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IM - COMMENTARY

Optimal management of major bleeding on DOACs: not only reversal agents

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Direct oral anticoagulants (DOACs) are currently prescribed in more than 50% of patients affected by non-valvular atrial fibrillation (FANV) or venous thromboembolism [1, 2]. Data from post-marketing studies confirmed the favourable risk–benefit profile of DOACs when compared with vitamin K antagonist (VKA) [3, 4]. However, all anticoagulant drugs carry an intrinsic unavoidable bleeding risk. Although rare, major and life-threatening bleedings required a timely management, given their high case-fatality rate and potential morbidity. Well-defined and widely available management protocols are crucial to address these emergency situations without delay. The development of a first reversal agent, e.g., idarucizumab, opened the new era of DOAC-specific antidote to restore haemostasis on time. As Andexanet alpha is not licensed in many countries, factor Xa inhibitors' reversal can be rapidly managed by bypass-agents, mainly prothrombin complex concentrate (PCC) [5]. Despite four-factor PCC being off-label for DOACs' reversal, it is recommended by several experts as the first-line measure to immediately restore haemostasis in absence of specific DOACs antidote [6]. Presently, data available about DOAC reversal by PCC derive from animal models, in vitro and ex vivo observational studies on healthy volunteers. However, a placebo-controlled study or a study with a comparator arm to investigate four-factor PCC efficacy and safety in bleeding patients with DOACs on board will be unlikely to be performed. Hence, in this scant background, data about four-factor PCC effectiveness derived from real-life studies represent a valuable knowledge contribution. In this journal, Sheikh-Taha provides informative data about current management procedures to accomplish apixaban or rivaroxaban reversal in 29 real-life patients who experienced major bleeding [7]. Clinical scenario was well detailed. Major bleedings were defined according to the ISTH definition [8], and all patients had taken their last DOAC dose within 24 h from hospital admission.

Operationally, all patients were treated with a single dose of 50 UI/kg four-factor PCC as endorsed by current algorithms for reversal managing. In addition, other supportive measures were implemented such as red blood cells and platelets transfusion. The effectiveness of reversal response was properly assessed on the basis of surrogate outcomes represented by objective ISTH criteria for haemostasis definition [9]. Clinical haemostasis was achieved in 72.4% of cases similar to what is reported in the Annexa-4 trial [10]. Therefore, in clinical practice, in the absence of a specific antidote, "*one shot*" four-factor PCC, at the maximum recommended dose for VKA users, appears an effective strategy for apixaban and rivaroxaban reversal in the majority of patients. On the basis of available knowledge, we have no compelling reasons to explain the failure of haemostasis restoration in about 30% of the study population: it could be a matter of dose. Given the expected wide range of DOACs plasma levels for standard dose, we can not exclude that a higher dose of four-factor PCC might be necessary for some patients: testing FXa inhibitors' plasma concentration could help physicians to reliably check haemostasis status before and after reversal agent administration for timely driving the decision-making process. However, it must be kept in mind that coagulation reversal does not exempt from treating the underlying bleeding cause. Actually, in the presence of a life-threatening bleeding, restoring coagulation is a necessary but not a sufficient step for saving life.

When measurement of FXa inhibitors plasma concentration is not available, some authors suggested to use routine coagulation tests. However, while all patients declared to have taken the DOACs daily dose, only 20.7% and 37.9% of them had an elevated aPTT and INR value, respectively. Therefore, in the absence of a specific test for DOACs

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plasma levels quantification, the decision to implement the anticoagulant reversal should be based only on clinical data, such as bleeding severity and information about drug exposure.

Of interest, about 80% of study population was represented by old patients (mean ± SD age was 73.8 ± 12.0 years) on DOACs for non-valvular atrial fibrillation (NVAF), and about half of them were receiving concomitant antiplatelet drugs and/or non-steroidal anti-inflammatory drugs. Elderly patients with NVAF are certainly a complex and heterogeneous population. Older age often matches poly pharmacotherapy and multiple comorbidities. The combination of these factors turns out to increase frailty and both thrombotic and bleeding risk. Prudence and caution are always advisable for DOACs prescription in this patients' category to prevent undesirable major bleeding evens. Patient's bleeding risk must be carefully balanced when we decide to introduce a DOAC, and any effort should be implemented to eliminate any removable bleeding risk factor, such as uncontrolled hypertension or unnecessary concomitant antiplatelet drugs.

Compliance with ethical standards

Conflict of interest Alessandro Squizzato received fees for lectures and/or advisory board meetings from Daiichi Sankyo, Pfizer, Bristol Myers Squibb, Bayer, Boehringer Ingelheim. Silvia Galliazzo, nothing to disclose.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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