A per-protocol initiation of sacubitril/valsartan in an advanced heart failure disease management programme in the Middle East Gulf Region

Bassam Atallah¹, Ziad G. Sadik¹, Mohamed Hisham¹, Oussama Kalagieh¹, Iman Hamour², Guirgis Gabra², Mosaad El Banna², Medhat Soliman², Antoine Cherfan¹ and Feras Bader²*

¹Department of Pharmacy Services, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates; ²Heart and Vascular Institute, Cleveland Clinic Abu Dhabi, Al Maryah Island, PO Box 112412, Abu Dhabi, United Arab Emirates

Abstract

**Aims** The aim of this study is to evaluate the utilization and success in therapy intensification after initiation of sacubitril/valsartan using a specified protocol within an advanced heart failure and transplant programme in the Middle East Gulf Region.

**Methods and results** We studied a single-centre, retrospective cohort in a 364-bedded multi-speciality hospital located in the United Arab Emirates (February 2016 to July 2017). The advanced heart failure and transplant programme formulated an institutional protocol for initiation of sacubitril/valsartan with defined criteria for switching from angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB). Prescribing this drug is intended for patients with heart failure with reduced ejection fraction with left ventricular ejection fraction ≤40%. We excluded patients (i) with age below 18 years or (ii) initiated on sacubitril/valsartan from an outside hospital with or without follow-up in our outpatient clinic. We included 102 patients with an average initial dose of 78.9 ± 44.2 mg twice daily. Only 17 patients were on target doses of ACEI or ARB prior to switching to sacubitril/valsartan. Up-titration was successful in 55 patients during the follow-up period. In addition, 6.9% patients were hospitalized with heart failure exacerbation. In patients with elevated baseline serum potassium prior to initiating this medication, the serum potassium levels decreased post-initiation by 0.5 ± 0.3 mmol/L (P = 0.0008).

**Conclusions** Initiating sacubitril/valsartan through a defined protocol selects for appropriate candidates and guides starting dose and titration. Overall, significant success can be achieved in replacing ACEI or ARB by sacubitril/valsartan in symptomatic heart failure with reduced ejection fraction patients.

**Keywords** Angiotensin II and neprilysin inhibitor; Heart failure

Received: 3 November 2018; Revised: 10 April 2019; Accepted: 26 April 2019

*Correspondence to: Feras Bader, Heart and Vascular Institute, Cleveland Clinic Abu Dhabi, Al Maryah Island, PO Box 112412, Abu Dhabi, United Arab Emirates. Tel: +971 56 360 3360; Fax: +971 2 410 8374. Email: baderf@clevelandclinicabudhabi.ae

The manuscript, or part of it, has neither been published (except in the form of abstract) nor is currently under consideration for publication by any other journal.

Introduction

Sacubitril/valsartan was Food and Drug Administration approved in July 2015 as a combination medication to reduce cardiovascular deaths and hospitalizations for heart failure (HF) with reduced ejection fraction (HFrEF) patients on the basis of the PARADIGM-HF study. Since then, many institutions added this medication to their formulary. In the PARADIGM-HF trial, patients were randomized to this combination of Angiotensin II and neprilysin inhibitor (ARNI), only after they tolerated sequential target doses of both enalapril and study medication.¹ Sacubitril/valsartan significantly reduced cardiovascular death or HF hospitalization (21.8 vs. 26.5%; hazard ratio, 0.8; P < 0.001) as well as all-cause mortality (17 vs. 19.8%; hazard ratio, 0.84; P < 0.001) when compared with angiotensin-converting enzyme inhibitor (ACEI). The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Failure

© 2019 The Authors. ESC Heart Failure published by John Wiley & Sons Ltd on behalf of the European Society of Cardiology. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
Society of America 2017 focused update of the 2013 guidelines for the management of HF recommends replacing ACEI or angiotensin II receptor blocker (ARB) with ARNI in patients who are tolerating these medications and with symptomatic HFrEF New York Heart Association (NYHA) Functional Classification Class II or III. The success of the adoption of ARNI outside of the clinical trial for patients who are not yet on target doses of ACEI is not known. The rate of persistence as well as achieving target doses following early switching to ARNI is also not documented. We report a real-world experience with utilization and success in therapy intensification after initiation of sacubitril/valsartan using a specified protocol within an advanced HF and transplant programme in the Middle East Gulf Region.

Methods

Study design

The single-centre, retrospective cohort was conducted in a 364-bedded multi-speciality hospital located in the United Arab Emirates. The advanced HF and transplant programme formulated an institutional protocol for initiation of sacubitril/valsartan with defined criteria for switching from ACEI and ARB. The sacubitril/valsartan initiation protocol as shown in Table 1 was approved by the pharmacy and therapeutics committee, following which the drug was added to the hospital formulary in February 2016. We obtained institutional review board approval for collecting data from our HF database. The protocol was created to serve as a guiding document for prescribers but did not actively confine them to its content other than the computerized order entry system’s restriction to cardiologists.

Patient population

All patients who received a prescription of sacubitril/valsartan from our outpatient pharmacy from 1 February 2016 to 31 July 2017 were enrolled in the study. As per our sacubitril/valsartan initiation protocol, prescribing this drug is intended for patients with HFrEF with left ventricular ejection fraction ≤40%. We excluded patients who were (i) below the age of 18 or (ii) initiated on sacubitril/valsartan from an outside hospital with or without follow-up in our outpatient clinic.

Data collection

Data collection was performed retrospectively through electronic chart review. Patient demographics were collected on the first prescription of sacubitril/valsartan, which was set to be the index date for the purpose of this study. Patients were followed from the index date until the day of data collection or until sacubitril/valsartan was discontinued. This constituted our follow-up period. We documented prior use of ACEIs or ARBs as well as days required to achieve target dose if the patient was maintained on target dose for at least 4 weeks. Data collection included baseline systolic blood pressure on initiation, serum potassium, serum creatinine, N-terminal pro-B-type natriuretic peptide (NT-proBNP), ejection fraction, and NYHA class of symptoms. Follow-up data of these investigations were collected only if available at least 8 weeks after initiation of sacubitril/valsartan. We documented the down-titration or drug discontinuation when such events persisted for at least 4 weeks and at the time of data collection. We also analysed the clinical outcome, defined as the number of emergency department visits and hospital readmissions due to worsening HF after initiation of sacubitril/valsartan. Maximum dose was defined as sacubitril/valsartan 97/103 mg twice daily based on the 2017 ACC/AHA/Heart Failure Society of America focused update of the management of HF.

Statistical analysis

Baseline characteristics of patients were explored with the use of descriptive statistics. Continuous variables such as age, follow-up period, and NT-proBNP were described using the mean with standard deviation or the median with interquartile range where appropriate. Independent sample t-test was employed to calculate the mean difference in the target dose achieved and sacubitril/valsartan initiation protocol groups; 95% confidence interval and P-value were also calculated. The two-sided P-value was considered to be significant if it was less than 0.05. Odds ratio with 95% confidence interval and P-values were calculated for such analyses. Data were analysed using Excel 2016 software (Microsoft Corp., Redmond, WA).

Results

Patient characteristics

Overall, 124 patients with a prescription for sacubitril/valsartan dispensed from our outpatient pharmacy were identified. A total of 102 patients were enrolled in our study, and the remaining 22 patients did not meet the inclusion criteria.

The total number of patients who received sacubitril/valsartan represented 37.3% of all patients actively followed at the advanced HF programme with HFrEF by 31 July 2017. Average follow-up period was 236 ± 141.5 days.
Hypertension, hyperlipidaemia, and diabetes were the most commonly reported co-morbidities. More than half of the patients had HF of ischaemic origin (53.7%), and the majority had NYHA Class II (70.1%). None of the patients had a NYHA Class IV as shown in Table 1. Furthermore, 96 patients (94.1%) were initiated on ARNI in the ambulatory setting, and 99 patients (97.1%) were initiated by an advanced HF consultant. Only three initiations were performed by other cardiologists and none by other disciplines.

### Table 1  Sacubitril/valsartan initiation protocol

Criteria for switching to sacubitril/valsartan from ACEI or ARB

| Indications (all must apply)                                                                 |
|---------------------------------------------------------------------------------------------|
| 1. Ejection fraction ≤40%                                                                    |
| 2. NYHA Class II–IV                                                                          |
| 3. On stable dose ACEIs or ARBs                                                              |
| 4. SBP > 100 mmHg                                                                            |

Caution: SBP 90–100 mmHg or moderate cirrhosis

Absolute contraindications

1. SBP < 90 mmHg
2. Concurrent use/need for ACEIs, ARBs, or aliskiren
3. Severe hepatic impairment (Child–Pugh C)
4. Angioedema related to ACEIs or ARBs
5. History of hereditary/idiopathic angioedema

Relative contraindications

1. Recent symptomatic hypotension—delay until stable
2. Current acutely decompensated heart failure—delay until stable
3. Clinically relevant ischaemic event (recent myocardial infarction or stroke), cardiovascular surgery, or CRT in past 3 months—wait until clinically stable more than 3 months
4. Creatinine clearance <30 mL/min within last 30 days—delay until stable
5. Serum creatinine changed by >25%—delay until two consecutive values <20%
6. Serum potassium >4.8 mmol/L—delay until normalizes

### Starting dose and titration of sacubitril/valsartan

| Current regimen          | Starting dose                                           | Titration steps                        |
|--------------------------|---------------------------------------------------------|----------------------------------------|
| **Switching from ACEIs** |                                                                                                       |
| • Lisinopril >10 mg/day  | Stop ACEI for 2 days (>36 h)                           | 1. After 4 weeks, increase as tolerated to sacubitril/valsartan 200 (97/103 mg) twice daily |
| • Enalapril >10 mg/day   | Start sacubitril/valsartan 100 (49/51 mg) twice daily   | 1. After 2 weeks, increase as tolerated to sacubitril/valsartan 100 (49/51 mg) twice daily |
| • Ramipril >5 mg/day     | Stop ACEI for 2 days (>36 h)                           | 1. After 2 weeks, increase as tolerated to sacubitril/valsartan 100 (49/51 mg) twice daily |
| • Perindopril >8 mg/day  | Start sacubitril/valsartan 50 (24/26 mg) twice daily   | 1. After 4 weeks, increase as tolerated to sacubitril/valsartan 200 (97/103 mg) twice daily |
| • Lisinopril ≤10 mg/day  | Start sacubitril/valsartan 100 (49/51 mg) twice daily   | 1. After 4 weeks, increase as tolerated to sacubitril/valsartan 200 (97/103 mg) twice daily |
| • Enalapril ≤10 mg/day   | Start sacubitril/valsartan 50 (24/26 mg) twice daily   | 1. After 2 weeks, increase as tolerated to sacubitril/valsartan 200 (97/103 mg) twice daily |
| • Ramipril ≤5 mg/day     | Start sacubitril/valsartan 50 (24/26 mg) twice daily   | 1. After 4 weeks, increase as tolerated to sacubitril/valsartan 200 (97/103 mg) twice daily |
| • Perindopril ≤8 mg/day  | Start sacubitril/valsartan 50 (24/26 mg) twice daily   | 1. After 2 weeks, increase as tolerated to sacubitril/valsartan 200 (97/103 mg) twice daily |

| **Switching from ARBs** |                                                                                                       |
| • Valsartan >160 mg/day | Start sacubitril/valsartan 100 (49/51 mg) twice daily                                             | 1. After 4 weeks, increase as tolerated to sacubitril/valsartan 200 (97/103 mg) twice daily |
| • Losartan >50 mg/day   | Start sacubitril/valsartan 50 (24/26 mg) twice daily                                              | 1. After 2 weeks, increase as tolerated to sacubitril/valsartan 200 (97/103 mg) twice daily |
| • Valsartan ≤160 mg/day | Start sacubitril/valsartan 50 (24/26 mg) twice daily                                              | 1. After 4 weeks, increase as tolerated to sacubitril/valsartan 200 (97/103 mg) twice daily |
| • Losartan ≤50 mg/day   | Start sacubitril/valsartan 50 (24/26 mg) twice daily                                              | 1. After 2 weeks, increase as tolerated to sacubitril/valsartan 200 (97/103 mg) twice daily |

**Special considerations**

- Severe renal impairment (eGFR < 30 mL/min)
- Moderate hepatic impairment (Child–Pugh B)
- Borderline hypotension (SBP 90–100 mmHg)

**Sacubitril/valsartan initial dose and titration**

The average initial dose at initiation was 78.9 ± 44.2 mg twice daily. Moreover, 50 mg twice daily (24/26 mg) was the most commonly prescribed dose at initiation for 61 patients (59.8%), whereas only nine patients (8.8%) were started on the maximum dose of 200 mg twice daily (97 mg/103 mg). Further, only 17 patients (17.2%) were on target doses of ACEI or ARB as defined by the ACC/AHA HF guideline prior to switching to sacubitril/valsartan.
Table 2 Characteristics of the patients at baseline

| Characteristic                             | Result no. of events/no. of patients (%) |
|-------------------------------------------|-----------------------------------------|
| Age (years), mean ± SD                    | 58.3 ± 12.9                             |
| Gender, n (%)                             |                                         |
| Male                                      | 66/102 (64.7)                           |
| Female                                    | 36/102 (35.3)                           |
| Co-morbidities, n (%)                     |                                         |
| Hypertension                              | 79/102 (77.5)                           |
| Diabetes                                  | 60/102 (58.8)                           |
| Hyperlipidaemia                           | 69/102 (67.6)                           |
| Atrial fibrillation                       | 20/102 (19.6)                           |
| Heart failure aetiology, n (%)            |                                         |
| Ischaemic                                 | 55/102 (53.7)                           |
| NYHA class, n (%)                         |                                         |
| Class I                                   | 1/87 (1.2)                              |
| Class II                                  | 61/87 (70.1)                            |
| Class III                                 | 25/87 (28.7)                            |
| ACEI or ARB prior to switching, n (%)     |                                         |
| ACEI                                      | 51/102 (50)                             |
| ARB                                       | 48/102 (47.1)                           |
| Beta-blocker, n (%)                       | 101/102 (99)                            |
| Target dose beta-blocker, n (%)           | 42/102 (41.2)                           |
| MRA, n (%)                                | 61/102 (59.8)                           |
| Target dose MRA, n (%)                    | 38/102 (37.3)                           |
| Diuretic, n (%)                           | 77/102 (75.5)                           |
| Ejection fraction <40%, n (%)             | 98/102 (95.9)                           |

ACEI, angiotensin-converting enzyme inhibitor; ARB, Angiotensin II; NYHA, New York Heart Association; MRA, mineralocorticoid receptor antagonist.

Adherence to protocol

Appropriateness based on the indication to switch from angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker

Overall, the adherence to the hospital implemented protocol of eligibility for switching to sacubitril/valsartan was 72.5%. The remaining patients had at least one factor that represented a deviation from this protocol. Hyperkalaemia (11.8%) prior to initiating sacubitril/valsartan was the most common reason for deviating from the protocol followed by 7.8% of the patients with a recent cardiovascular event as shown in Table 3.

Adherence to recommended dose at initiation

Considering the initial dose of sacubitril/valsartan at the time the patient was switched from the ACEI or ARB, 73.4% were adherent to the recommendation from the hospital protocol. Furthermore, only 11.7% were started at higher doses and 14.9% at more cautious lower initial dose.

Clinical and safety outcomes

Only one patient expired during the duration of the follow-up. In addition, 6.9% of patients were hospitalized with HF exacerbation (percentage increases to 9.8% when we include emergency department visits), and the remaining 92.1% of the patients survived with no HF associated readmissions. NT-proBNP did not vary before and after initiation (2201.8 ± 2954.8 vs. 2110.5 ± 2715.5; P = 0.89). No difference was observed in mean serum creatinine before and after initiation (90.1 ± 38.3 vs. 92.3 ± 34.8; P = 0.39) nor with mean serum potassium levels (4.3 ± 0.5 vs. 4.4 ± 0.7; P = 0.15). A total of 13.5% of patients had an episode of hyperkalaemia as defined by serum potassium level more than or equal to 5 mmol/L.

For patients with elevated baseline serum potassium (above 4.8 mmol/L) prior to initiating sacubitril/valsartan,

Table 3 Factors indicating deviation from protocol

| Variable                                              | No. of patients (%) |
|-------------------------------------------------------|---------------------|
| Serum potassium >4.8 mmol/L                          | 12 (11.8)           |
| Recent cardiovascular event                          | 8 (7.8)             |
| Initiated in hospital setting                        | 6 (5.9)             |
| Baseline ejection fraction 41–45%                    | 4 (4.1)             |
| Acute heart failure                                  | 4 (3.9)             |
| Was not previously on ACEI or ARB                    | 3 (2.9)             |
| Systolic blood pressure <100 mmHg                    | 2 (2)               |
| Recent symptomatic hypotension                       | 2 (2)               |
| Compromised renal function (CrCl <30 mL/min)         | 1 (1.3)             |
| NYHA Class I                                         | 1 (1.1)             |

ACEI, angiotensin-converting enzyme inhibitor; ARB, Angiotensin II; CrCl, creatinine clearance; NYHA, New York Heart Association.

Figure 1 Angiotensin II and neprilysin inhibitor (ARNI) dose titration (percentage).

![Figure 1](https://example.com/figure1.png)
the serum potassium levels decreased post-initiation by 0.5 ± 0.3 mmol/L (P = 0.0008).

Reasons for discontinuation varied for each patient and included symptomatic hypotension, increased cough, rising serum creatinine or blood urea nitrogen, and unspecified intolerance to the medication.

**Discussion**

We report the largest experience with utilizing sacubitril/valsartan in the Middle East Gulf Region. Our study highlights several points that further expand our comfort level with utilizing this novel drug therapy. In our study, most patients were not on target doses of ACEI or ARB prior to switching to ARNI. In the PARADIGM-HF trial, all patients were on an ACEI dose equivalent to at least 10 mg of enalapril daily before screening. Then, they went through a run in trial period that ensured their tolerance of sequential target doses of enalapril and ARNI before being randomized. Despite this fact, most patients in our cohort had ARNI continued or uptitrated by the end of our follow-up period. This is important to highlight because in a post hoc analysis from PARADIGM-HF trial, patients on lower than target doses of ACEI or ARNI had similar magnitude of benefit compared with patients on target doses in each study arm. While utilizing a carefully designed protocol by an advanced HF and transplant programme, patients demonstrated remarkable tolerance and successful intensification of therapy. This in turn allows for a larger pool of patients to be candidates for earlier utilization of an ARNI in the course of HF therapy.

Several factors have led to the adoption of sacubitril/valsartan in our programme for almost 40% of our HFrEF patients: first, the ease of switching patients which is due to the lack of need for complex third party payer preauthorization in our healthcare system; second, the availability of a predefined initiation protocol used by a dedicated advanced HF and transplant programme; and third, most of our patients who were initiated on sacubitril/valsartan had NYHA class II symptoms, consistent with the PARADIGM-HF study, and thus may have contributed further to provider confidence in utilizing ARNI in these more stable patients. Thus, experience with switching advanced HF patients with NYHA class IV symptoms remains very limited.

Luo et al. reported on early adoption of ARNI for patients with HFrEF among a real-world population discharged alive from hospitals in Get with the Guidelines—Heart Failure. In their study, only 2.3% of the hospitalized patients were discharged on the medication. In our study, we reported on initiating the medication in the outpatient setting with a different patient population from the Middle East Gulf Region. As reported in many cardiovascular studies from this region, the patient population in our study may have different characteristics than those in Western studies including a much higher prevalence of diabetes. Our newly established advanced HF and transplant programme has contributed to optimizing medical therapy for HF patients, achieving successful longitudinal titration of medications and adoption of new therapies including sacubitril/valsartan at our institution. This was achieved through developing internal HF guidelines and protocols. In addition, several educational sessions are regularly offered by members of the team at the institutional and regional level, which contribute to improving knowledge of all providers on new medications and adoption of guideline-directed medical therapies. Such programmes can guide and empower all providers involved in the care of the HF patient.

Our study has several limitations. Firstly, the retrospective design limits the ability to fully assess the adherence to our pre-specified protocol and patient outcomes. However, it is still necessary to evaluate the objective parameters set in our protocol for switching as they apply to the patients who were actually switched. Our electronic health records system is comprehensive and includes laboratory measurements and nurse and physician assessments and is integrated with our outpatient pharmacy. This allowed us with a certain degree of comfort to assess adherence while recognizing the inherent limitation of the study design.

The second limitation is that the median duration to achieve target dose was relatively long in our study. Per our protocol, patients should be achieving target dose in 6 weeks if they are started at the lowest dose and 4 weeks if they are started at the mid-range dose. This is likely due to the inability to accommodate all patients at the indicated intervals in our specialized clinic resulting in many patients having longer follow-up appointments that delayed sooner titration. In our programme, we have recently established a pharmacotherapy specialist-led HF medication optimization clinic to include a per-protocol medication titration, which will facilitate in accommodating the frequent visits required by these patients. As real-world experience with this medication increases, more providers outside of advanced programmes will be able to utilize and titrate this medication. Such care does not need to be limited to advanced HF programmes.

The third limitation is that hyperkalaemia was prevalent at baseline in our cohort of patients and was the main reason for deviation from our initiation protocol. However, none of those patients with elevated potassium at baseline had hyperkalaemia following initiation. Our programme providers were likely confident knowing that ARNI causes less hyperkalaemia as was evident in the PARADIGM-HF trial. This has also been supported by a recent secondary analysis of the trial that showed when combined with mineralocorticoid receptor antagonists, more patients in the ACEI group experienced hyperkalaemia. Moreover, we feel comfortable in liberalizing our protocol further to change our upper limit of

\[ P = 0.0008 \]

\[ 0.5 ± 0.3 \text{ mmol/L} \]
serum potassium to 5.2 mmol/L instead of 4.8 mmol/L for those patients being considered for the switch.

The fourth limitation is that although most of our patients are compliant with our programme and their follow-up visits, we were not able to track whether these patients were admitted elsewhere. Likewise, not all patients had labs performed at our cut-off values before and after initiation of within 2 weeks prior and at least 4 weeks after, respectively. Thus, our analysis reflects patients that had labs performed within these time frames. We did not collect information on concomitant medications (except for evidence-based HF medications) and number of hospitalizations within the last year prior to initiation. We collected serum creatinine at baseline when available, and we did not investigate a history of chronic kidney disease.

Conclusions

Initiating ARNI through a defined protocol utilized by an advanced HF and transplant programme selects for appropriate candidates and guides starting dose and titration in a healthcare system with minimal reimbursement complexity. Overall, significant success can be achieved in replacing ACEI or ARB by an ARNI in symptomatic HFrEF patients.

Conflict of interest

None declared.

References

1. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau AL, Shi VC, Solomon SD, Swedberg K, Zile MR, PARADIGM-HF Investigators and Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; 371: 993–1004.

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017; 136: e137–e161.

3. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, Teerlink JR, Desai AS, Lefkowitz M, Shi M, McMurray J, Solomon SD, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Investigators. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. *J Am Coll Cardiol* 2016; 68: 1228–1234.

4. Luo N, Fonarow GC, Lippmann SJ, Mi X, Heidenreich PA, Yancy CW, Greiner MA, Hammill BG, Hardy NC, Turner SJ, Laskey WK, Curtis LH, Hernandez AF, Mentz RJ, O'Brien EC. Early adoption of sacubitril/valsartan for patients with heart failure with reduced ejection fraction: insights from Get with the Guidelines—Heart Failure (GWTG-HF). *JACC Heart Fail* 2017; 5: 305–309.

5. Sulaiman K, Panduranga P, Al-Zakwani I, Alsheikh-Ali AA, AlHabib KF, Al-Suwaidi J, Al-Mahmeed W, AlFaleh H, Elasfar A, Al-Mutarreb A, Ridha M, Bulbanat B, Al-Jarallah M, Bazargani N, Asaad N, Amin H. Clinical characteristic, management, and outcomes of acute heart failure patients: observations from the Gulf acute heart failure registry (Gulf CARE). *Eur J Heart Fail* 2015; 17: 374–384.

6. AlHabib KF, Elasfar AA, AlBackr H, AlFaleh H, Hersi A, AlShaer F, Kashour T, AlNemer K, Hussein GA, Mimish L. Design and preliminary results of the heart function assessment registry trial in Saudi Arabia (HEARTS) in patients with acute and chronic heart failure. *Eur J Heart Fail* 2011; 13: 1178–1184.

7. Sadik GZ, Atallah B, Stapleton J, Bader F. Appropriateness of evidence based therapy in patients referred to a specialized heart failure clinic in a developing country. *J Card Fail* 2016; 22: S36.

8. Desai AS, Vardeny O, Claggett B, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Zile MR, Lefkowitz M, Shi V, Solomon SD. Reduced risk of hyperkalemia during treatment of heart failure with mineralocorticoid receptor antagonists by use of sacubitril/valsartan compared with enalapril: a secondary analysis of the PARADIGM-HF trial. *JAMA Cardiol* 2017; 2: 79–85.