pre sacubitril/valsartan and ejection fraction post sacubitril/valsartan were statistically different. The authors noted 129 positive differences, 14 negative differences and 19 observations with no difference between the ejection fraction readings pre and post administration of sacubitril/valsartan.

As shown in *Figure 2*, ejection fraction post sacubitril/valsartan histogram had shifted to the right in the percentage-unit axis with respect to ejection fraction pre sacubitril/valsartan. The authors therefore inferred that ejection fractions post sacubitril/valsartan (mean=37.02, standard deviation (SD)=10.83) are, on average, higher than the ejection fractions pre sacubitril/valsartan (mean=27.74, SD=6.58). There was an average improvement in ejection fraction of 9.28% for the cohort (*n*=162). In the bivariate analysis, a history of myocardial infarction, maximum dosage, ejection fraction pre sacubitril/valsartan had significant associations with improvement in ejection fraction (in both continuous and categorical forms), whereas age had significant associations with improvement in ejection fraction (only in continuous form).

The authors did not find any evidence of significant associations of sex, history of hypertension and smoking status with improvement in ejection fraction (in either categorical or continuous form). Hence, these three variables were not included in either of the multivariate models.

Figure 2. Histogram of ejection fraction readings pre and post Entresto (sacubitril/valsartan)





Multivariate analysis

In the multivariate analysis, predictors that were found not to have an association with the output variable from the bivariate analysis were not fed into the respective models and have been represented with '/' in *Table 3*. In the logistic-regression model (with improvement in ejection fraction as a dependent variable in categorial form), relative to those with no history of myocardial infarction, patients with a history of myocardial infarction had 0.276 (0.113–0.672) times lower odds to have an improvement in ejection fraction, adjusting for maximum dosage and pre-sacubitril/valsartan readings. On the other hand, patients who were given a maximum dosage of 97 mg/103 mg had 7.70 (2.812 – 21.078) times higher odds of having an improvement in ejection fraction than those who received a dosage of 24 mg/26 mg. The Nagelkerke R-squared for the model was 0.28.

Table 3. Results of multivariate analyses on improvement in ejection fraction

Predictors	**Categories**	**Improvement in ejection fraction (in categorical form): odds (95% CI); *P*-value**	**Improvement in ejection fraction (in continuous form): estimate (95% CI); *P*-value**
MI	Yes	0.276 (0.113 – 0.672); 0.005	-6.475 (-9.423 – -3.526); <0.001
	No	Ref.	Ref.
Maximum dosage (mg)	97/103	7.698 (2.812 – 21.078); <0.001	6.170 (2.371 – 9.696); 0.001
	49/51	2.664 (0.710 – 9.991); 0.146	0.783 (-4.644 – 6.209); 0.777
	24/26	Ref.	Ref.
Age	65+ years	/	-2.315 (-5.416 – -0.797); 0.145
	Less than 65 years	/	Ref.
EF pre Entresto	NA	0.936 (0.874 – 1.004); 0.063	-0.407 (-0.628– -0.187); <0.001
Sex	Male	/	/
	Female	/	/

History of hypertension	Yes	/	/
	No	/	/
Smoking status	Yes	/	/
	No	/	/

/: variable did not have a significant association or the association was not ‘approaching significance’ in the bivariate analysis (predictor was not used in the final model); CI: confidence interval; MI: myocardial infarction; NA: not applicable.

Of note, from the multivariate-linear-regression model (with improvement in ejection fraction as a dependent variable in continuous form), the authors found that patients with a history of myocardial infarction had a lesser improvement in ejection fraction by 6.475 percentage units (-9.423 – -3.526), on average, than patients without myocardial infarction history when adjusting for age, maximum dosage, and ejection fraction pre sacubitril/valsartan. Patients who were given a maximum dosage of 97 mg/103 mg had a higher improvement in ejection fraction by 6.17 percentage units (2.371–9.969), on average, than those who were given a maximum dosage of 24 mg/26 mg. From the linear-regression model, a negative relationship was found between ejection fraction pre sacubitril/valsartan and improvement in ejection fraction post sacubitril/valsartan. As patients’ ejection fraction pre sacubitril/valsartan went up by 1 percentage unit, improvement in ejection fraction post sacubitril/valsartan decreased by 0.4 percentage units, controlling for the other predictors in the model. The Omnibus test for model coefficients yielded a *P*-value less than 0.001.

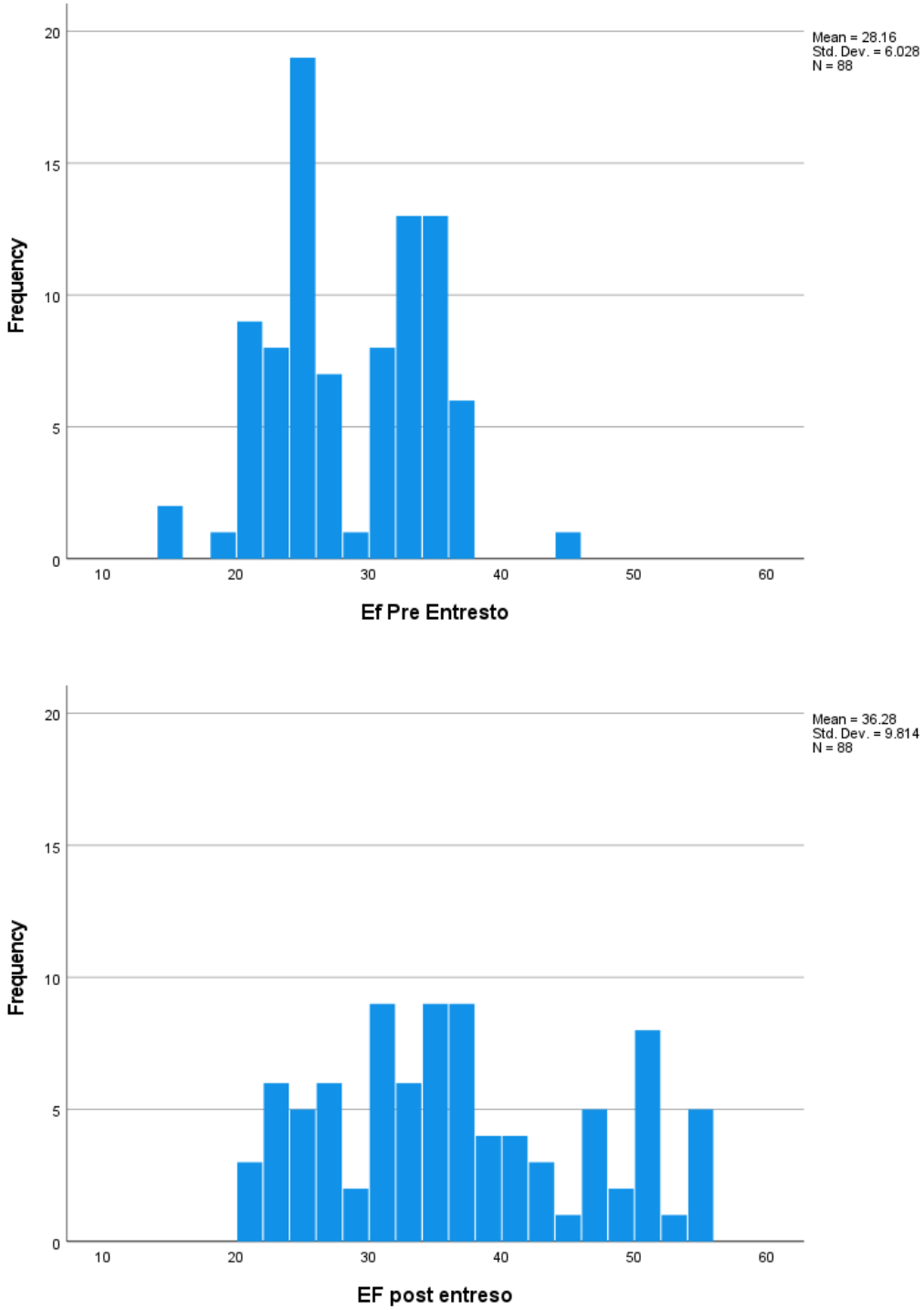
Effect of age at higher dose of sacubitril/valsartan

Of the 162 patients, 133 met the criteria for receiving the higher doses of sacubitril/valsartan (49 mg/51 mg or 97 mg/103 mg) and had ejection fraction recorded post sacubitril/valsartan. The mean age of this cohort was 68.88 years (SD=10.94). Of these, 45 patients were less than 65 years of age, and 88 patients were 65 years or above. The mean improvement in ejection fraction in this cohort of 133 patients was 10.36 percentage units. There were 114 patients in whom an improvement in ejection fraction was noted and for 19 others, there was a reported deterioration or no change in ejection fraction.

A negative correlation (Pearson’s correlation=-0.279; *P*-value=0.001) was found between age and improvement in ejection fraction (in continuous form) for this cohort of 133 patients. Using simple-logistic regression, it was also found that patients within this cohort who were aged 65+ years had 0.194 (0.043 – 0.882) times lower odds of having an improvement in ejection fraction post sacubitril/valsartan than patients aged less than 65 years. Additionally, using a simple linear-regression model, the improvement, if any, was lower by 6.608 percentage units (-10.409 – - 2.808), on average, than patients who were less than 65 years of age. However, on checking improvement in ejection fraction specifically for the older cohort of 133 patients, there were 71 cases of improvement, nine cases of deterioration and eight cases with no change. The Wilcoxon signed rank test demonstrated that ejection fraction pre sacubitril/valsartan (mean=28.2; SD=6.03) and ejection fraction post sacubitril/valsartan (mean=36.3; SD=9.81) samples were statistically different. Given that the histogram for ejection fraction post sacubitril/valsartan had shifted to the right in the percentage-unit axis with respect to the one for ejection fraction pre sacubitril/valsartan (*Figure 3*), it can be inferred that the ejection fraction readings post sacubitril/valsartan are, on average, higher than the ejection fraction readings pre sacubitril/valsartan for this cohort of older patients. Therefore, it can also be inferred that sacubitril/valsartan when given in

higher dosages of 49 mg/51 mg or 97 mg/103 mg improves ejection fraction in the older cohort, although this improvement is less marked than that observed in the younger cohort.

Figure 3. Histogram of ejection fraction readings pre and post Entresto for patients 65+ years of age and receiving higher dosages of Entresto (sacubitril/valsartan)



To assess the effect of age on NYHA classification and eGFR at higher dosages, Chi-squared test and Fisher's Exact test were used. It was found in these cases that age has no association with improvement in NYHA classification (*P*-value=0.216) and eGFR (*P*-

value=0.568), respectively, in the cohort that received higher sacubitril/valsartan dosages. Hence, no further analysis was carried out regarding these variables.

Discussion

In this cross-sectional, retrospective study, the authors examined the effects of sacubitril/valsartan on specific predictor variables, including ejection fraction, where baseline ejection fraction was ≤35%. Irrespective of sacubitril/valsartan dose (24 mg/26 mg, 49 mg/51 mg, 97/103 mg), the authors found significant improvements in ejection fraction measures in those aged under 65 years. In those over 65 years, as well as in those with a history of myocardial infarction, a change in ejection fraction was noted, but at the maximum twice daily dose of 97 mg/103 mg.

Heart failure is a prevalent condition that often co-exists with other comorbidities. It affects older and younger age groups. Data from large phase-3 clinical trials including the PARADIGM-HF trial, the PIONEER HF trial, the DAPA-HF trial, and the EMPEROR-reduced trial and, more recently, the DELIVER trial (McMurray et al, 2014; 2019; Velazquez et al, 2019; Packer et al, 2020; Solomon et al, 2022), have provided a weight of evidence to help clinicians support and manage patients with reduced ejection fraction, using optimum pharmacological treatments and guideline recommendations. Furthermore, the, 2021 (McDonagh et al, 2021) and, 2023 ESC guidelines (McDonagh et al, 2023) recommended using angiotensin-converting enzyme inhibitors, angiotensin receptor–neprilysin inhibitors and angiotensin II type-1 receptor blockers as a class IIb recommendation for patients with mildly reduced ejection fraction. For those with reduced ejection fraction, the use of angiotensin receptor–neprilysin inhibitors is a Class 1 recommendation (McDonagh et al, 2023). The American Heart Association heart-failure guidelines, together with the American College of Cardiology, also favour this pharmacological approach (Heidenreich et al, 2022).

Sacubitril/valsartan is generally well tolerated by patients and confers favourable clinical benefits, including cardiac remodelling, improved biomarkers and overall health-status improvements (Mohebi et al, 2022). It should be commenced in the early stages of hospital admission or immediately on discharge, and titrated upwards within the guidelines and as early as possible (Volterrani et al, 2024). Yet, despite evidence-based guideline advice, and trial evidence, target dosage is often underutilised in clinical practice (Peri-Okonny et al, 2019; Ozaki et al, 2021; Straw et al, 2021; Volterrani et al, 2024). Potential reasons for this include low socioeconomic status, limited access to care, drug intolerance, and poor adherence and early discontinuation by patients. Other reported reasons were concerned with advanced age, fragility and comorbidities (Seferović et al, 2021). However, the main reason patients do not receive the recommended dose is because of under-prescribing and sub-therapeutic dosage prescriptions (Volterrani et al, 2024). This is concerning, given the weight of evidence to support the benefits of the early-target dosage, supported by the present study through the observed improved ejection fraction in those aged under 65 years, and with a maximum dose of sacubitril/valsartan among those over 65 years of age as well.

Until recently, the effectiveness of early administration of sacubitril/valsartan had not been fully established. However, evidence suggests that higher doses of angiotensin receptor–neprilysin inhibitor, beta blockers and renin-angiotensin system inhibitors are associated with reduced hospitalisation and lower risk of cardiovascular-related deaths (D'Amario et al, 2022). Researchers differ on whether there are noted improvements in left-ventricular ejection fraction with sacubitril/valsartan, even using the same methodologies, with some

reporting no change in left-ventricular ejection fraction (Rashid et al, 2024), and others suggesting improvements in this parameter (Gao et al, 2023). However, there is no dispute that there are consistent reported reductions in heart failure, major adverse cardiovascular events, and improved NT-proBNP markers following sacubitril/valsartan administration (Rashid et al, 2024).

Conclusions

The present study examined whether there was an association between predictor sociodemographic and clinical variables and ejection fraction, with higher administered doses of sacubitril/valsartan. As heart failure is more prevalent with advancing age, this study also investigated whether age affected changes in ejection fraction, NYHA classification and eGFR with these higher doses. With a dose of 97 mg/103 mg, twice daily, patients in this study had higher odds of improvement in ejection fraction than those who received the lower dose of 24 mg/26 mg twice daily. Irrespective of drug dose administered, those aged under 65 years had a greater improvement in ejection fraction, relative to their older counterparts. A history of myocardial infarction was associated with lower odds of ejection fraction improvement than those without a history of myocardial infarction, and the authors found no association between age and improvement in NYHA or eGFR.

In 2021, the use of angiotensin receptor–neprilysin inhibitors was recommended as a Class Ib therapy for patients living with heart failure. It is one of the four pillars of heart-failure management. New and emerging evidence, guidelines, and changes in medications and class recommendations for the management of patients must always guide clinical practice. The initiation and optimisation of recommended therapies is essential to the wellbeing of patient cohorts. Collaborative work is imperative to the implementation of evidence-based practice and to addressing factors that obstruct this, such as sub-optimal prescribing. The aim is to keep patients as asymptomatic and as well as possible. Additional considerations include functional changes and markers of cardiac efficiency, which were addressed in the current study. The evidence from this study supports upward titration and optimisation of medication to achieve target doses. In this study, patients under 65 years of age benefitted most; however, patients over 65 years, as well as patients with a history of myocardial infarction, also reaped benefits from maximum-dose administration.

Strengths and limitations

This was a single-site, retrospective cross-sectional study, which only facilitates the drawing of inferences from the data. In the research site, there is a wait time of up to 1 year for echocardiograms; this accounts for some of the missing post-sacubitril/valsartan ejection-fraction measures. The authors acknowledge that the results would be more robust with the full data complement.

In addition, the same physiologist did not undertake all the echocardiogram scans in the site, thereby raising the potential for intra-operator variability in ejection-fraction reporting. With respect to eGFR, other cofounders impact this variable, such as comorbidities and other medications. The authors' clinical approach is to optimise one medication at a time, pending patients' observations, biochemical markers and physical assessment. Based on each individual assessment, other medications may be increased or introduced. Therefore, the effects cannot be attributed beyond doubt to sacubitril/valsartan.

On the positive side, this study was powered so inferences can be confidently drawn from the data. The authors carefully proofed and checked the data, so that all available data were retrieved and included in the analysis. Finally, there was a collaborative and interdisciplinary approach to this work, which is a strength in any study.

Key points

Heart failure is a global growing epidemic.

This study indicates a need for re-emphasising the importance of upward titration of sacubitril/valsartan as early as medically indicated, as optimum management can help support patients with heart failure and reduced ejection fraction to live more independently.

The four pillars of heart-failure therapy include angiotensin-converting enzyme inhibitors/angiotensin II type-1 receptor blocker/angiotensin receptor–neprilysin inhibitor, mineralocorticoid receptor antagonists, beta blockers and SGLT2 inhibitors. Sacubitril/valsartan is a combination of sacubitril, and an angiotensin II type-1 receptor blocker, valsartan, and is a Class I recommendation for patients with reduced ejection fraction as per ESC guidelines in 2021.

There is a need for further research in larger samples with respect to sacubitril/valsartan administration of those aged over and under 65 years.

Reflective questions

Why is rapid upward titration to target doses useful for patients with heart failure?

What special consideration is warranted among those with a myocardial infarction history when considering sacubitril/valsartan dosage?

Why is interprofessional/multidisciplinary research valuable in clinical practice?

How might the information from this study affect research, practice or policy?

Conflict of interest

The authors declare that there are no conflicts of interest.

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Data sharing

Data are available from the corresponding author upon reasonable request.

References

Beghini A, Sammartino AM, Papp Z et al. Update in heart failure. ESC Heart Fail. 2025;12(1):8–42. https://doi.org/10.1002/ehf2.14857

Bozkurt B, Coats AJ, Tsutsui H et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021;27(4):387–413. https://doi.org/10.1016/j.cardfail.2021.01.022

D'Amario D, Rodolico D, Rosano GMC et al. Association between dosing and combination use of medications and outcomes in heart failure with reduced ejection fraction: data from the Swedish Heart Failure Registry. Eur J Heart Fail. 2022;24(5):871–884. https://doi.org/10.1002/ejhf.2477

Gao J, Zhang X, Xu M, Deng S, Chen X. The efficacy and safety of sacubitril/valsartan compared with ACEI/ARB in the treatment of heart failure following acute myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Front Pharmacol. 2023;14:1237210. https://doi.org/10.3389/fphar.2023.1237210

Gibson G, Blumer V, Mentz RJ, Lala A. Universal definition and classification of heart failure: a step in the right direction from failure to function. American College of Cardiology; 2021. https://www.acc.org/Latest-in-Cardiology/Articles/2021/07/12/12/31/Universal-Definition-and-Classification-of-Heart-Failure (accessed 4 September 2025)

Heidenreich PA, Bozkurt B, Aguilar D et al. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145:e895–e1032. https://doi.org/10.1016/j.cardfail.2022.10.431

Mcdonagh TA, Metra M, Adamo M et al. 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. Eur Heart J. 2021;42(36):3599–3726. https://doi.org/10.1093/eurheartj/ehab368

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. Eur Heart J. 2023;44(37):3627–3639. https://doi.org/10.1093/eurheartj/ehad195

McMurray JJ, Packer M, Desai AS et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993–1004. https://doi.org/10.1056/NEJMoa1409077

McMurray J, Solomon S, Inzucchi S et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008. https://doi.org/10.1056/NEJMoa1911303

Mohebi R, Liu Y, Piña IL et al. Dose-response to sacubitril/valsartan in patients with heart failure and reduced ejection fraction. J Am Coll Cardiol. 2022;80(16):1529–1541. https://doi.org/10.1016/j.jacc.2022.08.737

Ozaki AF, Krumholz HM, Mody FV, Jackevicius CA. National trends in the use of sacubitril/valsartan. J Card Fail. 2021;27(8):839–847. https://doi.org/10.1016/j.cardfail.2021.05.015

Packer M, Anker SD, Butler J et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–1424. https://doi.org/10.1056/NEJMoa2022190

Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373–1379. https://doi.org/10.1016/S0895-4356(96)00236-3

Peri-Okonny PA, Mi X, Khariton Y et al. Target doses of heart failure medical therapy and blood pressure: insights from the CHAMP-HF registry. JACC: Heart Fail. 2019;7:350–358

Rashid M, Soto CJ, Virk GS et al. The safety and efficacy of the early use of sacubitril/valsartan after acute myocardial infarction: a meta-analysis of randomized controlled trials. Cureus. 2024;16(2):e53784. https://doi.org/10.7759/cureus.53784

Savarese G, Becher PM, Lund LH et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023;118(17):3272–3287. https://doi.org/10.1093/cvr/cvac013

Seferović PM, Polovina M, Adlbrecht C et al. Navigating between Scylla and Charybdis: challenges and strategies for implementing guideline-directed medical therapy in heart failure with reduced ejection fraction. Eur J Heart Fail. 2021;23(12):1999–2007. https://doi.org/10.1002/ejhf.2378

Solomon SD, McMurray JJV, Claggett B et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med. 2022;387(12):1089–1098. https://doi.org/10.1056/NEJMoa2206286

Straw S, Mcginlay M, Witte KK. Four pillars of heart failure: contemporary pharmacological therapy for heart failure with reduced ejection fraction. Open Heart. 2021;8(1):e001585. https://doi.org/10.1136/openhrt-2021-001585

Velazquez EJ, Morrow DA, Devore AD et al. Angiotensin–neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019;380(6):539–548. https://doi.org/10.1056/NEJMoa1812851