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ORIGINAL ARTICLE

Assessing suitability for sacubitril-valsartan therapy in an Irish cohort: challenges and opportunities

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Abstract

Introduction Sacubitril-valsartan has been shown by the PARADIGM-HF trial to decrease hospital admissions and improve mortality in patients with heart failure with reduced ejection fraction. The PARADIGM trial had stringent exclusion criteria. It is not known how applicable these trial criteria are to real-life practice. In this study, we sought to determine the percentage of patients eligible for sacubitril-valsartan therapy in a level 3 hospital without a dedicated heart failure service.

Methods All patients discharged from our service with a diagnosis of congestive cardiac using our hospital in-patient enquiry (HIPE) system underwent hierarchal analysis. In order to be deemed eligible for sacubitril-valsartan therapy, patients had to meet PARADIGM-HF inclusion criteria.

Results Our 143 patients represented a more clinically unwell, elderly cohort than the PARADIGM trial study population. Only 24 patients (16.66%) had an ejection fraction of 40% or less. Our results indicate that only 4/143 patients in a real-world setting (2.79%) were eligible for sacubitril-valsartan therapy at the point of discharge as per the PARADIGM-HF study criteria. This is primarily due to the higher than expected percentage of patients in our cohort with an ejection fraction of over 40% ($n = 120$) and the low percentage of patients on therapeutic doses of ACEI/ARB ($n = 15$).

Conclusions Our study showed that a smaller than expected proportion of our patients in real-world practice are suitable for sacubitril-valsartan therapy at discharge. Most patients were in the HFPEF cohort which does not currently have evidence for treatment with sacubitril-valsartan. Low rates of prescribing of basic heart failure medicatons and the absence of dedicated heart failure services in a non-tertiary centre may explain the poor compliance observed. Improving guideline adherence and increasing awareness of evidence-based medication use at primary and secondary care levels would be of benefit to Irish heart failure patients.

Keywords Entresto · Heart failure · HFREF · Sacubitril-valsartan

Introduction

Heart failure is a physiological state in which cardiac output is insufficient to meet the needs of the body and lungs. It is characterised by impairment of myocardial function, contractility and filling. Symptoms are typically either acute or chronic and presently it can be divided into three major phenotypes: heart failure with preserved ejection fraction (HFPEF), heart failure with mid-range ejection fraction (HFmrEF) and heart failure with reduced ejection fraction (HFREF) [1]. Typical signs and symptoms and the presence of echocardiographic abnormalities are required in order to establish the diagnosis [2]. In Ireland, it is estimated that approximately 90,000 patients have a diagnosis of heart failure, 160,000 people have asymptomatic heart failure and the annual cost exceeds €660 million to the Irish state [3].

Angiotensin-converting enzyme inhibitors (ACEi), beta blockers (BB), mineralocorticoid receptor antagonists (MRA) and ivabradine have all been shown to improve mortality in HFrEF and this is reflected in their primacy in the treatment guidelines [4–8]. In addition, digoxin, hydralazine and isosorbide mononitrate have been shown to improve symptoms for patients and are regularly used in order to reduce hospital admissions and exacerbations [9–11].

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Despite these treatments, prognosis for patients diagnosed with heart failure has remained relatively poor. It is still associated with a mortality equivalent to many malignancies and has a significantly negative impact on a patients' quality of life [12, 13].

Most notably, patients with NYHA class III–IV heart failure have a 1-year mortality of approximately 50% [14]. The quality of life in heart failure patients has also been shown to be comparable to patients with depression and is particularly dependent on NYHA class [15].

The PARADIGM-HF [16] trial compared sacubitril-valsartan (a novel combination angiotensin receptor neprilysin inhibitor; trade name entresto) with an ACE inhibitor for the treatment of patients with HFrEF. The results indicated that this novel agent reduced cardiovascular mortality, all-cause mortality and heart failure–related hospitalisations in the study cohort.

While these results are promising, it must be noted that PARADIGM had stringent inclusion and exclusion criteria. It is not known how applicable these trial criteria are to real-life practice. In this study, we sought to determine the percentage of heart failure patients eligible for sacubitril-valsartan therapy in our centre, an Irish level 3 hospital without a dedicated heart failure service.

Methods

Retrospective analysis of all patients discharged from our service with a HIPE (hospital in-patient enquiry)-coded diagnosis of heart failure from January 2015 to December 2016. HIPE coding is performed by HIPE coders based on the discharge summaries and chart subentry on a standard discharge completed by junior doctors.

Clinical notes, imaging reports, blood results and prescribing data were analysed for all patients.

We used this data to identify all inclusion and exclusion criteria for the PARADIGM trial. A hierarchical analysis was subsequently performed. To be deemed eligible for sacubitril-valsartan therapy, patients had to meet the following sequential criteria:

- Diagnosis of heart failure
- NHYA class II–IV symptoms
- Ejection fraction < 40%
- Systolic blood pressure > 100 mmHg
- eGFR > 30 ml/min/kg
- Serum potassium < 5.2 mmol/L
- On ACEI/ARB equivalent to enalapril 10 mg daily
- On beta blocker

We sought to assess the proportion of patients in our real-world heart failure cohort that would be suitable for consideration of sacubitril-valsartan therapy at the point of discharge. We also assessed the proportion of patients prescribed recommended medications in heart failure and the dosages these medications were prescribed at.

The primary outcome was to assess the percentage of patients eligible for sacubitril-valsartan therapy based on PARADIGM-HF criteria. To gain approval for reimbursement of sacubitril-valsartan in Ireland, physicians complete a PCRS online application which is based on the PARADIGM-HF study criteria. The secondary outcome was to investigate the percentage of patients prescribed ACEI, BB and MRA therapy on discharge. Furthermore, we sought to evaluate the percentage of patients prescribed therapeutic doses of ACEI, BB and MRA therapy on discharge.

The majority of patients in the study were prescribed frusemide but as a non-disease-modifying therapy, it was not a focus for data collection in this study. For study purposes, the sub-therapeutic doses of NICE recommended drugs for use in heart failure were defined as

ACE inhibitors: lisinopril < 10 mg per day, perindopril < 4 mg per day, ramipril < 5 mg per day, enalapil 10 mg BD

ARB: candesartan 32 mg once a day, losartan 150 mg once a day, valsartan 160 mg once a day

Beta blockers: bisoprolol < 5 mg per day, carvedilol < 25 mg per day, metoprolol < 50 mg per day

MRA: spironolactone < 25 mg per day, eplenerone < 25 mg per day

Chi-squared test was used to compare categorical data.

Student's *t* test was used to compare means between groups.

All statistical tests were two-tailed tests performed at a significance level of 0.05.

The R program was used for statistical analysis.

Results

We identified 143 patients discharged with a diagnosis of heart failure during the study period between 2015 and 2016. These patients had a mean age of 78.2 ± 9.09 years, a mean NYHA class of 2.76 ± 0.75 and a mean BNP of 4805.

Within the study population, all 143 patients had an NYHA of II–IV. Only 24 patients (16.66%) had an ejection fraction of 40% or less. All 24 had a systolic blood pressure of > 100 mmHg and 20 of these patients had an eGFR of > 30 ml/min/kg. Nineteen patients had a K+ of less than 5.2 mmol/L. Only 4 of these patients were on an ACEI/ARB dose equivalent to enalapril 10 mg daily. All four of these patients were on a beta blocker. As such, our results indicate that only 4/143 patients in a real-world setting (2.79%) were eligible for sacubitril-valsartan therapy at discharge as per the PARADIGM-HF study criteria. This is primarily due to the high numbers of patients in our cohort with an ejection fraction of over 40% ($n = 120$) and the low numbers of patients on therapeutic doses of ACEI/ARB (Table 2).

For patients with HFrEF, 4/24 (16.66%) patients were eligible for sacubitril-valsartan therapy based on PARADIGM-HF criteria. Introducing/increasing dosages of ACEI/BB

therapy would result in 19 patients being eligible for sacubitril-valsartan therapy as per the trial criteria. Alternatively, as per the prescribing guidelines, these patients could initiate sacubitril-valsartan therapy at the lower dose (26/24 mg BD). This would result in 13.19% (19/144) of patients in our entire cohort being eligible for sacubitril-valsartan therapy or 79.16% of the HFrEF population.

Table 1 details the proportion of patients taking ACEI, ARB, MRA and BB in our cohort. Table 2 examines the proportion of these medications that were prescribed therapeutically. Fig. 1 is a visual depiction of our hierarchical analysis of suitability for sacubitril-valsartan at discharge.

Discussion

Mechanism Sacubitril is a neprilysin inhibitor. Neprilysin is an intrinsic endopeptidase, an enzyme which degrades several vasoactive and natriuretic peptides, including ANP and BNP. Neprilysin inhibitors prevent this process and facilitate preservation of compounds like BNP that promotes vasodilation and natriuresis. Neprilysin also degrades angiotensin, hence the need for combination therapy with an angiotensin receptor blocker.

The PARADIGM-HF trial [16] was a double-blinded randomised controlled trial which prospectively compared sacubitril-valsartan to enalapril in patients with HFREF or NYHA II–IV heart failure. In the trial, 8399 HFREF patients were recruited from 1043 centres in 47 countries and randomised to the treatment arms. A single-blind run-in period of enalapril 10 mg daily was employed for 2 weeks followed by sacubitril-valsartan run-in, building to a dose of 200 mg twice daily over 4–6 weeks as tolerated, with 24-h drug washout intervals. The trial was stopped early after a median follow-up of 27 months due to crossing pre-specified criteria for overwhelming benefit; this was evident in the group receiving sacubitril-valsartan in terms of reduction in hospitalisations and a decreased risk of mortality.

When compared to enalapril, sacubitril-valsartan reduced death from cardiovascular causes by 20% ($P < 0.001$), all-cause mortality by 16% ($P < 0.001$) and hospitalisation for heart failure by 21% ($P < 0.001$). Sacubitril-valsartan also reduced the symptoms and physical limitations of heart failure ($P < 0.001$). The sacubitril-valsartan treatment group suffered higher levels of non-life-threatening angioedema and hypotension but in comparison to enalapril, patients suffered lower levels of cough, hyperkalaemia and renal impairment.

In Ireland, the NCPE (National Centre for Pharmaco-Economics) conducted a cost-effectiveness analysis and recommended the drug for reimbursement [17]. The drug cost was based on a factory price of 136.92 euro per 28 day tablet pack of sacubitril-valsartan. Of note, the PARADIGM decrease in hospitalisation is likely to majorly offset much of the cost associated with sacubitril-valsartan.

Table 1 No. of patients prescribed heart failure medications on discharge

Number of patients prescribed NICE recommended medications		
Total	143	100%
ACEI	47	32.8%
ARB	36	25.1%
No ACEI/ARB	60	41.9%
Beta blocker	114	79.7%
MRA	26	18.1%

Table 2 Percentage of heart failure medications prescribed at a therapeutic dose

Medication	Percentage of NICE recommended medications prescribed at a therapeutic dose
ACEi	6.2
ARB	1.3
B-Blocker	27
MRA	13.2

There have been several updates to practice guidelines following the PARADIGM-HF trial publication including:

ACC/AHA/ASHF Guidelines which state "In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality" *Class 1 strong recommendation with moderate quality evidence* [18].

European Society of Cardiology Guidelines which suggest "Sacubitril-valsartan is recommended as a replacement for an ACEi to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACEi, a beta blocker and an MRA" *Class I recommendation Level B evidence data from a single randomised trial* [19].

Finally, the Nice Guidelines recommend "Sacubitril-valsartan is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people: with New York Heart Association (NYHA) class II to IV symptoms and with a left ventricular ejection fraction of 35% or less and who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs)" [20].

The PARADIGM-HF study may represent a significant advance in the management of heart failure. However, it is yet to be seen how this will translate to real-world practice. A number of real-world barriers to guideline implementation

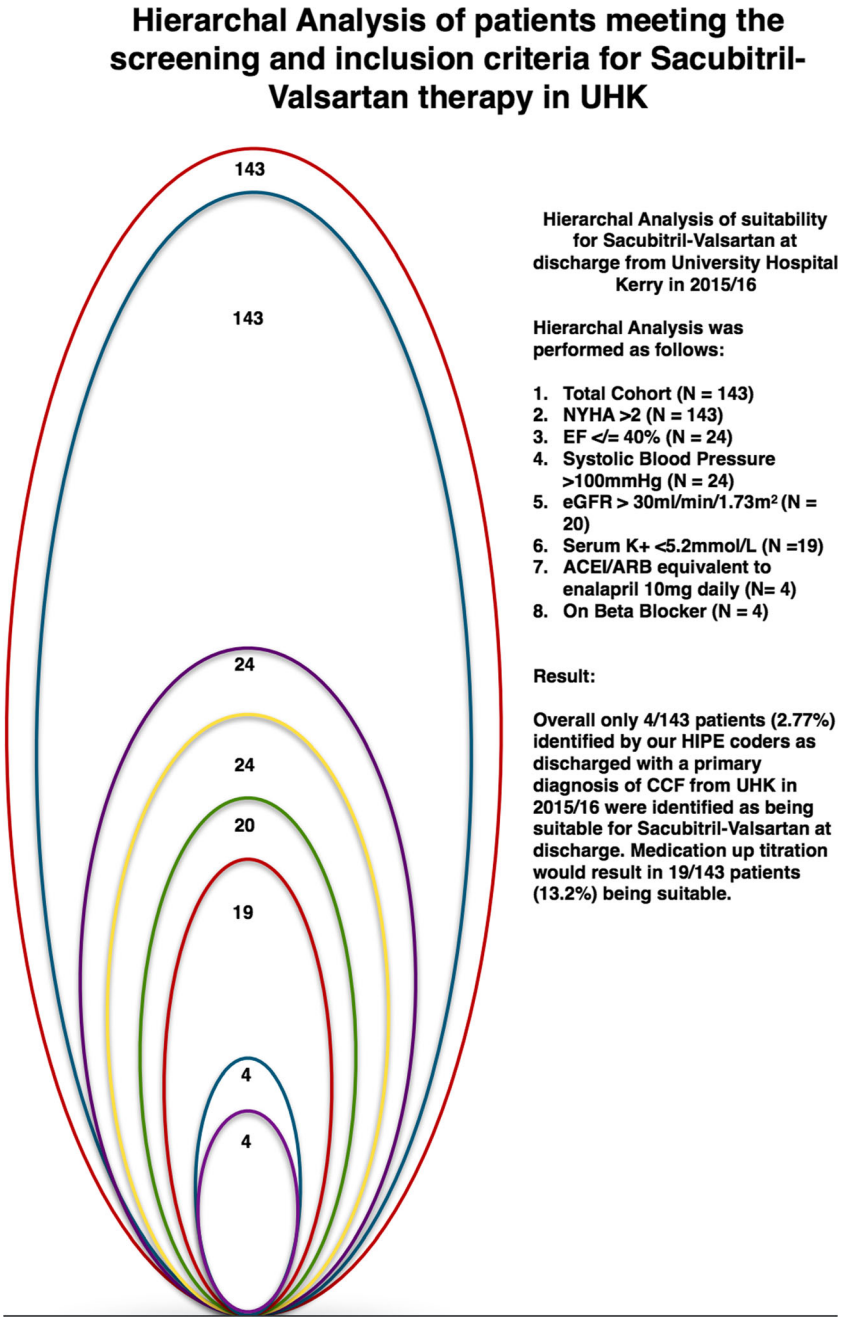

Fig. 1 Results of a hierarchical analysis re: suitability for sacubitril-valsartan on patients discharged from UHK

were notable. At discharge only 16.66% of our real-world HFrEF cohort were eligible for sacubitril-valsartan as per PARADIGM-HF inclusion criteria. The absence of crucial specialist input such as heart failure specialists, dedicated heart failure clinics, heart failure nurse specialists or dedicated patient supports is also challenging.

Limitations to our study include the accuracy of HIPE discharge primary diagnosis labelling by junior physicians. In addition, the overall accuracy of heart failure diagnosis by hospital physicians is variable. Co-morbid diagnoses can influence BNP level such as valvular heart disease, arrhythmia, pulmonary and renal disease, liver cirrhosis, hyperthyroidism and sepsis. However, data was not collected on these as the focus of this study was raised BNP in the setting of reduced left ventricular function necessitating treatment. The sample data was collected from only a single clinical centre. The study population represented largely unwell hospital inpatients as opposed to the stable well community-based patients targeted during the PARADIGM-HF study. The proportion of patients with a reduced rejection fraction was small. Furthermore, the study only incorporated a short period from 2015 to 2016 and did not benefit from variabilities in clinical course outside this time.

This study focused on a secondary care or district general hospital setting. No specialised heart failure services were

available on site which greatly limits the initiation, monitoring and optimisation of heart failure medications. The lack of specialist heart failure services is a significant rate-limiting step in this population. With regard to sacubitril-valsartan this study highlights challenges in applying guidelines to the real-world district hospital setting. A major portion of our study population had HFPEF. Indeed, the proportion with HFREF was below what one would expect from international data. Our study population was an older cohort than that of PARADIGM and it is well established [21] that HFPEF increases with age, even in relation to HFREF, and furthermore carries a worse prognosis than initially suspected.

The benefits of PARADIGM and the guideline induced implementation of sacubitril-valsartan are clearly a real-world challenge. Of note, PARADIGM focused on a stable outpatient patient cohort. However, several major advancements and trials are in progress. Recent and future studies include:

The PARAGON trial [22] seeks to investigate the efficacy and safety of sacubitril-valsartan in patients with HFPEF, which reflect most patients in the present trial. The estimated date of completion is 2019.

TRANSITION [23] plans to contrast the initiation of sabubitril-valsartan as an inpatient vs during the post discharge phase. Projected for completion in 2018.

PARADISE-MI [24] looks to assess mortality and hospitalisation on sabubitril-valsartan post myocardial infarction.

PARABLE [25] is a trial ongoing in Ireland to compare sabubitril-valsartan and Valsartan monotherapy in HFREF.

Conclusion

Our study showed that a small proportion of our patients in real-world practice are suitable for sacubitril-valsartan therapy at discharge. Entresto is currently not indicated in the context of HFPEF; however, ongoing trials are evaluating this question. If the evidence base for HFPEF evolves, then entresto may have significant clinical promise in the Irish setting. Rudimental evidence-based medications for the treatment of heart failure are infrequently prescribed and the absence of dedicated heart failure services in a non-tertiary centre may explain the poor compliance observed. Increased awareness of the evidence base and guideline adherence at the primary and secondary care level would likely provide significant benefit to heart failure patients in Ireland.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement This retrospective study was discussed with and approved by the Ethics Committee at University Hospital Kerry. As this was a retrospective analysis, informed consent was not required.

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