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BLEEDING DISORDER, A NEWLY RECOGNIZED ADVERSE EVENT FOLLOWING SACUBITRIL/VALSARTAN THERAPY

Yaser W. Al-Omari[1,2], Samer A. Mustafa[2], Ali H. Saleh[2], Wesam S. Abdel-Razaq[3,4]

[1] Department of Pharmacy, Prince Faisal Bin Alhussein Hospital, Ministry of Health, Zarqa-Rusaifeh, Jordan
[2] Department of Internal Medicine, Prince Faisal Bin Alhussein Hospital, Ministry of Health, Zarqa-Rusaifeh, Jordan
[3] College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia
[4] King Abdullah International Medical Research Centre, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia

Corresponding author's e-mail: razaqw@ksau-hs.edu.sa

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ABSTRACT

Introduction: Sacubitril/valsartan (Entresto) is the only currently approved angiotensin receptor–neprilysin inhibitor (ARNI) drug. It demonstrates important therapeutic outcomes in heart failure patients by reducing hospitalizations and deaths. ARNI is generally safe but concerns about adverse drug reactions (ADRs) exist. This report documents a potential bleeding disorder, evidenced by elevated prothrombin time (PT) and international normalized ratio (INR), as a newly identified ADR.

Case description: Despite not receiving anticoagulant medication, three male heart failure patients had elevated PT/INR values within 14 days to four months of initiating Entresto 50 mg twice daily. Temporary discontinuation (dechallenging) of Entresto resulted in a decline in PT/INR, while it increased upon re-challenge in at least one patient. Laboratory findings showed varying degrees of anaemia, occasional renal and hepatic abnormalities, with normal platelet counts. Naranjo scores (6–8) support a probable causal relationship between Entresto and the bleeding tendency, warranting careful coagulation monitoring during treatment.

Conclusion: This case series explicitly identified a probable causal relationship between Entresto (ARNI) and a potential bleeding risk as evaluated by the Naranjo ADR probability scale. By highlighting this previously unidentified ADR, this report attempts to raise awareness among healthcare practitioners regarding the need for vigilant monitoring of coagulation parameters in high-risk patients, even without concomitant anticoagulant treatment.

KEYWORDS

Sacubitril/valsartan, Entresto, adverse drug reaction, bleeding disorder, patient safety

LEARNING POINTS

- To our knowledge, this case series is the first report in the medical literature to specifically recognize a probable causal relationship between angiotensin receptor-neprilysin inhibitor treatment and a potential bleeding risk as evaluated by the Naranjo adverse drug reaction probability scale.
- Healthcare practitioners are urged to vigilantly monitor coagulation parameters in high-risk patients, even in the absence of concomitant anticoagulant treatment.

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INTRODUCTION

Entresto, a fixed-dose combination of sacubitril and valsartan, used for heart failure patients, is the only available medication in a new family of drugs called angiotensin receptor-neprilysin inhibitors (ARNIs)[1]. The recommended starting dose of Entresto is 50 mg twice daily. If a patient is not on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), the dose can be increased after two to four weeks to a target maintenance dose of 100 mg twice daily[2]. Current evidence advocates ARNI as a valuable treatment for heart failure patients who continue symptomatic despite optimized other therapies[3]. Several studies have consistently demonstrated momentous benefits of ARNI in reducing heart failure hospitalizations and cardiovascular death in patients with a reduced ejection fraction[4]. Early initiation of ARNI is crucial to ensure a lower mortality rate and improved symptoms[5]. This report aims to document a potentially serious, unexpected adverse drug reaction (ADR) associated with Entresto, specifically elevated prothrombin time (PT) and international normalized ratio (INR). This report also evaluates the causal relationship between Entresto and bleeding risk using the Naranjo probability scale[6].

CASE DESCRIPTION

A senior clinical pharmacist identified prominently elevated PT and INR values in three elderly patients during a review of medical records and lab results upon admission. Notably, these findings were observed despite the absence of anticoagulant therapy. Following the pharmacist's report of a plausible Entresto-related ADR, a panel of expert pharmacists and physicians at Prince Faisal Bin Alhussein Hospital convened to review the allegation and evaluate the concerning observation.

Case 1: On May 29, 2025, an 81-year-old male with a history of hypertension, heart failure and cerebellar stroke was initiated on Entresto 50 mg twice daily for heart failure. Laboratory findings on October 12, 2025, showed a markedly elevated PT (20.3 s) and INR (1.57) with a normal platelet count (255 $\times 10^3/\mu l$). The exact time to onset was assumed to be approximately four months, as it was not clearly stated. However, upon temporary discontinuation (dechallenging) of Entresto on October 13, 2025, values decreased (PT 17.7 s, INR 1.35). The haematology results showed several abnormalities indicating severe anaemia and pronounced leucocytosis. The chemistry results revealed elevated levels of direct bilirubin (11.4 mmol/l) and total bilirubin (20.6 mmol/l). No evidence of hepatic or renal dysfunction was observed.

Case 2: On Sept. 28, 2025, a 51-year-old male with a history of heart failure, upper respiratory infection and dyspnoea was started on Entresto 50 mg twice daily in combination with daily 5 mg bisoprolol and 40 mg furosemide. An elevated PT (26 s) and INR (2.3) were identified on October 10, 2025; the time to onset was set to 14 days. However, temporarily dechallenging led to a subsequent and progressive decline in both values. They

Question	Case 1	Case 2	Case 3	Notes
1. Are there previous conclusive reports on this reaction?	0 (No)	0 (No)	0 (No)	Not reported in any case
2. Did the adverse event appear after the suspected drug was administered?	+2 (Yes)	+2 (Yes)	+2 (Yes)	Elevated PT/INR while on ARNI
3. Did the adverse event improve when the drug was discontinued, or a specific antagonist was administered?	+1 (Yes)	+1 (Yes)	+1 (Yes)	Slight improvement upon dechallenging
4. Did the adverse event reappear when the drug was readministered?	0	+2	0	Not reported in cases 1 and 3
5. Are there alternative causes that could have caused the reaction?	+2 (No)	+2 (No)	+2 (No)	Slight improvement after withdrawal
6. Did the reaction reappear when a placebo was given?	0	0	0	Not applicable
7. Was the drug detected in any body fluid in toxic concentrations?	0	0	0	Not known or not done
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	0	0	0	Not applicable
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	0	0	0	No history reported
10. Was the adverse event confirmed by any objective evidence?	+1 (Yes)	+1 (Yes)	+1 (Yes)	Abnormal PT/INR documented in all cases
Total Score:	6	8	6	Scores 5–8 = Probable ADR

Table 1. *Naranjo causality assessment of an ARNI related bleeding disorder.*

Abbreviations: ANRI, angiotensin receptor-neprilysin inhibitor; PT, prothrombin time; INR, international normalized ratio.

Case	Age (years)	Sex	Comorbidities	Medication (dose)	Indication	Adverse Event	Time to onset (days)	Naranjo score
1	81	Male	CHF, cerebellar stroke	Sacubitril 24.3 mg / valsartan 25.7 mg twice daily	Heart failure	Bleeding disorder	~4 months	6
2	51	Male	Heart failure	Sacubitril 24.3 mg / valsartan 25.7 mg twice daily	Heart failure	Bleeding disorder	14 days	8
3	60	Male	CAD, CVA, HTN	Sacubitril 24.3 mg / valsartan 25.7 mg twice daily	Heart failure	Bleeding disorder	22 days	6

Table 2. Summary of clinical and laboratory features in three heart failure patients.

Abbreviations: CHF, congestive heart failure; CAD, coronary artery disease; CVA, cerebrovascular accident; HTN, hypertension.

were slightly reduced on October 12, 2025 (PT 25.2 s, INR 1.99). A further decline in both values over time were found on October 13, 2025 (PT 23.4 s, INR 1.83), and then on October 16, 2025 (PT 22.8 s, INR 1.78), respectively. Crucially, upon resuming Entresto, these values re-elevated on October 18, 2025 (PT 24 s, INR 2.09). The haematology lab results showed evidence of a mild anaemia. The chemistry results showed signs of kidney dysfunction and electrolyte imbalance.

Case 3: On June 15, 2025, a 60-year-old male with a history of coronary artery disease, cerebrovascular accident and hypertension was initiated on Entresto 50 mg twice daily for heart failure. Other medications included 5 mg bisoprolol, 20 mg atorvastatin and 30 mg lansoprazole. On July 28, 2025, lab results revealed elevated PT (24.2 s) and INR (1.9), suggesting a potential bleeding disorder. Again, the exact time to onset was assumed to be approximately 22 days, as it was not specified. Following the temporary dechallenging of Entresto, a slight reduction was noted on July 29, 2025 (PT 22.3 s, INR 1.73), which was then considerably reduced to near normal values (PT 18.2 s, INR 1.39) by August 3, 2025. Unfortunately, data regarding the resumption of Entresto were missing from the patient's record. The haematology results indicated mild anaemia. Other blood parameters were within their respective normal limits. The chemistry results on June 03, 2025, showed a high direct bilirubin level (6.3 mmol/l) and an abnormally low vitamin D level (16.5 ng/ml). However, in a subsequent chemistry lab result on July 31, 2025, multiple abnormalities were noted, including high levels of creatinine, urea, and direct bilirubin.

Naranjo causality scores were estimated *(Table 1)*, considering improved dechallenge (if any), and the absence of alternative causes. This scoring reflects strong evidence of ADR, supporting a probable causal relationship. *Table 2* summarizes the clinical and laboratory characteristics of the 3 patients with unexplained PT/INR elevations occurring 14 days to 4 months after Entresto initiation.

DISCUSSION

Despite the lack of anticoagulant therapy, an inexplicable, substantial elevation in PT/INR levels was recognized in three elderly male heart failure patients receiving Entresto. Upon temporary discontinuation (dechallenging) of the drug, a consistent decline in PT/INR was observed across all cases. Causality assessment using the Naranjo scale revealed a probable association between Entresto and significant PT/INR elevations. Notably, in one case, a re-challenge resulted in a prompt re-elevation of PT/INR, strengthening the causal association. While the patients exhibited varying degrees of anaemia and minor chemistry imbalances, hepatic enzymes remained within normal limits, suggesting that Entresto mostly impacted coagulation rather than having a deleterious effect on liver function.

The safety profile of Entresto was established in two large-scale trials (PARADIGM-HF[7] and PARAGON-HF[8]), which characterize ARNI as generally safe and well tolerated with a favourable safety profile comparable to ACEI or ARB. Although studies involved thousands of patients, Entresto was not specifically linked to significant PT/INR elevation or bleeding disorders. The PARADIGM-HF study reported a low incidence of anaemia (3%) without significant indications of bleeding or coagulation disorders. Furthermore, pharmacokinetic research indicates that Entresto does not interfere with warfarin protein binding stability[9].

Although the current findings may represent a rare, idiosyncratic ADR of Entresto in the elderly that may be unique to specific individuals, further investigation is still warranted to confirm a strong temporal relationship and determine the causal mechanism.

REFERENCES

1. Fala L. Entresto (Sacubitril/Valsartan): First-in-Class Angiotensin Receptor Neprilysin Inhibitor FDA Approved for Patients with Heart Failure. *Am Health Drug Benefits* 2015;**8**:330-334.
2. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. *N Engl J Med* 2019;**380**:539-548. doi: 10.1056/NEJMoa1812851. Erratum in: *N Engl J Med* 2019;**380**:1090. doi: 10.1056/NEJMx190009
3. Al Habeeb W, Tash A, Elasfar A, Almasood A, Bakhsh A, Elshaer F, et al. 2023 National Heart Center/Saudi Heart Association Focused Update of the 2019 Saudi Heart Association Guidelines for the Management of Heart Failure. *J Saudi Heart Assoc* 2023;**35**:71-134. doi: 10.37616/2212-5043.1334
4. Hernandez AV, Pasupuleti V, Scarpelli N, Malespini J, Banach M, Bielecka-Dabrowa AM. Efficacy and safety of sacubitril/valsartan in heart failure compared to renin-angiotensin-aldosterone system inhibitors: a systematic review and meta-analysis of randomised controlled trials. *Arch Med Sci* 2023;**19**:565-576. doi: 10.5114/aoms/159113
5. Sun Y, Song S, Zhang Y, Mo W, Zhang X, Wang N, et al. Effect of angiotensin receptor neprilysin inhibitors on left atrial remodeling and prognosis in heart failure. *ESC Heart Fail*;**9**:667-675. doi: 10.1002/ehf2.13691
6. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239-245. doi: 10.1038/clpt.1981.154
7. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993-1004. doi: 10.1056/NEJMoa1409077
8. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2019;**381**:1609-1620. doi: 10.1056/NEJMoa1908655
9. Kulmatycki KM, Langenickel T, Ng WH, Pal P, Zhou W, Lin TH, et al. Pharmacokinetics and safety of sacubitril/valsartan (LCZ696) in patients with mild and moderate hepatic impairment. *Int J Clin Pharmacol Ther* 2017;**55**:728-739. doi: 10.5414/CP202988