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CE - RESEARCH LETTER TO THE EDITOR

Direct oral anticoagulants in factor VII deficiency patient

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Dear Sir,

Factor VII (FVII) is a vitamin K-dependent coagulation factor synthesized in the liver which plays a major role in the coagulation extrinsic pathway which is initiated at tissue damage sites, following the formation of a complex between activated FVII (FVIIa) and tissue factor. Plasma levels range around 0.35–0.60 mg/L (for a normal coagulant activity comprised between 70 and 140%), which is 10 times less than other vitamin K-dependent factors. Its half-life is extremely short (4–6 h) [1]. Inherited FVII deficiency, with an estimated prevalence of 1:300,000 population in European countries, is the most common among the rare congenital coagulation disorders, characterized by autosomal recessive inheritance. As with other forms of hemophilia, FVII deficiency can also be caused by medications such as vitamin K antagonists (VKA), medical conditions or malabsorption [2, 3]. Suspicion of FVII deficiency arises in presence of a reduced FVII coagulant activity (FVII:C), a prolonged prothrombin time and an elevated international normalized ratio (INR) in the setting of normal liver function and a normal activated partial thromboplastin time [1]. Clinical phenotypes correlate poorly with FVII activity levels although hemorrhage rarely appears when FVII:C is above 30% and complete absence of FVII in plasma is usually incompatible with life and individuals die shortly after birth due to severe hemorrhage [4]. Nevertheless, venous and arterial thrombotic events have been reported in 3–4% of patients with FVII deficiency. Thus, in some cases, "antithrombotic effect" of FVII deficiency seems to be overwhelmed by the presence of thrombotic risk factors underlying the need of an antithrombotic prophylaxis even in these patients [5]. However, it is not well established how to manage the anticoagulation therapy and the available evidences are based only on few case reports. Here, we describe a case of FVII deficiency patient affected by atrial fibrillation (AF) treated with a direct oral anticoagulant (DOAC). In October 2017, an 89-year-old woman presented to the emergency department complaining of acute post-prandial pain in peri-umbilical region. On past medical history, she reported factor VII deficiency, diagnosed at the age of 62 at the time visiting an anesthesiologist for a planned intervention of cholecystectomy. On this occasion, INR was 2 and the assays of VK-dependent factors showed a reduced FVII:C of 15%; at the time the patient was not taking any therapy. In 2011, she was hospitalized for acute heart failure caused by hypertension and AF: the physicians did not prescribe anticoagulants for hemorrhagic risk due to FVII deficiency. In 2015, she was admitted to Neurology for a cerebellar ischemic stroke and was in treatment with clopidogrel at discharge. The patient had no other comorbidities including diabetes or dyslipidemia; she regularly took furosemide, bisoprolol and clopidogrel. She weighed 58 kg, and was 161 cm high (body mass index 22.4). Upon physical examination, the patient was awake, alert and oriented to time, person, place and situation. Her blood pressure was 120/90 mmHg, heart rate of 90 beats/min with irregular rhythm. The abdomen was soft, slightly tender in the lower quadrants. Laboratory test showed increased white blood cells (12,170/uL), elevated INR (2.4), while C-reactive protein, amylase and troponin were within normal range. Creatinine was 0.89 mg/dl, alanine and aspartate transaminase were 27 IU/L and 33 IU/L, respectively. Fibrinogen was 2.4 g/L, D-dimer was 0.8 ug/ml, aPTT was 30 s, and FVII:C was reduced to 10%. Her ECG showed atrial fibrillation. A contrast-enhanced CT scan was then performed, confirming the clinical suspicion of acute mesenteric ischemia: CT showed an occlusion of

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Table 1 Use of anticoagulant therapy in patients with FVII deficiency and atrial fibrillation

Patient (reference)	Sex/age (years)	FVII:C (%)	Diagnosis of FVII deficiency (timing)	Anticoagulant	Medical history and outcomes
1. Davidson et al. [7]	M/50	15	After starting warfarin	Warfarin	After 18 months, no bleeding or thrombotic events, despite the INR being in the therapeutic range only 32% of the time
2. Baltodano et al. [8]	F/77	14	After starting warfarin	Warfarin	Physicians considered that the risks with warfarin outweighed the benefits and the patient was switched to aspirin because of difficult INR management
3. Arellano-Rodrigo et al. [9]	M/80	10	Before starting warfarin	Warfarin	FVII:C decreased to 5%. Given the risk of bleeding, warfarin was discontinued and low-molecular-weight heparin initiated
4. Paulus et al. [10]	F/70	33	Before starting warfarin	Warfarin	Mildly prolonged PT with persistent vaginal bleeding treated with endometrial cryotherapy. The patient made a dosing error and developed recurrent vaginal bleeding, and her FVII:C was found to be 10%, which prompted warfarin discontinuation
5. Arletti et al. [11]	M/71	28	Before starting DOAC	Dabigatran	Treatment with dabigatran 110 mg bid was well tolerated without bleeding or thrombotic events
6. Arletti et al. [11]	F/86	15	Before starting warfarin	Warfarin switched to dabigatran	Warfarin was started because of pulmonary embolism and AF. Two years later, an arterial ischemia developed. So dabigatran 150 mg bid treatment was started, switched to 110 mg bid after 6-month period. Neither hemorrhagic nor any thrombotic events occurred
7. Arletti et al. [11]	M/77	16	After starting warfarin	Warfarin switched to dabigatran	At the time of admission to the emergency department due to a cerebral ischemic lesion, INR value was 2.79. Warfarin was discontinued, but after 10 days INR was still 2.0: FVII deficiency was diagnosed. After 1 month, dabigatran 110 mg bid was started, without any clinical event

DOAC direct oral anticoagulant, *FVII:C* FVII coagulant activity, *INR* international normalized ratio, *PT* prothrombin time

superior mesenteric artery and its main branches. The patient was admitted to the department of Gastroenterology and she started therapy with enoxaparin 0.4 bid: immediately she resumed feeding after improvement in the symptoms. 2 days later, the patient was confused, dysarthric: she was diagnosed with an occipital ischemic stroke confirmed by a brain

CT, treated with aspirin with full neurological recovery after few days. The patient was discharged after 15 days and the neurologist recommended her to take aspirin 100 mg daily and enoxaparin, in addition to furosemide and bisoprolol. In December 2017, 2 months after discharge, she was evaluated as an outpatient in our "Anticoagulation" clinic: the patient did not experience cardiovascular or neurological disorders. Her ECG showed AF and FVII:C was 10%. Despite the hemorrhagic risk related to FVII deficiency, an anticoagulation therapy was considered mandatory because of her high thromboembolic risk. Because of low body weight (58 kg), age of 89 years and the bleeding caused by Factor VII deficiency, we treated our patient with apixaban 2.5 mg bid; aspirin was stopped. The patient was scheduled for 1-month follow-up and subsequently was periodically seen in the anticoagulation clinic every 3 months. Despite the FVII:C value ranging from 5 to 12%, she did not report any clinical events (bleeding event or thromboembolic recurrence) and at the last visit (April 2019) she indicated a complete well-being. Thus, even in patients with FVII deficiency, an anticoagulation therapy may be indicated in patients with AF or venous thromboembolism despite the high haemorrhagic risk of this condition [5]. Unfortunately, evidence regarding the management of anticoagulation therapy in this setting is extremely limited and it is not clear whether the antithrombotic drug and the dose are associated with a best profile of safety and efficacy. According to the International Society on Thrombosis and Haemostasis Scientific Standardization Committee for congenital FVII deficiency, severe disease is defined as FVII:C < 10% with risk for spontaneous major bleeding, moderate deficiency 10–20% with mild spontaneous or provoked bleeding and mild deficiency 20–50% (generally asymptomatic patients). However, data from the literature suggest a poor association between FVII coagulant activity level and hemorrhagic manifestation [6]. Use of anticoagulant therapy in patients with mild and moderate FVII deficiency has been described in a few case reports, including five treated with warfarin and, very recently, three with DOAC (see Table 1) [7–11]. However, lack of a defined optimal target INR (already elevated in FVII deficiency) is a potential challenge of warfarin therapy. In general, DOACs have been shown to be more effective and safer than VKAs in non-valvular AF, so they are currently recommended as first-line therapy in AF [12–14]. Furthermore, VKAs may affect to a greater extent FVII and FIX compared to other Vitamin K-dependent coagulation factors further reducing FVII:C and potentially exposing these patients to an increased risk of bleeding complications [15]. Conversely, DOACs may offer a more stable anticoagulation control and they may carry a lower risk of bleeding complications since they do not directly affect FVII levels. Here, we described a case of FVII deficiency treated with DOAC. This case seems to confirm the safety profile of DOACs even in this particular setting and our patient did not report any complication after more than 1 year of treatment with apixaban despite FVII level being persistently low during follow-up and despite the high risk related to the patient's age and comorbidities. In conclusion, DOACs may be an adequate therapeutic option in patients with mild or moderate FVII deficiency, when an anticoagulation therapy is indicated. Nevertheless, further studies are required to confirm these preliminary findings.

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Compliance with ethical standards

Conflict of interests The authors state that they have no conflict of interest.

Statement of human and animal rights This article does not contain any studies with animals performed by any of the authors. All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. As the case report is retrospective, discussion in the Ethics Committee was waived.

Informed consent Informed consent was obtained from the patient included in the study.

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