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Real-World Evidence for the Tolerance and Effectiveness of the First Drug (Sacubitril/Valsartan) in a New Class-ARNI in Afro-Caribbean Patients with Heart Failure with Reduced Ejection Fraction

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Abstract

Background: The guidelines have recommended Sacubitril/Valsartan as a substitute to Angiotensin Converting Enzyme Inhibitors (ACEIs), to further reduce the risk of hospitalization and death in ambulatory patients with Heart Failure with reduced Ejection Fraction (HFrEF). However, extensive real-world evidence for its tolerance, safety and efficacy in Blacks, has been lacking. We present additional data on real world about the use of Sacubitril/Valsartan in the unique Afro-Caribbean population with HFrEF.

Methods: A cohort of 44 patients (Age 58 ± 1.91 years-old, 61.36% Male, Hypertensive 72.7, Diabetic 25%, Ischemic Cardiomyopathy 47.7)) with HFrEF (LVEF: 27.37 ± 1.19) seen at the Heart Institute of the Caribbean in Jamaica between August 2017 and September 2018 was examined. Clinical Data, heart failure features and the frequency of Prospectively Identified Adverse Events (PIAE) were extracted from Electronic Medical Records. Patients were prescribed Sacubitril/Valsartan following the manufacturer recommendations. Echocardiographic Ejection Fraction (EF) at baseline and post intervention was analyzed. Wilcoxon signed-rank test and paired sample t-test were used to compare these features before and after treatment.

Results: The most frequent PIAE were symptomatic hypotension 13.63%, cough 6.81% and renal dysfunction 2.27%. None of the treated patients developed angioedema. Post-treatment echocardiograms of 28 patients, demonstrated an average of 14.6% (SE=1.8%) increase in EF, from 28.92% to 43.81% ($p<0.0001$) over a median of 5.59 months of therapy.

Conclusion: Sacubitril/Valsartan was demonstrated to be safe, well tolerated and associated with significant functional improvement among Afro-Caribbean patients with HFrEF.

Keywords: Afro-Caribbean region; Black; Heart failure; Drug therapies, Combination

Introduction

The goals of treatment in patients with Heart Failure (HF) are to improve their clinical status, functional capacity, quality of life, prevent hospital admission and reduce mortality [1]. Neurohormonal antagonists such as Angiotensin Converting Enzyme Inhibitors (ACEI), mineralocorticoid-Receptor Antagonists (MRA) and beta-blockers have been shown to improve survival in patients affected by Heart Failure with reduced ejection fraction (HFrEF). They are recommended for the treatment of all patients with HFrEF unless contraindicated or not tolerated as they have been demonstrated to be associated with a significant reduction in mortality and frequency of hospitalizations [2]. Angiotensin II Receptor Blocker Neprilysin Inhibitor (ARNI) is a new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system that has been recently developed. In ARNI, an Angiotensin Receptor Blocker (ARB) is combined with an inhibitor of neprilysin, which is an enzyme that degrades natriuretic peptides, bradykinin, adrenomedullin, and other vasoactive peptides. The first drug in its class, Sacubitril/Valsartan, has been recommended as a substitute to ACEIs, 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 (BB) and a MRA [3]. To facilitate initiation and titration, the approved ARNI is available in 3 doses (including a dose that was not tested in the HF trial), where the target dose used in the trial was 97/103 mg twice daily [4]. Despite the superiority of Sacubitril/Valsartan over enalapril in the PARADIGM-HF trial, relevant safety measures must be made during its initiation, in clinical practice [5]. The use of ARNI is associated with the risk of hypotension and renal insufficiency and may also lead to angioedema. Importantly, the number of Black patients (mostly African American), in this study, at an increased risk of angioedema was relatively small: 213. From a total of 4187 patients just 5.1% were black. The PARADIGM-HF Trial population was 63.8 ± 11.5 years old and 59.9% were patients with ischemic cardiomyopathy [5]. In previous studies, we have demonstrated that although the most important risk factors associated with HFrEF in Afro-Caribbean patients are Hypertension and

Diabetes most of them (55%) show develop angiographycally normal coronary arteries (Non Ischemic Dilated Cardiomyopathy, NIDCM) and just 45% show angiographycally Obstructive Coronary Artery Disease (ObCAD) [6,7]. These findings coincide with the observations of Dungu et al. [8] on 211 Afro-Caribbean patients living in the UK. In this cohort the most common cause of heart failure was NIDCM (27.5% among black patients *vs.* 19.9% among white patients; P<0.001) [8]. Because the proportion of African-American and black patients in the PARADIGM-HF trial was relatively modest compared to whites, additional data on real world effectiveness and safety of the medication in this population are needed. In addition there are no studies on the use of Sacubitril/Valsartan in the unique Afro Caribbean patients with HFrEF.

Objective

The aim of this paper is to present the Real-World clinical experience of the use of sacubitril/valsartan, concerning the tolerance and safety in an Afro-Caribbean population, with Heart Failure and reduced Ejection Fraction (HFrEF). Additionally, for the first time, we assessed the effect of ARNI on the systolic function (expressed in changes in the Ejection Fraction) in a cohort of Black Afro-Caribbean out-patients of the Heart Institute of the Caribbean in Jamaica.

Methods

Study design

This retrospective cohort study aimed to explore the tolerance, safety, and effectiveness of the drug Sacubitril/Valsartan in the Caribbean region (Jamaica).

Study patients

The Cohort were at least 18 years with evidence of heart failure, New York Heart Association (NYHA) class II to IV and an ejection fraction of 40% or less. Patients taking any dose of an ACE inhibitor or an ARB were considered for participation, and they were required to be on a stable dose (at least four weeks) of a beta-blocker and an ACE inhibitor (or ARB) equivalent to at least 10 mg of enalapril daily. Patients with a systolic blood pressure of less than 100 mm Hg, an estimated Glomerular Filtration Rate (eGFR) below 30 ml per minute per 1.73 m^2 of body surface, a serum potassium level of more than 5.2 mmol per litre or a history of angioedema or unacceptable side effects during receipt of ACE inhibitors or ARBs were excluded.

Study procedures

Data from the Electronic Medical Records were collected about patient's clinical characteristics, medical history of hypertension, diabetes, myocardial infarction and clinical features of Heart Failure: New York Heart Association (NYHA) functional class, Ischemic *vs.* Non Ischemic cardiomyopathy category, ejection fraction (prior to initiating therapy and after a period of therapy in some patients), and other variables: ECG pattern, serum potassium level during therapy, estimated glomerular filtration rate (eGFR), and concomitant heart failure medications used (Table 1). Prospectively Identified Adverse Events (PIAE) was also documented. As recommendation for the Manufacturer after 36 hours of washout, the patients were switched from the ACE inhibitor (mostly enalapril or ramipril) or ARB (mostly losartan or valsartan) to an open treatment regimen with Sacubitril/Valsartan (Vymada, a trademark of Novartis AG in the Caribbean region). All the manufacturer precautions were utilized in the prescription of the drug and Sacubitril/Valsartan was initially administered at a dose of 50 mg or 100 mg twice daily (depending on the initial level of blood pressure), which was increased up to 200 mg twice daily, over a 4 to 8-week period, when tolerated. Patients were evaluated every 2 to 8 weeks during the 1st 4 months of therapy and every 1 to 2 months thereafter. Following the recommendations, the dose of the study drug was reduced in patients who had unacceptable side effects at target doses.

Characteristics n=44	**Results**
Age-years	58 ± 1.91
Male Sex-no (%)	27 (61.36)
SBP-mmHg	138.26 ± 3.42
Heart Rate-beats/min	78.83 ± 2.51
Potassium level-mmol/L	4.40 ± 0.1
eGFR>60 ml/min/m^2-no (%)	24 (85.71)
Medical History-no (%)	
Hypertension	32 (72.73)
Diabetes	11 (25)
Myocardial Infarction	9 (22.5)
Baseline ECG-no (%)	
Atrial Fibrillation	9 (22.5)
Left Bundle Branch Block	8 (19.5)
Clinical Features of Heart Failure	
LVEF-%	27.37 ± 1.19
NYHA Functional Class II-no (%)	32 (80)
Evidence of Ischemic Cardiomyopathy-no (%)	21 (47.7)
Treatment-no (%)	
Beta Blocker	42 (95.4)
Mineralocorticoid Antagonist	41 (93.18)
Digoxin	24 (54.54)
Nitrates	33 (75)

Table 1: Characteristics of Patients at Baseline. eGFR: estimated Glomerular Filtration Rate; ECG: Electrocardiogram; LVEF: Left Ventricular Ejection Fraction; NYHA: New York Heart Association; Plus-minus values are means ± standard error.

Statistical analysis

Data were analyzed using Stata multiprocessor version 14. The data were presented as absolute numbers with percentages in the case of nominal data and means with standard deviation and 95% confidence intervals, in the case of continuous data. Wilcoxon signed-rank test was used to compare paired samples, to assess the significance of the

change, for non- normally distributed data. Paired sample t-test was used to assess normally distributed data. A p-value <0.05 was considered statistically significant (two-sided).

Results

Study patients

From August 10, 2017, to June 27, 2018, a total of 50 consecutive outpatients form the Heart Institute of the Caribbean, Jamaica were treated. Of these patients, six were excluded as they were lost to follow up or had poor adherence with the medications, mostly for financial constrictions. Most of the patients were receiving the recommended pharmacologic therapy for chronic heart failure according to the guidelines mentioned earlier (Table 1). Echocardiogram parameters were available for review in twenty-eight of the patients after a period of initiating therapy with Sacubitril/Valsartan (Table 2).

Characteristics n=28	Results
Age-years	57.22 ± 2.49
Male Sex-no (%)	15 (53.57)
Hypertension-no (%)	19 (67.86)
Diabetes-no (%)	6 (13.63)
Ischemic Cardiomyopathy-no (%)	3 (23.08)
Pre-Treatment Ejection Fraction-% [95% CI]	28.92% [25.86-31.91]
Post-Treatment Ejection fraction-% [95% CI]	43.81% [39.74-47.87]
Ejection Fraction increase-% [95% CI]	14.58% [10.65-18.50]
Percent increase in Ejection Fraction-% [95% CI]	57.70% [39.24-76.17]

Table 2: Characteristics of Patients with Echocardiogram Assessment Following Therapy. Plus-minus values are means ± standard error

Study-drug follow-up

The median duration of follow-up (during which adverse effects were monitored) was 3.22 months.

Ejection fraction

Date of the baseline and follow up echocardiographic Ejection Fraction, after a median of 24.3 weeks of initiating treatment, was available for 28 patients (Table 2 and Figure 1). The ejection fraction at the time of follow up was found to significantly differ from the baseline ejection fractions (p<0.0001). A mean percent increase of 57.7% (95% CI=39.23-76.17) was noted, from the mean baseline EF of 28.9% to 43.7% among these participants. Coronary Angiography (CA) and/or Myocardial Perfusion Scan (MPS) was available in 13 (46.4%) of this subgroup of patients and was reported normal in 10 (76.9%) of this patients.

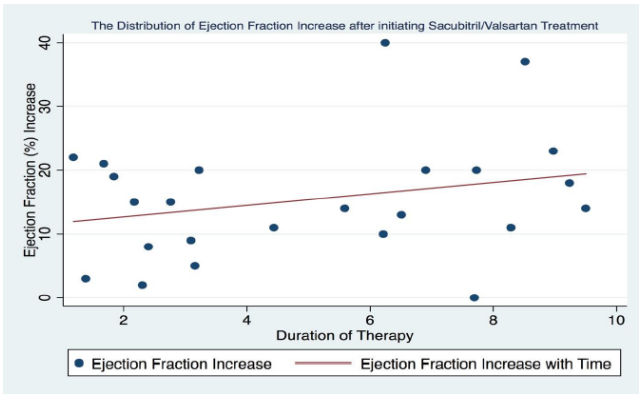

Figure 1: Two-way Scatterplot of the Ejection Fraction increase and Duration of Therapy.

Tolerance and safety

During the treatment period one (2.27%) of the patients withdrew due to an adverse event (renal dysfunction). The most frequent prospectively identified adverse events of the study drug are summarized in Table 3. None of the adverse events, with the exception of one case of renal dysfunction, led to discontinuation of the drug and none of the study patients report angioedema.

Adverse Events	Frequency (%) n=44
Symptomatic hypotension	13.63
Cough	6.81
Renal dysfunction	2.27
Gastrointestinal disturbances	2.27

Table 3: Frequency prospectively identified adverse events.

Discussion

While clinical trials (RCT) remain the gold standard requirement for new drug registration, it is becoming increasingly apparent that the necessarily standardized, selective and artificial conditions under which they are conducted may provide little or no information on how a drug performs in the clinical practice setting. Real-world evidence gathered from post-approval observational studies has a crucial role to play in perfecting and personalizing treatment delivery. In this initial clinical experience with ARNI in the Caribbean region (Jamaica), we demonstrate that the use of Sacubitril/Valsartan is well tolerated and safe in the Afro-Caribbean population with Heart Failure and reduced Ejection Fraction (HFrEF). In addition, Sacubitril/Valsartan was found to improve the ejection fraction beyond the effects of concomitant Optimal Medical Therapy (OMT).

Prospectively identified adverse events

The adverse effects experienced by our patients are summarized in Table 3. Of note, none of the patients experienced angioedema. The incidence of adverse effects in this population in Real-World is important to note, as this has not been previously documented among

Afro-Caribbean persons. In the PARADIGM-HF Trial, among 4187 patients, assigned to Sacubitril/Valsartan, 213 (5.1%) were Black [5]. Similarly, of the 4212 participants assigned to the enalapril group, 215 (5.1%) were black. The incidence of adverse effects experienced differed between the LCZ696 and enalapril groups, where symptomatic hypotension was reported in 14% *vs.* 9.2 %, cough in 11.3% *vs.* 14.3 %, elevated serum creatinine (>2.5 mg/dl) in 3.3 *vs.* 4.5% and angioedema in 0.2% *vs.* 0.1 % [5]. The frequencies of adverse effects and degree of response to Sacubitril/Valsartan experienced in patients with HFrEF have also been shown to differ based on race [9]. In the Racial Differences, Outcomes and Response to Sacubitril/Valsartan in Heart Failure with Reduced Ejection Fraction: PARADIGM-HF sub study. Among 428 self-described African-American black patients, angioedema occurred in 2 patients (0.005%) during run-in and 5 patients (0.012%) post-randomization with sacubitril/valsartan, whereas 2 patients (0.005%) experienced angioedema during run-in and 1 patient (0.002%) post-randomization with enalapril [9]. Treatment with Sacubitril/Valsartan is expected to be associated with a higher degree of symptomatic hypotension compared to treatment with enalapril, due to its more potent vasodilatory effects; however, the rate of discontinuation due hypotensive symptoms was not increased [9]. A potential contributor to hypotension in our cohort may have been the concomitant use of nitrates. A Randomized Clinical Trial (RCT) conducted in self-identified black patients (defined as being of African descent) showed that addition of the combination of hydralazine and isosorbide dinitrate to conventional therapy (ACEI, beta-blocker and MRA) reduced mortality and HF hospitalizations in patients with HFrEF and NYHA Classes III – IV. In this African-American Heart Failure Trial (A-HeFT) combination therapy with nitrates had a slight but significant blood-pressure-lowering effect at six months [10]. In the other hand, Sacubitril/Valsartan may be associated with renal impairment as a result of renal hypoperfusion, due to its significant hypotensive effect, or its effect on the renin-angiotensin-aldosterone system [4]. Hence, it is critical to monitor for an increase in the serum creatinine levels, prior to and during its initiation. The drug of interest was discontinued in one of our patients, related to renal impairment. This was a 77 years-old male with diabetes and hypertension patient with mild renal impairment prior to starting the drug. He experienced a significant decrease in the eGFR, after three months of initiating therapy. However, the primary safety concern with Sacubitril/Valsartan, especially in African descendant population, is the increased risk of severe angioedema. None of the patients in our study experienced this adverse effect. Sacubitril/valsartan (an angiotensin receptor neprilysin inhibitor) has been shown to have superior clinical benefits *vs.* the angiotensin-Converting Enzyme Inhibitor (ACEI) enalapril in patients with HFrEF [5]. However, this may be at the expense of more risks, such as angioedema. Co-inhibition of ACE and neprilysin may increase the risk of angioedema. This adverse event was of particular interest as understanding racial differences in safety and efficacy of heart failure therapies is essential. In the Racial Differences, Outcomes and Response to Sacubitril/Valsartan in Heart Failure with Reduced Ejection Fraction: PARADIGM-HF Sub Study, among the 428 African-American patients that were enrolled, sacubitril/valsartan was associated with a higher incidence of angioedema compared to enalapril (2.5% *vs.* 0.5%), however, the benefits substantially outweighed the risk [9]. Angioedema is a known, but rare, adverse effect of ACEIs (to a lesser extent, ARBs) and is thought to be primarily mediated by bradykinin [10,11]. Other endopeptidases that target bradykinin include neprilysin and aminopeptidase P [12]. In contrast with omapatrilat, sacubitril/valsartan combines the ARB valsartan with a more specific inhibitor of neprilysin. The main reason for the difference between omapatrilat and sacubitril/valsartan may also be the lower risk of angioedema with an ARB *vs.* an ACE [11-13]. Although this continues to be a topic of great interest, currently, the mechanism of the absence of angioedema observed in black Afro-Caribbean is unknown [14,15]. This was likely not demonstrated due to the small sample size; however, it could be a racial or ethnic peculiarity. As we address before while clinical trials remain the gold standard requirement for new drug registration, Real-world evidence gathered from post-approval observational studies has a crucial role to play in perfecting and personalizing treatments.

Ejection fraction improvement achieved with Sacubitril/Valsartan in Afro-Caribbean patients with heart failure and reduced ejection fraction

This is the first study to-date to describe improvements in EF (a percent increase in Ejection Fraction of 57.70% was noted) with Sacubitril/Valsartan in Afro Caribbean patients with HFrEF Akin to BB, ACEI, ARB and MRA therapies. Our results demonstrate the ability of Sacubitril/Valsartan to improve LVEF significantly. It was possibly associated with cardiac reverse remodelling [16] in a real-world setting outside of the context of clinical trials. Almufleh et al. [17] in a single-center retrospective cohort study of 48 patients (70 ± 11.1 years-old, Hypertension 47%, Non-ischemic etiology 53.2%) with HFrEF from the Heart Function clinic at the University of Ottawa Heart Institute (treated with Sacubitril/Valsartan for a median duration of 3 months (Interquartile range 2-6 months), found that Sacubitril/Valsartan use was associated with an average 5% (± 1.2) increase in EF, from a mean baseline of 25.33% to 30.14% ($p<0.001$). Significant improvement in left ventricular remodeling parameters, including reductions in LVESD (3.36 ± 1.6 mm), LVEDD (2.64 ± 1.1 mm), and LV mass index (14.4 ± 3.9 g/m^2), were also demonstrated.

Limitations

Though our results are encouraging, our observational Real-World study needs validation using a larger cohort with more extended follow-up periods and Bio Markers monitoring (NT-proBNP Testing). Another limitation of our study is that we did not present specific data of changes in the ventricular geometry associated with reverse remodelling. Additionally, echocardiograms following the initiation of Sacubitril/Valsartan were available just for 63% of the sample. Furthermore, there was a lack of a comparator group precluding a direct comparison of Sacubitril/Valsartan patients to those with just Heart Failure optimal medical therapy (OMT).

Conclusion

This Real Word study has demonstrated that Sacubitril/Valsartan is safe and well tolerated among Afro-Caribbean patients. Adverse effects reported were symptomatic hypotension, cough and renal dysfunction. No cases of angioedema were documented during the whole period of observation. Furthermore, to note, Sacubitril/Valsartan was associated with significant functional improvement among Afro-Caribbean patients with HFrEF treated with ARNI medication.

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Conflict of Interest

Dr. Felix Nunura and Dr. Edwin Tulloch-Reid has received in the past a speaker honorarium from Drug Company Novartis. The Authors do indicate that they do not own any shares of Drug Company. The Authors confirm that we have not any financial relationship in the way of sponsorship for the Research with the Drug Company.

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