# MEDICATION TITRATION AND OUTPATIENT APPOINTMENT REQUIREMENTS FOR HEART FAILURE PATIENTS WITH REDUCED EJECTION FRACTION IN IRELAND

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## BACKGROUND

- Sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor, (ARNI) is licensed in Europe to treat heart failure (HF) patients with reduced ejection fraction (HFrEF). (1)
- Sacubitril/valsartan is reimbursed under the community drug schemes in Ireland subject to the following criteria being met:

  - ✓ Left ventricular ejection fraction (LVEF) of ≤ 35%
  - ✓ Symptomatic with NYHA functional class II to IV symptoms
  - ✓ Receiving optimal medical therapy for HF including angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin-receptor blocker (ARB), and other HF therapies including a beta-blocker and mineralocorticoid receptor antagonist (MRA) as necessary
  - ✓ Systolic blood pressure ≥ 100 mmHg
  - ✓ Serum potassium (K+) ≤ 5.4 mmol/L(2)

- The European Society of Cardiology (ESC) guidelines were updated in 2021 to recommend the use of an ARNI as a replacement for an ACEi in suitable patients who remain symptomatic on an ACEi, beta-blocker and a MRA. However an ARNI may also be considered as a first-line therapy instead of an ACEi. (3)
- In addition to the ESC guidelines, the American College of Cardiology and the Canadian Cardiovascular Society recommend sacubitril/valsartan ahead of ACEi/ARBs.(4,5)
- These guidelines were updated to reflect the clinical evidence which was collected further to the pivotal PARADIGM-HF Phase III trial, in the PIONEER-HF, PROVE-HF, TRANSITION and TITRATION trials.(6-9)
- To meet the reimbursement criteria for treatment with sacubitril/valsartan in Ireland, HFrEF patients must first be titrated to the maximum tolerated dose (MTD) of an ACEi or ARB medication.(2)
- There are approximately 6,500 patients treated with sacubitril/valsartan in Ireland (January 2023).(10)

## OBJECTIVES

- The objective is to determine the number of appointments required to achieve MTD of ACEi, ARB and ARNI (sacubitril/valsartan) medications in patients with HFrEF. Secondly, we aim to estimate the cost of outpatient appointments to titrate medicines.
- This research will also aim to determine whether there have been any changes to the availability of services and clinics for HF patients in the year preceding the survey.

## METHODS

- A survey was developed and sent via email by Novartis Ireland to the Irish Association of Heart Failure nurses (IAHFN) in November 2021 to obtain information on the number of appointments required to titrate patients to MTD of ACEi, ARB and ARNI medications in patients with HFrEF.
- The survey asked respondents how long it took to titrate patients on the most commonly used ACEi (enalapril, lisinopril, perindopril and ramipril) and ARBs (candesartan, losartan and valsartan), with an other option to allow for inclusion for the less frequently used ACEi or ARBs. The same question was asked regarding ARNI.
- The cost of an outpatient appointment was obtained via email communication with the Healthcare Pricing Office (HPO) in October 2021.
- In addition to questions on appointment requirements and to gauge service availability in relation to HF, the survey asked if the respondent worked in a public or private hospital, had clinic capacity reduced since the COVID-19 pandemic and also what was the waiting time for an echo in their hospitals.
- The number of patients waiting on an outpatient cardiology appointment was determined from the National Treatment Patient Fund (NTPF) outpatient national numbers.

## RESULTS

- Thirty-three responses were received from HF nurses across Ireland, a response rate of 35%. 97% of respondents worked in the public system, with 3% in private practice.
- On average, it takes four outpatient titration appointments for patients on ACEi or an ARB to reach MTD. It takes three outpatient titration appointments for patients to be titrated to MTD on an ARNI.
- The results for each type of ACEi/ARB treatment can be seen in Table 1.
- According to the HPO, the cost of an outpatient appointment in Ireland is €178. The cost of the four outpatient titration appointments for ACEi/ARB titration and three appointments for ARNI titration is therefore estimated as €712 and €534 respectively.
- HF clinic capacity has reduced by an average of 37.7% in the preceding year with a range of reductions from 10-50%. Referrals have also increased in this timeframe by 41.4%.
- Wait times for echo averaged 2.9 months in urgent cases and 12.2 months in non-urgent cases.
- As of the 23rd of February 2023, there are 33,735 patients on the NTPF adult cardiology outpatient waiting list. (11)

**Table 1: Results of the Heart Failure Medication Titration Survey**

| ACEi Titration | Number of Titration Appointments | | |
|---|---|---|---|
| Medication | Range | | Mean |
| Enalapril | 1- 10 appointments | | 4.5 |
| Lisinopril | 1 – 10 appointments | | 4.9 |
| Perindopril | 1- 7 appointments | | 4.0 |
| Ramipril | 1 – 8 appointments | | 4.9 |
| Other ACEi | 1 – 8 appointments | | 3.9 |
| ARB Titration | | | |
| Candesartan | 1- 10 appointments | | 4.4 |
| Losartan | 1- 9 appointments | | 4.0 |
| Valsartan | 2- 8 appointments | | 4.7 |
| Other ARB | 1- 8 appointments | | 4.2 |
| ARNI Titration | | | |
| Sacubitril/valsartan | 2 – 7 appointments | | 3.7 |
| Heart Failure Clinic Capacity | | | |
| | Range of capacity reduction in the past year | | |
| Clinic reduction | 10% - 50% reduction | | 37.7% |
| Increase in referrals | 0% - 90% increase in referrals | | 41.4% (SD 22.4) |
| Echo Waiting Time | | | |
| Non-urgent | Min 3 months | Max 24 months* | 12.2 months |
| Urgent | Mon 0 months | Max 24 months* | 2.9 months |

*max option of 24 months

## CONCLUSIONS

- Prior to treatment with an ARNI, patients require on average four titration appointments to reach MTD of an ACEi/ARB.
- There is an opportunity to reduce the number of outpatient HF appointments used for the initiation of sacubitril/valsartan should the treatment be initiated earlier in the patient pathway, as recommended by various clinical guidelines. This could free up appointments for patients on the cardiovascular outpatient waiting list and create efficiencies within the healthcare system.
- Clinic capacity has reduced and the number of referrals have increased. Removing the requirement for ACEi/ARB titration to MTD prior to ARNI initiation could assist with increasing the number of outpatient appointments available.
- Initiating sacubitril/valsartan could also act as a cost saving measure with respect to the number of outpatient appointments- considering the cost of an outpatient appointment in Ireland as €178, the cost of the four appointments for ACEi/ARB titration is €712 per patient.

## LIMITATIONS AND FURTHER RESEARCH

- This research focuses only on appointments for medication titration and does not consider factors which may deem a patient unsuitable for treatment with sacubitril/valsartan.
- A costing study could be considered as an option for further research to get a true picture of the cost of beginning patients on sacubitril/valsartan earlier in the treatment pathway; this could include- the cost of sacubitril/valsartan in comparison with ACEi/ARB, the improved mortality outcomes with sacubitril/valsartan vs ACEi/ARB and the reduced hospitalisation in sacubitril/valsartan treated HFrEF patients.

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