https://doi.org/10.31925/farmacia.2023.1.6 **ORIGINAL ARTICLE**

ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITORS (ARNI) AND TOLERABILITY IN HEART FAILURE PATIENTS - A RETROSPECTIVE OBSERVATIONAL STUDY FROM PRINCE SULTAN CARDIAC CENTRE

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Abstract

Angiotensin receptor neprilysin inhibitor (ARNI) is a new class of drugs for heart failure with reduced ejection fraction (HFrEF). According to the guidelines' recommendations, replacing angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) with an ARNI is recommended to further reduce morbidity and mortality. This study aimed to assess the extent of the clinician's adherence to the equivalent doses of ARNI and the patient tolerability to ARNI doses. This is a retrospective observational study that took place at Prince Sultan Cardiac Centre, Riyadh, Saudi Arabia, conducted on heart failure patients who were shifted from ACE inhibitors or ARBs to ARNI from January 2017 to November 2019. A descriptive analysis was conducted to assess the prevalence and sociodemographic factors of the study population. Of 450 patients, 304 (67.5%) started on the equivalent dose of ARNI, the dose intolerance occurred in 21 patients (30%) who received a dose higher than the equivalent dose, as compared with 13 (5.4%) patients who received an equivalent dose (odds ratio, 7.52; 95% confidence interval [CI], 3.52 - 16.03; $p < 0.001$). Among patients whose treatments were changed from ACE inhibitors or ARBs to ARNI, only 65.5% of them were switched to the equivalent doses of ARNI. Moreover, our study found that switching to a higher dose might increase the incidence of dose intolerance by 7.52 times more than that of switching to an equivalent dose. A generation of standardized protocols and electronic decision support would help to facilitate the switching to a proper dose and ensure better dose tolerability.

Rezumat

Inhibitorii receptorului de angiotensină-neprilizină (ARNI) sunt substanțe noi, folosite pentru insuficiența cardiacă cu fracție de ejecție redusă (HFrEF). Conform recomandărilor ghidurilor, înlocuirea inhibitorilor enzimei de conversie a angiotensinei (ECA) sau a blocanților receptorilor angiotensinei II (BRA) cu un ARNI este recomandată pentru a reduce și mai mult morbiditatea și mortalitatea. Acest studiu și-a propus să evalueze gradul de aderență la dozele echivalente de ARNI și tolerabilitatea pacientului la dozele de ARNI. Acesta este un studiu observațional retrospectiv care a avut loc la Centrul Cardiac *Prince Sultan*, Riyadh, Arabia Saudită, efectuat pe pacienți cu insuficiență cardiacă care au fost transferați din punct de vedere medicamentos de la inhibitori ECA sau ARA la ARNI din ianuarie 2017 până în noiembrie 2019. A fost efectuată o analiză descriptivă pentru a evalua prevalența și factorii socio-demografici ai populației studiate. Testul Chi-pătrat a fost utilizat pentru analiza variabilelor categorice ori de câte ori a fost aplicat. Datele au fost analizate folosind SPSS Inc., Chicago, IL, SUA, iar valoarea $p < 0,05$ a fost considerată semnificativă statistic. Din 450 de pacienți, 304 (67,5%) au început cu doza echivalentă de ARNI, intoleranța la doză a apărut la 21 de pacienți (30%) care au primit o doză mai mare decât doza echivalentă, comparativ cu 13 (5,4%) pacienți care a primit o doză echivalentă (*odds ratio* 7,52; interval de încredere [IC] 95%, 3,52 - 16,03; $p < 0,001$). Dintre pacienții ale căror tratamente au fost schimbate de la inhibitori ai ECA sau ARB la ARNI, doar 65,5% dintre aceștia au fost trecuți la doze echivalente de ARNI. Mai mult, studiul a constatat că trecerea la o doză mai mare ar putea crește incidența intoleranței de 7,52 ori mai mult decât cea a trecerii la o doză echivalentă. Se impune crearea unor protocoale standardizate, alături de suportul electronic decizional, pentru facilitarea alegerii unei doze adecvată și pentru asigurarea unei toleranțe superioare.

Keywords: heart failure, angiotensin receptor neprilysin inhibitor, dose intolerance, sacubitril/valsartan

Introduction

Heart failure (HF) is a major public health problem in Saudi Arabia and still has a significant disease burden worldwide despite advances in therapy [1]. The standard management has been focused on multiple mechanisms, including the blockade of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system [2, 3]. The natriuretic peptide system is a

counter-regulatory system and one of the compensatory mechanisms that promote vasodilatation and natriuretic [2]. Angiotensin receptor Neprilysin inhibitor (ARNI) is a new class of drugs that can block the renin-angiotensin-aldosterone system and enhance the natriuretic peptide system [2]. Sacubitril/valsartan is a drug combination. It consists of Valsartan, an "angiotensin receptor blocker" (ARB) and the Sacubitril "Neprilysin inhibitor" [3]. More recently, the sacubitril/ valsartan combination has been approved in more than 57 countries including Saudi Arabia [3].

The food drug and administration (FDA) approved the sacubitril/valsartan combination in July 2015 for the treatment of patients with New York Heart Association (NYHA) class II to IV, HF symptoms and a reduced ejection fraction (HFrEF) based on the results of the PARADIGM-HF trial [4]. It has now been included as a Class I B recommendation by the 2016 ESC and Class I recommendation by the 2017 ACC/AHA/HFSA [5-7]. As *per* the 2016 ESC and 2017 ACC/AHA/HFSA recommendations, the replacement of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) by an ARNI is recommended to further reduce morbidity and mortality for patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB [6-8]. However, switching from ACE inhibitor or ARB doses to ARNI doses has specific equivalent doses provided by the drug company that should be followed to ensure that the patient received the appropriate ARNI dose in terms of efficacy and safety.

As *per* the Get with the Guidelines Heart Failure Registry in the United States, there is variation among the hospitals in the pattern of ARNI initiation, and further research addressing this topic is needed [9]. Switching to the equivalent ARNI dose will ensure that the patient is on the optimal therapy and help to reach the target dose that has been shown the mortality benefit on the trial at an appropriate time without exposing the patient to any risk of dose intolerance. To the best of our knowledge, the extent of the clinician's adherence to the equivalent doses of ARNI provided by the drug company has not been studied yet in Saudi Arabia. This retrospective study was conducted at Prince Sultan Cardiac Centre to assess the appropriateness of switching to ARNI in heart failure patients and to know the impact of prescribing an inappropriate initial dose on patient tolerability.

Materials and Methods

Study design

A retrospective observational study was carried out at Prince Sultan Cardiac Centre conducted on heart failure patients who were switched from ACE inhibitors or ARBs to ARNI from January 2017 to November 2019. The primary endpoint was the adherence of the clinicians to shift to the equivalent doses of ARNI provided by the drug company. The secondary end-point was to evaluate the patient's tolerability and dose intolerance. To assess the primary endpoint, the ACE inhibitor or ARB doses were recorded as well as the ARNI doses, to know the pattern of prescribing ARNI after switching from ACE inhibitors or ARBs. To assess the secondary endpoint, the patients who started on equivalent doses and doses higher than the equivalent doses were followed in a retrospective manner to assess their tolerability and dose intolerance.

Dose intolerance

ARNI dose intolerance at follow-ups was defined as systolic blood pressure (SBP) of less than 95 mmHg or symptomatic hypotension, a decrease in the eGFR of more than 35%, or serum potassium level of more than 5.4 mmol *per* litre. These three criteria have been taken from the exclusion criteria at randomization of the PARADIGM-HF trial [4]. Patients who were switched from ACE inhibitors or ARBs to ARNI were included. The exclusion criteria are as follows: patients who start ARNI without previous use of ACE inhibitors or ARBs and hypotension with SBP less than 90 mmHG or symptomatic hypotension at the time of switching.

Equivalent ARNI dose

As *per* the drug company, the starting dose of ARNI could be either 24/26 mg twice daily or 49/51 mg twice daily (full dose). Unless the patient is on a high dose of ACE inhibitor or ARB, start with 24/26 mg twice daily, and then double the dose every 2 to 4 weeks as tolerated [10].

ACE inhibitor (low dose): total dose *per* day of ≤ 10 mg of enalapril or therapeutically equivalent dose of another ACE inhibitor (*e.g.*, lisinopril ≤ 10 mg, ramipril ≤ 5 mg), ARB (low dose): total dose *per* day of ≤ 160 mg of valsartan or therapeutically equivalent dose of another ARB (*e.g.*, candesartan ≤ 16 mg olmesartan ≤ 10 mg, losartan ≤ 50 mg), ACE inhibitor (high dose): total dose *per* day of > 10 mg of enalapril or therapeutically equivalent dose of another ACE inhibitor (*e.g.*, lisinopril > 10 mg, ramipril > 5 mg), ARB (high dose): total dose *per* day of > 160 mg of valsartan or therapeutically equivalent dose of another ARB (*e.g.*, candesartan > 16 mg, olmesartan > 10 mg, losartan > 50 mg) [10].

Datasheet

Details of every patient were recorded, including the patient's demographic data (age, gender), drug side effects, ACE inhibitor dose, or ARB dose, and the prescribed ARNI dose.

Statistical analysis

The Chi-square test was used to assess the differences between categorical variables. Values of $p < 0.05$ indicate statistically significant results. The Statistical Package for Social Science (SPSS) version 25 was used to analyse the study data.

Results and Discussion

From January 2017 to November 2019, 564 patients with a prescription of sacubitril/valsartan were identified. A total of 450 (79.7%) patients met our inclusion criteria. The mean age of the patients was 56.8 ± 1.2 years (Table I) and 120 (26.6%) were women and 330 (73.3%) were men (Figure 1). Among the patients, 148 (32.8%) of them were given 100 mg of sacubitril/valsartan, while the majority of them were prescribed 291 (64.6%) 50 mg strength of sacubitril/valsartan, only 11 (2.4%) of them were given 200 mg of sacubitril/valsartan (Figure 2).

Table I

Characteristics of the participants and the primary outcome

Variables	Based on the Initial ARNI dose no (%)			
	Overall 450	Higher than the equivalent 104 (23.1)	Equivalent dose 304 (67.5)	Lower than the equivalent 42 (9.4)
Age	56.8	56.1	57.8	57
Gender				
Male— no. (%)	330 (73.3)	74 (71.2)	222 (73)	34 (81)
Female—no. (%)	120 (26.6)	30 (28.8)	82 (27)	8 (19)

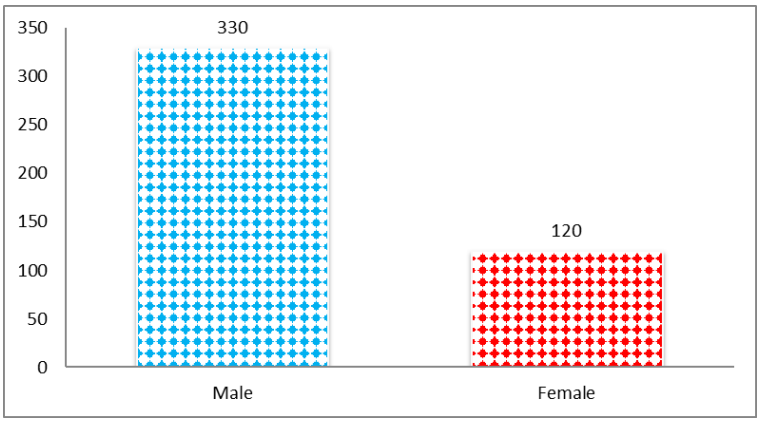

Figure 1.
Demographics of the participants

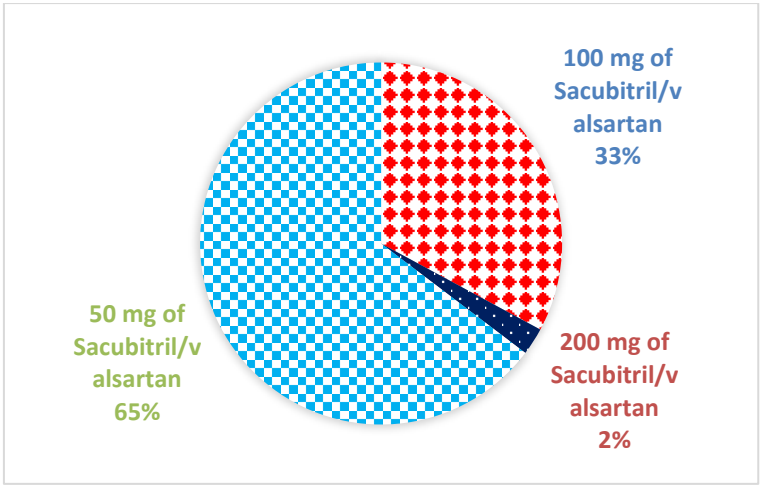

Figure 2.
Strength of sacubitril/valsartan among study participants

Around 34% of the males and 30.8% of the females were on 100 mg dose of sacubitril/valsartan tablets, while 80% of the males were found on 200 mg strength of sacubitril/valsartan tablets. There was a significant association between the strength of taking sacubitril/valsartan tables and gender (p = 0.0001). The association between gender and the strength of taking sacubitril/valsartan were given in Table II. With regards to clinician adherence to the equivalent doses of ARNI, of the 450 patients, 304 (67.5%) started on the equivalent dose of ARNI, while 104 (23.1%) started on a dose higher than the equivalent dose, and 42 (9.4%) started on a dose lower than the equivalent dose.

Table II

Association between the strength of medication taking and gender

	Number of Respondents		p-value
Male			0.0001
Sacubitril/valsartan 100 mg Tablets	Count % within sex % within the medication name	111 33.7% 75%	
Sacubitril/valsartan 50 mg Tablets	Count % within sex % within the medication name	210 63.8% 72.2%	
Sacubitril/valsartan 200 mg Tablets	Count % within sex % within the medication name	8 2.4% 80%	
Female			
Sacubitril/valsartan 100 mg Tablets	Count % within sex % within the medication name	37 30.8 25%	
Sacubitril/valsartan 50 mg Tablets	Count % within sex % within the medication name	81 67.5% 27.8%	
Sacubitril/valsartan 200 mg Tablets	Count % within sex % within the medication name	02 1.7% 20%	

Dose intolerance

Out of 304 patients who started on an equivalent dose, 13 (4.28%) did not tolerate this dose necessitating dose reduction at their follow-ups. A total of 228 (75%) patients tolerated the dose without any evidence of dose intolerance, while 63 (20.72%) were lost to follow-up. Out of 104 patients who started on a dose higher than the equivalent dose, 21 (20.19%) did not tolerate this dose necessitating dose reduction at their follow-ups. A total of 49 (47.12%) patients tolerated the dose without any evidence of dose intolerance, while 34 (32.69%) were lost to follow-up. Dose intolerance occurred in 21 (30%) patients who received a dose higher than the equivalent dose, as compared with 13 (5.4%) patients (Table III) who received an equivalent dose (odds ratio, 7.52; 95% confidence interval [CI], 3.52 - 16.03; $p < 0.001$) (Table IV).

Table III

Incidence of hypotension between two groups

Variables	Equivalent dose	High dose	p-value*
Side effect			
Hypotension	13 (5.4%)	21 (30)	< 0.001
Tolerated	228 (94.6)	49 (70)	

* Chi-square test

Table IV

Dose intolerance at follow-ups

Variable	Equivalent dose (N = 241)	Higher dose (N = 70)	Odds ratio (95% CI)	p-value
Dose intolerance	13 (5.4%)	21 (30%)	7.52 (3.52 - 16.03)	< 0.001

Reasons for dose intolerance

Of the 34 patients who had dose intolerance, 23 (76.5%) did not tolerate it due to symptomatic hypotension or SBP less than 95 mmHG, while 5 (14.7%) due to elevation of serum potassium level of more than 5.4 mmol *per* litre and 3 (8.8%) did not tolerate due to a decrease in the eGFR of more than 35%.

Sacubitril/valsartan is a much-needed therapeutic advance in the avenue of CV disease and the number of patients treated with sacubitril/valsartan is expected to continue to increase over the coming years [11, 12]. Adherence to the equivalent doses of ARNI provided by the drug company is not well documented. In this observational study, we evaluated clinicians' adherence to prescribing equivalent doses of ARNI provided by the drug company. There are three doses of sacubitril/valsartan, 24 mg/26 mg, 49 mg/51 mg and 97 mg/103 mg. Out of 450 patients with HF who were shifted to ARNI on one of these three doses, only 67.5% of patients switched to the equivalent dose of ARNI. This finding was consistent with The Guidelines Heart Failure Registry in the United States, that there is variation among the hospitals in the pattern of ARNI

initiation, suggesting that there is a lack of adherence to the equivalent doses of ARNI provided by the drug company [9]. Consequently, lower adherence might be associated with an un-desirable prognosis. These findings suggest that more efforts should be taken to ensure better adherence to the equivalent doses of ARNI when the clinician decided to switch. The target dose used in the PARADIGM-HF trial was 97/103 mg twice daily [4]. In the transition study, a starting dose of 49/51 mg twice daily sacubitril/valsartan was one of the predictors of up-titration success [13]. For these proposed reasons, some clinicians tend to use higher doses upon switching from ACE inhibitors or ARBs regardless of the previous dose of ACE inhibitors or ARBs which might result in dose intolerance. Our current study found that switching to a dose of ARNI that is higher than the equivalent dose may increase the incidence of dose intolerance by 7.52 times that with the equivalent dose. Furthermore, a post hoc analysis of the PARADIGM-HF trial found that patients who required dose reduction due to dose intolerance were at higher risk for major cardio-vascular events than those who did not have a dose reduction [14].

Our study is the first study that addressed the incidence of dose intolerance of ARNI, knowing the incidence of the dose intolerance due to using a dose that is higher than the equivalent dose would help to predict the consequences of starting inappropriate doses. In contrast to the previous studies, we directly measured the adherence of the clinicians to shift to the equivalent doses of ARNI provided by the drug company and measured the incidence of dose intolerance. We also found that only 7.55% of the patients did not tolerate the ARNI doses. This percentage is like the rate of patients who did not complete the run-in period due to adverse events in the PARADIGM-HF trial [4]. Hypotension was the main cause of dose intolerance (76.5% of cases). Our study found that the incidence of dose intolerance due to hyperkalaemia was 14.7% and the incidence of dose intolerance due to renal impairment was 8.8%. These findings show some similarities relative to the existing literature [4, 11].

Our study has several limitations. First, there was a lack of proper and complete documentation of dose intolerance and missing data. With our study design, we could not assess the causes of switching to doses that were higher than the equivalent doses or lower than the equivalent doses. Another limitation was the loss of follow-up which might affect the study's generalizability.

Further research studies are required to investigate the causes of switching to doses that are higher than the equivalent doses or lower than the equivalent doses. Additional research is needed to know the long-term impact of switching to a dose that is lower than the equivalent dose. Despite these limitations, our study provides essential knowledge to clinicians about the importance of adhering to the equivalent dose of ARNI and the probability of dose intolerance.

Conclusions

In conclusion, this study showed that among patients who were shifted from ACE inhibitors or ARBs to ARNI, only 65.5% of them were switched to the equivalent doses of ARNI, which points to the fact that more effort should be invested to ensure better adherence to evidence-based guidelines. In addition, our study found that switching to a higher dose may increase the incidence of dose intolerance by 7.52 times more than that of switching to an equivalent dose. The generation of standardized protocols and electronic decision support would help to facilitate the switching to a proper dose and ensure better dose tolerability.

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Conflict of interest

The authors declare no conflict of interest.

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