Editorial

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New Prospective for Reversal Strategies in Bleedings on Patients Assuming Direct Oral Anticoagulants

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Editorial

Direct oral anticoagulants (DOAC) are an effective and safe therapeutic option for venous thromboembolism or non-valvular atrial fibrillation (NVAF). Four trials on non-valvular atrial fibrillation patients (RE-LY for dabigatran, ROCKET-AF for rivaroxaban, ARISTOTLE for apixaban, and the ENGAGE-AF for edoxaban) evaluated the efficacy and safety of DOACs in comparison to vitamin K antagonists (VKAs), showing a lower incidence of intracranial haemorrhage and fatal bleeding [1-6].

Considering their more predictable and stable pharmacokinetic profile, no need for routine coagulation monitoring and a limited drug and food interaction, these drugs rapidly became an effective alternative for patients requiring short-term and lifelong anticoagulation. However, recent evidences showed that DOACs are associated with an increased risk of gastrointestinal bleeding when compared to warfarin and the absence of a specific reversal agent could be an obstacle to their extensive use in frail patients [7-10].

The Einstein studies on rivaroxaban reported that patients showing major bleedings had a relatively milder presentation and a better prognosis in comparison to patients on warfarin therapy [8]. Berger et al. [9] reported that dabigatran use was associated to a higher risk for gastrointestinal haemorrhage compared with warfarin in emergency department patients, and these findings are in contrast to data from the FDA Mini-Sentinel database [11].

Considering the relatively short half-life of the DOACs, cessation of assumption could often be sufficient to reverse the anticoagulant effect in case of non-severe bleedings [12].

However, in the occurrence of a major life-threatening bleeding, haemostasis could be promptly restored both by non-specific pro-haemostatic therapies and specific antidotes [13].

Dabigatran has a low level of plasma protein binding, therefore haemodialysis could be effective in reducing plasmatic concentrations and it was associated with a reduction in the severity of bleedings [14,15].

Currently, several guidelines proposed the use of the four-factor prothrombin complex concentrates (4F-PCC) as a reversal strategy for oral factor Xa inhibitor anticoagulants and for direct thrombin inhibitors, despite the lack of strong evidences on the real clinical effectiveness [16]. In particular, a prothrombotic effect is reported at relatively high doses of PCC [17]. A controlled trial showed that the administration of PCC was able to normalize the prothrombin time and restore depressed thrombin generation after rivaroxaban treatment [18].

Studies on a specific reversal of anti-factor Xa agent are currently ongoing; in particular, Ciraparantag is an antidote, which binds directly to edoxaban via hydrogen bonds, blocks the anticoagulant effect and restores the prothrombin time in vitro [19,20].

Andexanet-alfa is an analogue of factor Xa protein, effective for neutralizing the anti-coagulant effect of apixaban and rivaroxaban in healthy volunteers, without prothrombotic activity [20]. Recently US Food and Drug Administration approved an antidote targeted to reverse dabigatran, idarucizumab, which is a humanized monoclonal antibody [20, 21].

Considering recent evidences, several reversal strategies for DOACs are being developed, but their clinical utility is likely to remain restricted to serious haemorrhage or in patients on DOACs who require immediate invasive procedures.

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