

## CASE REPORT

# Use of four-factor prothrombin complex concentrate for the mitigation of rivaroxaban-induced bleeding in an emergent coronary artery bypass graft

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## Introduction

Over 40% of patients being treated with oral anticoagulation are prescribed a direct oral anticoagulants (DOACs) according to a recent study assessing prescribing patterns [1]. Pivotal trials for the DOACs have reported noninferiority or superiority of these agents to warfarin, a vitamin K antagonist (VKA), for multiple indications including non-valvular atrial fibrillation (AF) and venous thromboembolism (VTE) [2–5]. Furthermore, several of these studies also demonstrated similar or lower rates of minor and major bleeding and eliminates the need for frequent laboratory monitoring of these DOACs in comparison with warfarin. Despite these benefits, dabigatran, a direct thrombin inhibitor, is the only DOAC with an FDA-approved reversal agent idarucizumab currently on the market [6]. Currently, other DOACs such as rivaroxaban, apixaban, and edoxaban, lacks an FDA-approved reversal agent, although there are currently multiple agents in the pipeline for reversing these newer anticoagulants [7]. As a result, the current mainstay management of factor Xa inhibitor-induced bleeding is

### Key Clinical Message

We presented the first case of four-factor prothrombin complex concentrate (4F-PCC) for the alleviation of bleeding for emergent on-pump coronary artery bypass graft (CABG) with the patient discharged by postoperative day (POD) 9 with no sequelae. Until direct antidotes are available, 4F-PCC may play a role in the management of mitigating rivaroxaban-induced bleeding in surgical procedure.

### Keywords

Bleeding, cardiothoracic, coronary artery bypass, four-factor prothrombin complex concentrate, rivaroxaban.

supportive care with traditional blood products such as packed red blood cells (pRBC), as the anticoagulant effects of rivaroxaban can be expected to last 24 h or more [8]. Four-factor prothrombin complex concentrate (4F-PCC), the only PCC formulation currently available in the United States, contains factors II, VII, IX, and X, proteins C and S, and heparin. This agent is currently only FDA-approved for the management of acute major bleeding or need for urgent surgery or invasive procedures in patients on VKA, with dosing recommendations based on international normalized ratio (INR) values. The 2012 CHEST antithrombotic guideline provides a level 2C recommendation for 4F-PCC in the management of VKA-associated major bleeds over plasma products [9], although the guideline supplement is published 1 year after rivaroxaban is initially approved in the United States.

## Case Report

We report the following case of a 69-year-old Caucasian male anticoagulated with rivaroxaban 20 mg orally every morning with meals for chronic nonvalvular AF

(CHA<sub>2</sub>DS<sub>2</sub>VASc=5), admitted to the cardiothoracic intensive care unit for emergent on-pump coronary artery bypass graft due to ST-elevated myocardial infarction and hemodynamic instability secondary to confirm thrombosis of a previously inserted left anterior descending (LAD) artery stent. The patient had a past medical history of chronic nonvalvular AF, coronary artery disease with two coronary stents of the LAD and first diagonal branch arteries, systolic heart failure, type II diabetes mellitus, and hypertension. The patient has no known history of allergies or significant social history.

Patient denied taking any alternative medicine or over-the-counter medications. He had been experiencing angina that wax and wane for the past week that intensified prompting admission to an outside facility. He deteriorated overnight and was initiated on intravenous (IV) unfractionated heparin and bivalirudin, and sedated and intubated at the facility. Emergent left heart catheterization was performed and found thrombosis of the LAD stent with a left ventricular end-diastolic pressure of 15 mmHg necessitating placement of a 1:1 intra-aortic balloon pump placement. Overnight at the facility, bivalirudin was discontinued, and in the morning, he received rivaroxaban 20 mg once at that facility, and he was immediately transferred to our facility via the air ambulance for emergent on-pump coronary artery bypass graft (CABG). On admission at 5 h estimated time prior to the scheduled emergent on-pump CABG, IV heparin was continued at 1200 units/h. The patient's calculated creatinine clearance (CrCl) via the Cockcroft–Gault equation is 95 mL/min based on his admission serum creatinine of 0.8 mg/dL and actual weight of 77.1 kg; actual weight was used as his ideal body weight is 77.6 kg. Urine output captured 5 h as admission is 500 mL, which is equivocal to 1.2 mL/kg/h based on his actual body weight. Relevant admission hematologic laboratory markers revealed an elevated INR and activated partial thromboplastin time (aPTT) (Table S1). Four-factor prothrombin complex concentrate 2500 units (30 units/kg) IV at 200 units/min for one dose was administered 3 h prior to the scheduled CABG; the dose of 30 units/kg was chosen based on the review of available literature demonstrated survival for majority of patients that have received 4F-PCC dosing ranging from 25 to 40 units/kg (Table S2). Two-vessel on-pump CABG of the LAD and first diagonal branch was performed and required ~4 h of intraoperative time. In the operating room, the patient lost a total of 650 mL of blood necessitating 2 units of both pRBC and platelets, respectively.

Following the procedure, he was transferred to the cardiothoracic intensive care unit for hemodynamic optimization with fluids, vasopressors, and inotropes. On postoperative days (PODs) 1–3, he received additional

units of pRBC for optimization of oxygen delivery by maintaining target hemoglobin of 10 g/dL. By POD 2, the intra-aortic balloon pump was weaned off, he was successfully extubated from mechanical ventilation, and was initiated on a regular enteral diet. No significant events occurred between PODs 2–7 and by POD 7, and he was transferred to the cardiothoracic stepdown unit for observation. He was scheduled for discharge on POD 8, but due to case management issues, he was discharged by POD 9 without any complications and was prescribed for rivaroxaban 20 mg orally every morning with meals. According to the patient, he prefers to take it in the morning despite recommendation by the manufacturer to take the medication in the evening for the indication of nonvalvular AF. A follow-up visit 1 month after discharged did not reveal any new significant event, and a chest X-ray obtained during the visit revealed an almost complete resolution of postoperative effusions and atelectasis. Ultrasound of bilateral lower extremities was negative for VTE.

## Discussion

Rivaroxaban inhibits coagulation factor Xa, hindering the downstream coagulation cascade that involves activation of factor II, I, and XIII thus preventing thrombogenesis [10–12]. In patients with a CrCl greater than 50 mL/min, the recommended dosing of rivaroxaban for nonvalvular AF is 20 mg by mouth every evening with meals. The drug's reported half-lives with a CrCl greater than 50 mL/min 5–9 h in adults and 11–15 h in the elderly. Approximately 66% of rivaroxaban undergoes renal elimination, and the drug has a time to peak plasma concentration of 2–4 h. In addition, it has a large volume of distribution at approximately 50 L and is highly protein bound to albumin between 92% and 95% making it virtually non-dialyzable.

Several blood products like 4F-PCC have been suggested by experts as reversal agents for the DOACs. Despite being approved for urgent reversal of VKA, some experts believe that 4F-PCC may still be beneficial when used for severe bleeding or urgent reversal with DOACs as it replenishes Factor II, VII, IX, X, and proteins C and S based on published case reports and series across different patient population, although the dosing and outcomes of these publications have been conflicting, and very limited or no information was provided on potential confounders (e.g., INR, concurrent disease states) for several of these cases (Table S2) [13–16]. While bivalirudin is known to cause false elevation in INR, it is unlikely contributory to the initial INR elevation upon admission as the medication was discontinued overnight, and the serum concentration of the drug on admission is most

likely negligible based on the drug's reported half-life of 25 min with a CrCl greater than 90 mL/min [17].

While there is conflicting publications regarding the utility of 4F-PCC in the reversal of bleeding from rivaroxaban and other DOACs, the case presented demonstrated both the efficacy and safety of 4F-PCC for the migration of rivaroxaban-induced bleeding for emergent CABG. Our patient received 30 units/kg of 4F-PCC, 2 units of pRBC, and 2 units of platelets which differ from other cases where patients have received between 25 and 50 units/kg of 4F-PCC, and between 1 and 10 units of pRBC. As there is no established standard on the dosing of 4F-PCC for DOACs across hospitals, the risk of administration and excessive dosing must be weighed as 4F-PCC carries a black box warning for thromboembolic events. As the cases evaluated demonstrated survival between 25 and 40 units/kg, we have chosen 30 units/kg as an approximate median value based on risk versus benefit. Furthermore, cost should also be a consideration for appropriate utilization of the drug as the average wholesale price for each vial of 1000 units is approximately \$1400, and most patients will require multiple vials. Ultimately, more data are needed to determine the risks versus benefits of 4F-PCC in the optimal dosing of 4F-PCC and the management of severe bleeding from DOACs. Recently, there is a proposed management algorithm for patients on DOACs based on urgency, including the use of alternative reversal agent such as activated charcoal, although the algorithm lacks dosing recommendation for 4F-PCC, any information in regard to the pipeline factor Xa inhibitor antidote such as andexanet alfa, and any concrete evidence supporting its use [18].

## Conclusion

We present the first case of 4F-PCC for the alleviation of bleeding for emergent on-pump CABG with the patient discharged by POD 9 with no sequelae. While 4F-PCC may play a role in the management of rivaroxaban-induced bleeding in surgical procedures, safe and effective therapies for reversing such bleeds are urgently needed as the outcomes of 4F-PCC on other DOACs have been conflicting.

## Conflict of Interest

None declared.

## Authorship

ML: Substantial contributions to the case report: identified case, reviewed literature, drafted and revised manuscript, and final approval of the version to be published

CA: Reviewed literature, drafted and revised manuscript  
UD: Cardiothoracic surgeon for the case, provided expert feedback.

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## Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

**Table S1.** Relevant hematologic parameters.

**Table S2.** Case reports and series on 4F-PCC for DOACs.