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## Effects of Sacubitril/Valsartan dose on sociodemographic and clinical predictor variables: an Irish cross-sectional study.

--Manuscript Draft--

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| <b>Full Title:</b>                                   | Effects of Sacubitril/Valsartan dose on sociodemographic and clinical predictor variables: an Irish cross-sectional study.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
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| <b>Corresponding Author:</b>                         | Mary Mooney, PhD<br>Trinity College Dublin School of Nursing and Midwifery<br>Dublin 2, IRELAND                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Corresponding Author Secondary Information:</b>   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Corresponding Author's Institution:</b>           | Trinity College Dublin School of Nursing and Midwifery                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Corresponding Author's Secondary Institution:</b> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>First Author:</b>                                 | Mary Mooney, PhD                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>First Author Secondary Information:</b>           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Order of Authors:</b>                             | Mary Mooney, PhD<br>Sharon Maher, M.Sc. and Advanced Nurse Practitioner.<br>Jill Cummins, Higher Diploma Cardiovascular Nursing.<br>Patrice Berry, Higher Diploma Cardiovascular Nursing.<br>Aviejay Paul, MSc                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Order of Authors Secondary Information:</b>       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Abstract:</b>                                     | <p>Title: Effects of Sacubitril/Valsartan dose on sociodemographic and clinical predictor variables: an Irish cross-sectional study.</p> <p>Background: The syndrome of heart failure is a recognised epidemic affecting between 1%-2% of adults in the developed world. Several landmark clinical trials have led to improvements in heart failure management over the past two decades.</p> <p>Aims: We examined the association between socio-demographic and clinical variables and change in ejection fraction (EF), and whether age affected improvement in EF, New York Heart Association (NYHA) classification and estimated glomerular filtration rate (eGFR) following higher doses of Sacubitril/Valsartan.</p> <p>Methods: In this cross-sectional Irish study, we used descriptive and inferential statistical analyses.</p> <p>Results: We had post Sacubitril/ Valsartan EF measurements on 162 people, and 198 measures for both NYHA classification and eGFR post Sacubitril/ Valsartan. With a dose of 97mg/103mg, twice daily, patients had 7.70 (2.812 – 21.078) times higher odds of improvement in EF than those who received the lower dose of 24mg/26mg twice daily. Irrespective of drug dose administered, patients under 65 years have a greater improvement in EF, relative to those over 65 years. Patients with myocardial infarction (MI) history had lower odds of EF improvement than those with no MI history. There was no association between age and improvement in NYHA or eGFR.</p> <p>Conclusion: Sacubitril/Valsartan is effective in improving ejection fraction. This improvement is greater among patients under 65 years. Higher dosages lead to higher odds of improvement, when adjusted for age and history of MI.</p> <p>Keywords: Heart Failure, Sacubitril/Valsartan, Ejection Fraction, Glomerular Filtration</p> |

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|                               | <p>Rate, New York Heart Association Classification.</p> <p>Declarations: The authors have nothing to declare and have no conflicts of interest.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Response to Reviewers:</b> | <p>Responses to reviewer comments: Ref. No. bjca.2024.0077R1</p> <p>Reviewer number 1, comments</p> <p>Abstract</p> <p>1.At the end of the Background section add 'following Sacubitril/Valsartan dose' to aid clarity;</p> <p>Response: I don't believe this would fit at the end of the background section, but seems to sit well at the end of the aims; I imagine this was the reviewer's intention as it reads better when placed here.</p> <p>Background</p> <p>2.I would remove 'is a major and chronic cardiovascular disease' - HF is not always cardiovascular in aetiology.</p> <p>Response: Removed.</p> <p>3.Thanks for the sentence re diuretics - it would sit better at the end of the paragraph on 4 pillar therapy.</p> <p>Response: Moved to end of paragraph.</p> <p>4.Paragraph re PARADIGM - last sentence I think you should have HFrEF not HFpEF.</p> <p>Response: I can only find two references to preserved EF in the paper, both of which I believe to be appropriate. One is in the background where the acronym is explained, the second relates to the use of diuretics, and this is correct in that they are class 1 for mildly reduced and preserved EF. The last sentence states "This drug combination has since been recommended by the European Society of Cardiology (ESC) for patients with HFrEF, pending satisfactory blood pressure and renal function."</p> <p>5.ESC recommendation dose 49mg/51mg - I would add the caveats of low BP/ poor renal function here also.</p> <p>Response: As requested, I have added this again here.</p> <p>Methods</p> <p>6.Refer to smoking status as a socio demographic factor, to aid clarity that a socio demographic variable was used as per title.</p> <p>Response:This has been added, with a slight change to the overall sentence to make it easier to follow, and the variables are now included in parenthesis for the same reason.</p> <p>Results - first paragraph</p> <p>7.I understood history of MI led to less improvement - this is not what is stated here. Also in terms of what showed most improvement in EF be clearer about the variable - for example, was it a higher or lower EF at the beginning that was associated with more improvement (I understand it to be lower), and age - was it older or younger (I understand it to be younger)</p> <p>Response: In this paragraph we are only reporting the results from bivariate analysis. The purpose of this is only to check whether or not we have evidence of significant associations between the individual predictors and the outcome variables. Here we do not adjust for any other variables and hence reporting anything more than presence of significant associations in this paragraph (such as which predictor "showed most improvement", direction of the relationship such as "higher or lower") would not be appropriate. Details on the direction of association from the final 'adjusted' models are reported under the "Multivariate analysis" subsection.</p> <p>Multivariate analysis - last paragraph</p> <p>8. I found the second half of this paragraph difficult to follow. It needs a rewrite to aid readability and clarity.</p> <p>Response: I have made some small changes. I believe readers will find that the wording is clear.</p> <p>Table 2</p> <p>9.Can you add p values?</p> <p>Response: No, p-values would not make any sense here. We are neither</p> |

|                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                        | <p>hypothesising nor modelling anything. We are only reporting descriptive statistics here.</p> <p>What is the difference between Improvement in EF line and Improvement in EF categorised line?</p> <p>Response: I have changed the wording for improvement in EF in Table 2, which will assist understanding this difference.</p> <p>Conclusion</p> <p>10. Need to summarise the key findings after the study re aims. The rest of the conclusion then follows.</p> <p>Response: These have been summarised after the aim.</p> |
| <b>Additional Information:</b>                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Question</b>                                                                        | <b>Response</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Please enter the word count of your manuscript, <b>excluding references and tables</b> | 3721                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

**Title: Effects of Sacubitril/Valsartan dose on sociodemographic and clinical predictor variables: an Irish cross-sectional study.**

**Authors' names, affiliations and appointments.**

**Name:** Dr Mary Mooney

**Institutional Affiliation:** School of Nursing and Midwifery, Trinity College Dublin, 24 D'Olier Street, Dublin 2, D02T283, Ireland.

**Current Appointment:** Associate Professor in general nursing.

**Email:** [mooneyma@tcd.ie](mailto:mooneyma@tcd.ie)

**Co authors**

**Name:** Ms. Sharon Maher

**Current Appointment:** Advanced Nurse Practitioner

**Affiliation:** Midlands Regional Hospital, Tullamore, County Offaly, Ireland.

**Email:** [Sharon.maher@hse.ie](mailto:Sharon.maher@hse.ie)

**Name:** Ms. Patrice Berry

**Current Appointment:** Clinical Nurse Specialist,

**Affiliation:** Midlands Regional Hospital, Tullamore, County Offaly, Ireland.

**Email:** [patrice.berry@hse.ie](mailto:patrice.berry@hse.ie)

**Name:** Ms. Jill Cummins

**Current Appointment:** Clinical Nurse Specialist,

**Affiliation:** Midlands Regional Hospital, Tullamore, County Offaly, Ireland.

**Email:** [jill.cummins1@hse.ie](mailto:jill.cummins1@hse.ie)

**Name:** Mr. Aviejay Paul,

**Current Appointment:** PhD student.

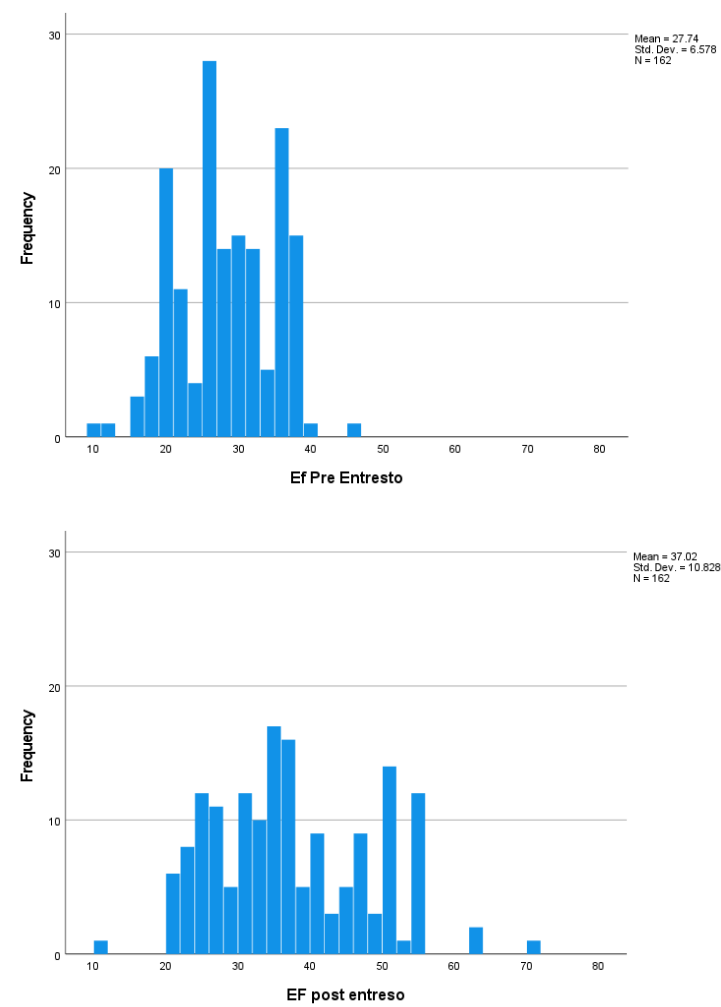
**Affiliation:** School of Computer Science and Statistics, Trinity College Dublin.

**Email:** [paulav@tcd.ie](mailto:paulav@tcd.ie)

**Conflict of interest:** None

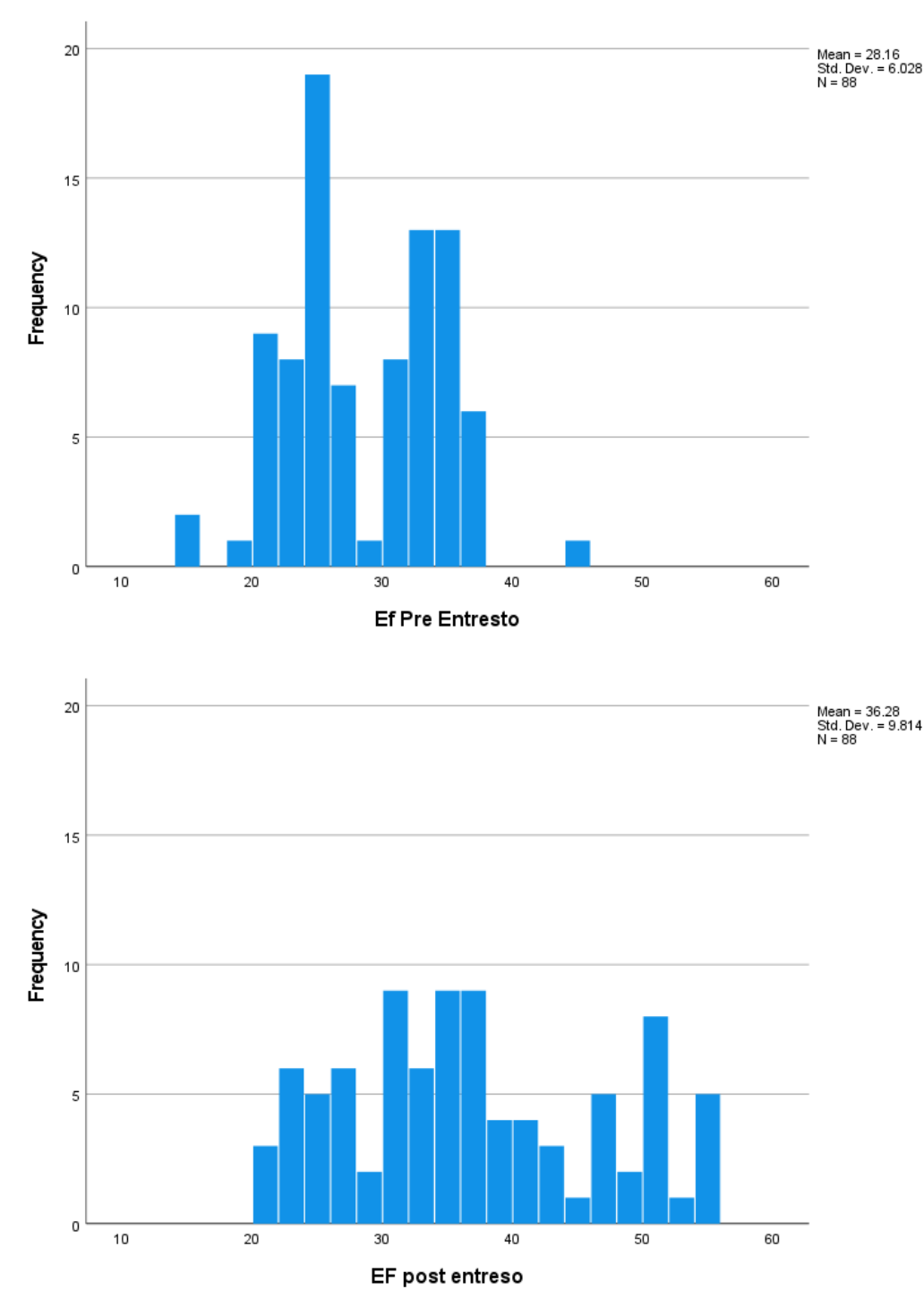
Figure 2:

Histogram of EF readings pre and post Entresto



**Figure 3:**

**Histogram of EF readings pre and post Entresto for patients 65+ of age and receiving higher dosages of Entresto**





**Variable descriptives****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        | /                               | 66, 33.2             |
|                       | 65+                 | /                               | 133, 66.8            |
| EF pre Entresto       | /                   | 28.21, 6.44                     | /                    |

‘/’ means not applicable.



**Table 3****Results of multivariate analyses on improvement in EF**

| Predictors              | Categories   | Improvement in EF (in categorical form): odds (95%CI); p-value | Improvement in EF (in continuous form): estimate (95%CI); p-value |
|-------------------------|--------------|----------------------------------------------------------------|-------------------------------------------------------------------|
| Myocardial Infarction   | 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+          | /                                                              | -2.315 (-5.416 – -0.797); 0.145                                   |
|                         | Less than 65 | /                                                              | 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           | /                                                              | /                                                                 |

‘/’ means variable did not have a significant association or the association was not “approaching significance” in the bivariate analysis. Hence, the predictor was not used in the final model.

NA means not applicable

Background

Heart failure (HF) is a chronic clinical syndrome. It is most often caused by a structural and/or functional cardiac abnormality and associated with elevated natriuretic peptide levels and/or evidence of pulmonary or systemic congestion (Savarese et al, 2022; Beghini et al, 2024). While the incidence of heart failure has declined over the years, the prevalence is increasing owing to improved survival rates following myocardial infarction, an increase in comorbidities, an aging population with increased longevity and improvements in heart failure management (McDonagh et al, 2021, Beghini et al, 2024). The classification of HF is dependent on left ventricular ejection fraction (LVEF). It includes HF with reduced (HFrEF), mildly reduced (HFmrEF), preserved EF (HFpEF) and HF with improved ejection fraction (HFimpEF) (Bozkurt et al, 2021; Savarese et al, 2022; McDonagh et al, 2023) (Figure 1).

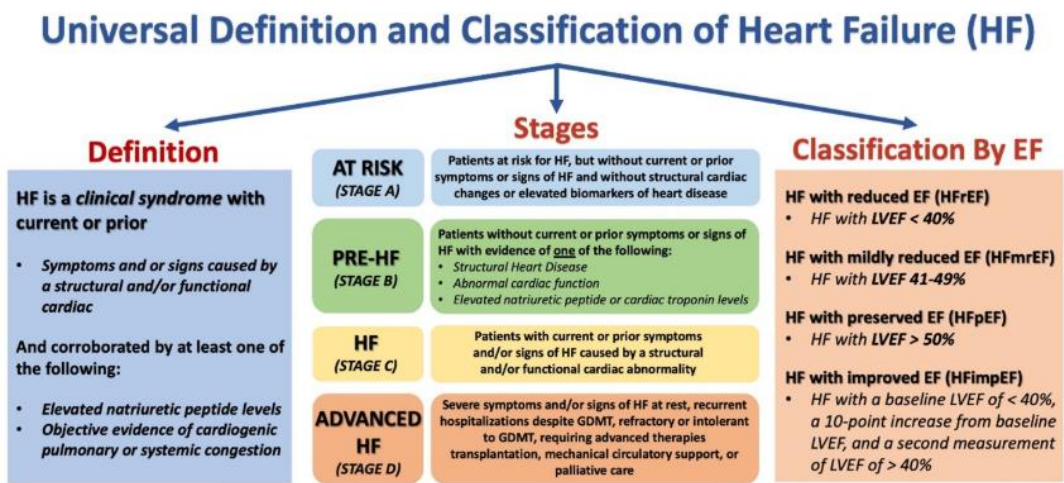


Figure 1: Definition and Classification of Heart Failure (Gibson et al. 2021).

The management of HF with reduced ejection fraction (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 (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 heart failure and reduced or mildly reduced EF. These are drugs that target the renin-angiotensin-aldosterone system, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin II type-1 receptor blockers (ARB), angiotensin receptor–neprilysin inhibitors (ARNi), beta

blockers and mineralo-corticoid 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 mildly reduced and preserved ejection fraction (McDonagh et al, 2023).

Ten years ago, the PARADIGM-HF trial (McMurray et al, 2014) hailed the beginning of a dramatic alteration in the pharmacological management of patients with heart failure with reduced ejection fraction (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 HF and reduced EF. 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 European Society of Cardiology (ESC) for patients with HFrEF, pending satisfactory blood pressure and renal function.

The European Society of Cardiology (ESC) recommend a start dose of 49mg/51mg of Sacubitril/Valsartan twice daily, pending satisfactory blood pressure and renal function, with a target dose of 97mg/103mg 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 ARNIs remains suboptimal (Straw et al, 2021; Volterrani et al, 2024). As clinicians in heart failure, we are conscious of the important role of ARNIs, as one of the four pillars of HF management. In this study we examined whether there was an association between predictor socio-demographic and clinical variables and EF, with higher administered doses of Sacubitril/Valsartan. And as heart failure is more prevalent with advancing age, we also investigated whether age affected changes in EF, NYHA classification and estimated glomerular filtration rate (eGFR) with these higher doses.

## Methods

### Design and procedures.

This 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 (reference: 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 were retrieved from the Health Service Executive database and contained demographic and clinical variables including ejection fraction (EF) pre and post administration of Sacubitril/Valsartan. All those included in the analysis had an EF of  $\leq 35\%$  at baseline. As the data were collected in the course of daily work, and they were being fully anonymised prior to analysis, there was no ethical requirement for individual patient consent at the site. We were interested to identify if, and how, sociodemographic variables (such as age, gender and smoking status), and clinical variables (such as history of hypertension and myocardial infarction, and EF pre Sacubitril/Valsartan readings) affected EF readings post Sacubitril/Valsartan. The study also aimed to understand if, and how, age affected EF, NYHA classification, and eGFR readings on receipt of the higher doses of 49mg/51mg or 97mg/103mg of Sacubitril/Valsartan. Patients on the low dose in this 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 SPSS v27.

### Sample size calculation.

The required sample size estimated using G-power to perform multiple linear regression using 8 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 our estimation of the required the sample for logistic regression from G-Power, we needed to choose one main predictor. We selected myocardial infarction as the main predictor in this case. The probability to make a positive difference in the post Sacubitril/Valsartan EF 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 EF Sacubitril/Valsartan readings without myocardial infarction (that is  $\Pr(Y=1|X=1)H_0$ ) was calculated to be 0.90 from our 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 EPV perspective, the EPV in our case is 14.75, which is also acceptable (Peduzzi et al, 1996).

As this the study focused on changes in the output variables of EF, NYHA classification and eGFR, only those cases that had pre Sacubitril/Valsartan and post Sacubitril/Valsartan readings for the 3 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 (24mg/26mg, 49mg/51mg, or 97mg/103mg), smoking status and EF pre Sacubitril/Valsartan. Of the 199 cases in the study, 37 patients did not have a recorded EF post Sacubitril/Valsartan, and in one case we had 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 EF, and 198 for both NYHA classification and eGFR. Also, post Sacubitril/Valsartan data on EF, NYHA classification and eGFR with higher Sacubitril/Valsartan dosages of 49mg/51mg or 97mg/103mg was available for 133 participants. Thus, the remaining patients' data were excluded from the analysis part that looked at the effect of age on these three parameters for patients who were given the higher dosages.

## **Statistical analyses**

Descriptives statistics for predictor and output variables are shown in Tables 1 and 2 respectively. Improvement in EF was determined by the difference between EF post and pre Sacubitril/Valsartan. A positive difference was classified as an improvement, 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 less than or equal to 60 mL/min/1.73m<sup>2</sup> and greater than 60 mL/min/1.73m<sup>2</sup>. A movement from the former to the latter class was classified as an improvement while the opposite was classified as a deterioration.

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 3 or 2 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 was 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 "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 EF 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 EF when adjusted for the other predictors, whereas the multivariate linear regression model (with improvement in EF in continuous form as the dependent/outcome variable) was used to quantify the improvement where an improvement in EF was found.

## **Results**

### *Association between demographic predictors and improvement in EF*

The Shapiro-Wilk test (p-value < 0.001) and Kolmogorov-Smirnov test (p-value < 0.001) confirmed that improvement in EF readings were not normally distributed, and the Wilcoxon signed rank test (p-value < 0.001) was used to establish that as paired observations, EF pre Sacubitril/Valsartan and EF post Sacubitril/Valsartan were

statistically different. We noted there were 129 positive differences, 14 negative differences and 19 observations with no difference between the EF readings pre and post administration of Sacubitril/Valsartan. As shown in Figure 2, EF post Sacubitril/Valsartan histogram had shifted to the right in the percentage-unit axis with respect to EF pre Sacubitril/Valsartan. We therefore inferred that EFs post Sacubitril/Valsartan (mean = 37.02, standard deviation = 10.83) are, on average, higher than the EFs pre Sacubitril/Valsartan (mean = 27.74, standard deviation = 6.58). There was an average improvement in EF of 9.28% for the cohort (N=162). In the bivariate analysis, a history of MI, maximum dosage, EF pre Sacubitril/Valsartan had significant associations with improvement in EF (in both continuous and categorical forms) whereas age had significant associations with improvement in EF (only in continuous form). We did not find any evidence of significant associations of sex, history of hypertension and smoking status with improvement in EF (in either categorical or continuous form). Hence, these 3 variables were not included in either of the multivariate models.

#### *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 EF as a dependent variable in categorical form), relative to those with no history of MI, patients with an MI history had 0.276 (0.113 – 0.672) times lower odds to have an improvement in EF, adjusting for maximum dosage and pre-Sacubitril/Valsartan readings. On the other hand, patients who were given a maximum dosage of 97mg/103mg had 7.70 (2.812 – 21.078) times higher odds to have an improvement in EF than those who received a dosage of 24mg/26mg. The Nagelkerke R-squared for the model was 0.28.

Of note, from the multivariate linear regression model (with improvement in EF as a dependent variable in continuous form), we found that patients with a history of MI had **lesser** improvement in EF by 6.475 percentage units (-9.423 — -3.526), on average, than patients without MI history when we adjusted for age, maximum dosage, and EF pre Sacubitril/Valsartan. Patients who were given a maximum dosage of 97mg/103mg had higher improvement in EF by 6.17 percentage units

(2.371 - 9.969) on average than those who were given a maximum dosage of 24mg/26mg. Also from the linear regression model, a negative relationship was found between EF prior to Sacubitril/Valsartan administration (EF pre Sacubitril/Valsartan) and improvement in EF after Sacubitril/Valsartan was administered (EF post Sacubitril/Valsartan). As patients' EF pre Sacubitril/Valsartan went up by 1 percentage unit, improvement in EF 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 on EF, NYHA classification and eGFR at higher dose Sacubitril/Valsartan*

One hundred and thirty-three patients out of the 162 met the criteria for receiving the higher doses of Sacubitril/Valsartan (49mg/51mg or 97mg/103mg) and had EF recorded post Sacubitril/Valsartan. The mean age of this cohort was 68.88 (std. dev. = 10.94). Of these, 45 patients were less than 65 years of age, and 88 patients were 65 or above. The mean improvement in EF in this cohort of 133 patients was 10.36 percentage units. There were 114 patients in whom an improvement in EF was noted and for 19 others there was a reported deterioration or no change in EF.

A negative correlation (Pearson's correlation = -0.279; p-value = 0.001) was found between age and improvement in EF (in continuous form) for this cohort of 133 patients. Using simple logistic regression, it was also found for this cohort that patients who were aged 65+ had 0.194 (0.043 – 0.882) times lower odds of having an improvement in EF post Sacubitril/Valsartan than patients less than 65 years of age. Also, using a simple linear regression model, it was found that 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 EF specifically for the older cohort of 133 patients, it was found that there were 71 cases of improvement, nine cases of deterioration and eight cases with no change. The Wilcoxon signed rank test demonstrated that EF pre Sacubitril/Valsartan (mean = 28.2; std.dev = 6.03) and EF post Sacubitril/Valsartan (mean = 36.3; std.dev = 9.81) samples were statistically different. Given that the histogram for EF post Sacubitril/Valsartan had shifted to the right in the percentage-



unit axis with respect to the one for EF pre Sacubitril/Valsartan (Figure 3), it can be inferred that the EF readings post Sacubitril/Valsartan are, on average, higher than the EF readings pre Sacubitril/Valsartan for this cohort of older patients. And therefore, it can also be inferred that Sacubitril/Valsartan when given in higher dosages of 49mg/51mg or 97mg/103mg improves EF in the older cohort too, although this improvement is less marked than that in the younger cohort.

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 for these variables.

## **Discussion**

In this cross-sectional, retrospective study, we examined the effects of Sacubitril/Valsartan on specific predictor variables, including EF, where baseline EF was equal to or less than 35%. Irrespective of Sacubitril/Valsartan dose (24mg/26mg, 49mg/51mg, 97/103mg), we found significant improvements in EF measures in those under 65 years. In those over 65 years and, also in those with a history of MI, a change in EF was noted, but at the maximum twice daily dose of 97mg/103mg.

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; McMurray et al, 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 EF, using optimum pharmacological treatments and guideline recommendations. Furthermore, the 2021 (McDonagh et al, 2021) and 2023 ESC guidelines recommended using ACEIs, ARNIs and ARBs as a class IIb recommendation for patients with mildly reduced EF. And for those with reduced EF, the use of ARNIs is a Class 1 recommendation (McDonagh et al, 2023). The

American Heart Association HF 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 socio-economic 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 don't 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, which our study supports through the observed improved ejection fraction in those under 65 years, and with a maximum dose of Sacubitril/Valsartan, among those over 65 years also.

Until recently, the effectiveness of early administration of Sacubitril/Valsartan had not been fully established, but evidence suggests that higher doses of ARNi, beta blockers and RASi 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 LVEF with Sacubitril/Valsartan, even using the same methodologies, with some reporting no change in LVEF (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).

## **Conclusion**

This study examined whether there was an association between predictor socio-demographic and clinical variables and EF, with higher administered doses of Sacubitril/Valsartan. And, as heart failure is more prevalent with advancing age, we also investigated whether age affected changes in EF, NYHA classification and estimated glomerular filtration rate (eGFR) with these higher doses. With a dose of 97mg/103mg, twice daily, patients in this study had higher odds of improvement in EF than those who received the lower dose of 24mg/26mg twice daily. Irrespective of drug dose administered, those under 65 years had a greater improvement in EF, relative to their more aged counterparts. A history of myocardial infarction (MI) was associated with lower odds of EF improvement than those without a past history of MI, and we found no association between age and improvement in NYHA or eGFR.

In 2021 the use of ARNIs was recommended as a Class Ib therapy for patients with heart failure. It is one of the four pillars of HF management. New and emerging evidence provides us with ongoing guidelines, and changes in medications and class recommendations for the management of patients must always guide our practice. The initiation and optimisation of recommended therapies is essential to the wellbeing of our patient cohorts. It is imperative that we work collaboratively to implement evidence-based practice and to address factors that obstruct this, such as sub-optimal prescribing. The aim is to keep patients as asymptomatic and as well as possible. Additional considerations including functional changes and markers of cardiac efficiency, which were addressed in this study. The evidence from this study supports upward titration and optimisation of medication to achieve target doses, and in this study patients under 65 years benefitted most, but patients over 65 years and also patients who had a history of myocardial infarction also reaped benefits from maximum dose administration.

### **Strengths and Limitations**

This was a single site, retrospective cross-sectional study, so using this research design, we can only draw inferences from our data. In this research site there is a wait time of up to one year for echocardiograms; this accounts for some of the missing post-Sacubitril/Valsartan EF measures. We acknowledge that our results

would be more robust if we had the full data complement. In addition, the same physiologist did not undertake all the ECHO scans in the site, thereby raising the potential for intra-operator variability in EF reporting. With respect to eGFR, we are mindful that other cofounders impact this variable, such as co-morbidities and other medications. Our 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, our study was powered so we can confidently draw inferences from the data. We 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.

Our 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 EF to live more independently.

The four pillars of heart failure therapy include ACE inhibitors/ARB/ARNI, MRA, beta blockers and SGLT2 inhibitors. Sacubitril/Valsartan is a combination of Sacubitril, and an ARB, Valsartan and is a Class I recommendation for patients with reduced EF as per ESC guidelines in 2021.

There is a need for further research in larger samples with respect to Sacubitril/Valsartan administration of those 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 an MI 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?

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Table 2

Descriptives of the output variables

| Variable                           | Number of patients included | Variable categories    | Mean, standard deviation | n, Percentage |
|------------------------------------|-----------------------------|------------------------|--------------------------|---------------|
| Improvement in EF                  | 162                         | /                      | 9.28, 10.74              | /             |
| Improvement in EF 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       |

‘/’ means not applicable.