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SACUBITRIL/VALSARTAN AND ELEVATED PROTHROMBIN TIME/INTERNATIONAL NORMALIZED RATIO IN THE ABSENCE OF ANTICOAGULANT THERAPY: A NEWLY RECOGNIZED POTENTIAL ADVERSE DRUG REACTION

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ABSTRACT

Introduction: Sacubitril/valsartan is the first approved angiotensin receptor–neprilysin inhibitor (ARNI) and a cornerstone therapy for heart failure with reduced ejection fraction (HFrEF). While its clinical benefits are well established, adverse drug reactions (ADRs) beyond the recognized profile of hypotension, hyperkalaemia, and renal impairment remain incompletely characterized.

Case description: We report a case of isolated elevation in prothrombin time (PT) and international normalized ratio (INR) in a 58-year-old male with HFrEF receiving sacubitril/valsartan 49/51 mg twice daily, without any concurrent anticoagulant therapy. Approximately 6 weeks after initiation, PT was 18.4 seconds and INR was 1.7. Temporary discontinuation (dechallenge) led to normalization within 2 weeks; cautious re-challenge resulted in recurrent INR elevation. Naranjo Adverse Drug Reaction Probability Scale criteria yielded a score of +9, consistent with a probable drug-induced adverse event.

Conclusion: This case highlights a potentially underrecognized coagulopathic ADR associated with sacubitril/valsartan, manifesting as elevated PT/INR without anticoagulant use. Clinicians should consider periodic coagulation monitoring in patients on ARNI therapy. Further pharmacovigilance studies and mechanistic investigations are strongly warranted.

KEYWORDS

Sacubitril/valsartan, prothrombin time, INR, adverse drug reaction, heart failure

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LEARNING POINTS

- Sacubitril/valsartan may cause isolated elevation of prothrombin time and international normalized ratio in the absence of anticoagulant therapy, liver disease, or vitamin K deficiency; a potentially underrecognized adverse drug reaction (ADR).
- The dechallenge–rechallenge pattern, together with a Naranjo score of +9, provides robust pharmacovigilance evidence implicating angiotensin receptor-neprilysin inhibitor therapy as the causative agent and supports baseline and periodic coagulation monitoring.
- Clinicians prescribing sacubitril/valsartan should be vigilant for this coagulopathic ADR, especially in patients at elevated bleeding risk, and should report cases to pharmacovigilance registries to facilitate systematic signal detection.

INTRODUCTION

Heart failure (HF) is a major global health burden associated with significant morbidity, mortality, and healthcare expenditure. Sacubitril/valsartan, the first-in-class angiotensin receptor–neprilysin inhibitor (ARNI), has fundamentally altered the therapeutic landscape for HFwith reduced ejection fraction (HFrEF). The landmark PARADIGM-HF trial — a randomized, double-blind study involving 8,442 patients with symptomatic HFrEF (New York Heart Association, NYHA class II–IV; left ventricular ejection fraction, LVEF ≤40%) — demonstrated that sacubitril/valsartan significantly reduced the composite risk of cardiovascular death or HF hospitalization by 20% relative to enalapril (HR 0.80; 95% CI 0.73–0.87; p <0.001)[1]. The trial was prematurely terminated due to overwhelming benefit observed during the pre-specified interim analysis[1].

Sacubitril functions as a prodrug that, upon hepatic metabolism, generates the active moiety sacubitrilat. Sacubitrilat inhibits neprilysin — a neutral endopeptidase responsible for the breakdown of natriuretic peptides (atrial natriuretic peptide - ANP, B-type natriuretic peptide - BNP), adrenomedullin, angiotensin II, substance P, and bradykinin[2,3]. By preventing neprilysin-mediated degradation of these vasoactive peptides, sacubitril promotes vasodilation, natriuresis, and diuresis. The valsartan component concurrently suppresses renin-angiotensin-aldosterone system (RAAS) activation through angiotensin II type 1 receptor blockade, counteracting the accumulation of angiotensin II that would otherwise result from neprilysin inhibition alone[3,4].

The established adverse effect profile of sacubitril/valsartan includes symptomatic hypotension, hyperkalaemia, renal impairment, cough, dizziness, and angioedema (the latter particularly when initiated within 36 hours of an angiotensin-converting enzyme, ACE, inhibitor)[5,6]. Rare post-marketing cases of drug-induced liver injury have been reported[7]. However, coagulopathy — specifically, elevation in prothrombin time (PT) and the international normalized ratio (INR) — has not been widely recognized as an adverse drug reaction (ADR) associated with ARNI therapy. PT and INR are standardized assessments of the extrinsic and common coagulation pathways; isolated elevation outside the context of anticoagulant therapy or hepatic dysfunction warrants thorough investigation[8].

A recent case series by Al-Omari et al. (2026) documented elevated PT/INR in 3 male heart failure patients within 14 days to 4 months of initiating sacubitril/valsartan 50 mg twice daily, with normalization following temporary discontinuation and re-elevation upon re-challenge in at least one patient[9]. This emerging evidence underscores the need for further case documentation. We report an additional case fulfilling Naranjo ADR criteria for a probable sacubitril/valsartan-associated coagulopathy.

CASE DESCRIPTION

A 58-year-old male with a 5-year history of ischemic cardiomyopathy and HFrEF (LVEF 35% confirmed on recent transthoracic echocardiography) presented for routine cardiology follow-up. His comorbidities included hypertension, type 2 diabetes mellitus, and hyperlipidemia. He was a non-smoker with no history of alcohol use, chronic liver disease, or any prior bleeding or clotting disorder. There was no personal or family history of coagulopathy, thrombophilia, or hematological malignancy.

His medications prior to ARNI initiation included carvedilol 12.5 mg twice daily, spironolactone 25 mg once daily, furosemide 40 mg once daily, metformin 500 mg twice daily, and atorvastatin 40 mg at bedtime. He was not receiving anticoagulants (warfarin, heparin, direct oral anticoagulants), antiplatelet agents, vitamin K antagonists, herbal supplements, broad-spectrum antibiotics, or any agent known to interact with coagulation pathways. His baseline coagulation profile was entirely within normal limits: PT 11.8 seconds; INR 1.0; activated partial thromboplastin time (aPTT) 30.2 seconds. Hepatic function tests, renal function, complete blood count, and serum vitamin K levels were all within reference ranges at baseline.

In accordance with the American Heart Association/American College of Cardiology/Heart Failure Society of America 2022 Heart Failure Guidelines, which afford sacubitril/valsartan a Class I, Level of Evidence A recommendation for patients with HFrEF who tolerate RAAS inhibition, the patient's lisinopril was discontinued.

After a mandatory 36-hour washout period, sacubitril/valsartan was initiated at 49 mg/51 mg (sacubitril/valsartan) twice daily, with plans for up-titration to the target dose of 97/103 mg twice daily as tolerated[4].

Approximately 6 weeks after initiation, routine follow-up laboratory testing revealed a PT of 18.4 seconds (reference range: 11–13.5 seconds) and an INR of 1.7 (reference range: 0.9–1.1). The aPTT was mildly elevated at 33.1 seconds (reference range: 25–35 seconds). Platelet count remained normal at 215 $\times 10^3$/µl. Serum alanine aminotransferase, aspartate aminotransferase, total bilirubin, and alkaline phosphatase were all within normal limits, excluding significant hepatic dysfunction as a contributing cause. Serum vitamin K was measured and confirmed within normal limits. Specific coagulation factor assays revealed mildly reduced factor VII and factor X activity, consistent with a defect in the extrinsic and common coagulation pathways. No clinically apparent bleeding was observed at any point during follow-up.

The patient denied any dietary changes, new medications, over-the-counter supplement use, or gastrointestinal illness in the interval between baseline and the 6-week evaluation. Repeat testing at the same laboratory excluded inter-laboratory variation. A comprehensive hematological workup — including peripheral blood film, fibrinogen, D-dimer, prothrombin complex activity, lupus anticoagulant, and anticardiolipin antibodies — did not reveal any primary hematological, autoimmune, or consumptive etiology for the coagulopathy. All laboratory values are summarized in *Table 1*.

Given the absence of any identifiable alternate etiology and the clear temporal relationship between ARNI initiation and the laboratory abnormalities, sacubitril/valsartan was temporarily discontinued (dechallenge). Within 2 weeks of discontinuation, PT normalized to 12.3 seconds, INR to 1.1, and factor VII and factor X activity returned to reference ranges. The patient was maintained on the remainder of his HF regimen (carvedilol, spironolactone, furosemide) during this period, with no hemodynamic deterioration.

Following multidisciplinary discussion involving cardiology, hematology, and clinical pharmacology — and with written informed consent from the patient — sacubitril/valsartan was cautiously reintroduced (re-challenge) at the lower starting dose of 24/26 mg twice daily. Within 3 weeks of re-challenge, PT rose to 16.9 seconds and INR to 1.6. The drug was permanently discontinued, and the patient was transitioned to an ACE inhibitor-based regimen under close monitoring. No overt bleeding events occurred throughout the clinical course.

Causality assessment using the Naranjo Adverse Drug

Parameter	Baseline (pre-drug)	Week 6 (on drug)	Week 8 (post-dechallenge)
Prothrombin Time (seconds)	11.8	18.4 ↑	12.3
INR	1	1.7 ↑	1.1
aPTT (seconds)	30.2	33.1	30.8
Platelet count ($\times 10^3$/µl)	220	215	218
Haemoglobin (g/dl)	13.4	12.9	13.2
Factor VII activity (%)	98	62 ↓	95
Factor X activity (%)	95	68 ↓	93
Fibrinogen (mg/dl)	290	285	292
D-dimer (µg/ml)	0.3	0.4	0.3
ALT (U/l)	28	34	29
AST (U/l)	24	30	25
Total bilirubin (mg/dl)	0.8	0.9	0.8
Serum creatinine (mg/dl)	1.1	1.2	1.1
Serum potassium (mEq/l)	4.2	4.5	4.3
Vitamin K level	Normal	Normal	Normal
Lupus anticoagulant	Negative	Negative	—

Table 1. *Laboratory parameters at baseline, during sacubitril/valsartan therapy (week 6), and 2 weeks after dechallenge.*

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; aPTT, activated partial thromboplastin time; INR, international normalized ratio; ↑, above reference range; ↓, below reference range.

Reaction Probability Scale yielded a total score of +9, consistent with a probable adverse drug reaction *(Table 2)*.

DISCUSSION

This case documents a probable ADR associated with sacubitril/valsartan, manifesting as isolated elevation of PT and INR without anticoagulant therapy, liver disease, vitamin K deficiency, or other coagulopathic states. The dechallenge–rechallenge pattern and Naranjo score of +9 provide robust pharmacovigilance evidence implicating ARNI therapy as the causative agent.

The mechanistic basis for sacubitril/valsartan-induced coagulopathy remains speculative, and several pathways deserve consideration. First, neprilysin is a membrane-bound metalloendopeptidase expressed broadly across tissues including the liver, kidney, vascular endothelium, and brain[10]. Neprilysin degrades not only natriuretic peptides but also bradykinin, adrenomedullin, substance P, and angiotensin II, among other vasoactive substrates[2,3]. Neprilysin expression in hepatic stellate cells and pericentral hepatocytes suggests it may influence hepatic synthetic function via poorly characterized downstream signalling. The vitamin K-dependent coagulation factors (II, VII, IX, X) are synthesized in the liver; any subtle perturbation in hepatocyte synthetic function — even below the threshold detectable by standard transaminase assays — could impair clotting factor production and prolong PT/INR[11]. The predominant reduction in factor VII activity in our patient, with preservation of normal fibrinogen and platelet count, is consistent with an isolated extrinsic pathway defect and supports a hepatic synthetic mechanism rather than consumptive coagulopathy.

Second, natriuretic peptides — whose degradation is blocked by sacubitrilat — have demonstrated anticoagulant and antifibrinolytic properties in experimental models. ANP has been shown to inhibit platelet aggregation, reduce thrombin generation, and modulate fibrinolysis in vitro[12]. Sustained elevation of circulating ANP and BNP secondary to neprilysin inhibition could theoretically shift the haemostatic milieu toward a hypercoagulable state, particularly in patients with already elevated natriuretic peptide levels as seen in HFrEF.

Third, valsartan is a substrate of the hepatic uptake transporters OATP1B1 and OATP1B3[13]. Sacubitril in vitro inhibits these same transporters, potentially increasing hepatic valsartan exposure and indirectly altering the hepatic handling of co-substrates relevant to coagulation factor biosynthesis[13]. Although speculative, pharmacokinetic interactions at the level of hepatic uptake transport pathways warrant formal investigation.

The differential diagnosis for PT/INR elevation was systematically excluded. Vitamin K deficiency was ruled out by direct measurement. Liver disease was excluded by normal transaminases, bilirubin, albumin, and absence of clinical stigmata. No new medications, dietary changes, or herbal supplement use were identified. The absence of significant aPTT prolongation beyond the upper reference limit, the presence of reduced factor VII (a short half-life vitamin K-dependent factor), and normal fibrinogen and D-dimer collectively exclude disseminated intravascular coagulation, consumptive coagulopathy, and acquired inhibitors. Autoimmune workup (lupus anticoagulant, antiphospholipid antibodies) was negative.

Question	Response	Score
1. Are there previous conclusive reports on this reaction?	Yes	+1
2. Did the ADR appear after the suspected drug was administered?	Yes	+2
3. Did the ADR improve when the drug was discontinued (dechallenge)?	Yes	+1
4. Did the ADR reappear when the drug was re-administered (re-challenge)?	Yes	+2
5. Are there alternative causes that could have caused the reaction?	No	+2
6. Did the reaction reappear when a placebo was given?	No	0
7. Was the drug detected in blood or other fluids in toxic concentrations?	Not assessed	0
8. Was the reaction more severe when the dose was increased?	Not assessed	0
9. Did the patient have a similar reaction to the same or similar drug?	No	0
10. Was the ADR confirmed by any objective evidence?	Yes	+1
Total Score	—	**+9 (Probable ADR)**

Table 2. Naranjo adverse drug reaction probability scale assessment. Interpretation: score 1–4 = possible; score 5–8 = probable; score ≥9 = definite. A score of 9 in this patient indicates a probable ADR to sacubitril/valsartan.

Abbrevations: ADR, adverse drug reaction.

The index case series by Al-Omari et al. (2026) — documenting 3 male heart failure patients with elevated PT/INR within 14 days to 4 months of sacubitril/valsartan initiation — represents the first formal documentation of this ADR in the peer-reviewed literature[9]. Our case constitutes a second independent report, collectively strengthening the pharmacovigilance signal. Importantly, both reports demonstrate the characteristic dechallenge–rechallenge pattern, which is the gold standard for establishing drug causality for ADRs[14].

Regarding clinical significance: the PT/INR elevation observed in both our patient (INR 1.7) and the Al-Omari series was moderate and did not precipitate overt bleeding. However, the potential for clinically meaningful coagulopathy at higher INR values is a valid concern, particularly in patients undergoing invasive procedures, receiving dual antiplatelet therapy, or possessing underlying

haemostatic vulnerability. Of note, the effect appeared to be dose-related in our case, as re-challenge at a lower dose (24/26 mg) still produced measurable PT/INR elevation, suggesting a pharmacodynamically driven rather than idiosyncratic mechanism.

We recommend that clinicians prescribing sacubitril/valsartan consider obtaining a baseline PT/INR prior to initiation and repeat assessment at four to eight weeks after starting therapy, particularly in patients at elevated bleeding risk, those with mild baseline hepatic impairment, or patients on drugs that may have additive coagulopathic effects. If PT/INR elevation is detected in the absence of an alternative explanation, temporary dechallenge with coagulation monitoring is a reasonable clinical approach. Reporting such cases to national pharmacovigilance centres (e.g., the Food and Drug Administration's (FDA's) MedWatch program or equivalent national systems) is strongly encouraged to facilitate systematic signal detection.

This case has important limitations. It is a single-patient report and cannot establish incidence, prevalence, or causal mechanism with certainty. The patient's concurrent use of spironolactone and furosemide — though neither is known to significantly affect coagulation — cannot be entirely excluded as contributing factors. Formal pharmacokinetic studies, dose-finding analyses, and large-scale pharmacovigilance database reviews (e.g., FDA Adverse Event Reporting System analysis) are needed to characterize the true frequency and mechanistic basis of this potential ADR.

CONCLUSIONS

We report a probable ADR to sacubitril/valsartan characterized by isolated, clinically significant elevation of PT and INR without anticoagulant use, hepatic disease, or vitamin K deficiency. PT and INR normalized upon drug discontinuation and re-elevated upon re-challenge, with a Naranjo score of +9 supporting probable drug causality. This coagulopathic effect represents a potentially underrecognized adverse effect of ARNI therapy. Clinicians should be vigilant for this ADR, and baseline plus periodic coagulation monitoring is recommended, particularly in patients at elevated bleeding risk. Systematic pharmacovigilance, mechanistic investigations into neprilysin substrate interactions and hepatic coagulation factor synthesis, and prospective studies are urgently needed to validate and characterize this emerging safety signal.

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