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Editorial

North America anticoagulation forum guidance on reversal of direct oral anticoagulants

The direct oral anticoagulants (DOACs) (apixaban, rivaroxaban, betrixaban, edoxaban and dabigatran) have gradually replaced vitamin K antagonists (VKAs) as the mainstay anticoagulation therapy. However, lack of specific reversal agents has been consistently raised as a concern since the introduction of the DOACs. Major bleeding and invasive procedures are common clinical settings where DOAC reversal may be required; further a high frequency of co-morbid conditions makes it likely that patients treated with DOACs will require such interruptions of their therapy. Currently only idarucizumab (Praxbind, Boehringer Ingelheim) and andexanet alfa (Andexxa, Portola Phamaceuticals) are approved by regulatory agents as specific DOAC reversal agents [1,2]. Non-specific prohemostatic agents such as prothrombin complex concentrate (PCC) (multiple brands) and activated prothrombin complex (APCC) (FEIBA [anti-inhibitor coagulant complex], TAKEDA Pharmaceutical Company) have also been widely used "off-label" for DOAC reversal [3–5].

Idarucizumab is a monoclonal antibody approved for the reversal of the direct thrombin inhibitor, dabigatran, whereas andexanet alfa is a factor Xa decoy approved for the reversal of the direct factor Xa inhibitors, apixaban and rivaroxaban [1,2]. Four factor PCC and aPCC both contain factors II, VII (activated VII in aPCC), X and are used as non-specific anticoagulant reversal agents [4,5]. The US Food and Drug Administration (FDA) label for Andexxa ® indicates usage for "life-threatening or uncontrolled bleeding"; this ambiguous approval leaves many questions unanswered for clinicians.

The clinical guidance review published in March 2019 by the Anticoagulation Forum, a North American panel of anticoagulation providers and experts, provides a comprehensive framework for DOAC-reversal [6]. It provides a set of guidance statements that address some of the key questions surrounding DOAC-reversal agents, including when they should be used, their recommended dosing and strategies for their effective utilization by health systems. In this guidance document, Cuker and colleagues identified, discussed and listed key questions pertaining to DOAC reversal based on group consensus. Available evidence was gathered via PubMed search and a manual screening of relevant articles. The guidance statements each answer a key clinical question and represents the unanimous consensus decision of the authors. A final summary was provided with a flow chart that guides key steps in DOAC reversal decision making (Fig. 1).

The authors concluded that in most cases of bleeding, supportive measures should be considered first and DOAC reversal should only be considered if there is life-threatening bleeding, critical site bleeding or major bleeding that does not respond to supportive measures [6]. Other guidance documents such as the 2017 American College of Cardiology (ACC) Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants also recommend non-specific resuscitative and supportive interventions as the first treatment step in all bleeding events, irrespective of the perceived severity of bleeding [7]. In many cases, supportive measures alone can mitigate bleeding and avoid the use of a specific DOAC reversal agent. Avoidance of use is encouraged by the high cost of specific reversal agents; idarucizumab ($2800/dose) and andexanet alfa ($25,000 to $50,000/dose) [8,9].

If a patient is to undergo a procedure, the authors specified two criteria that indicates need to consider DOAC reversal; 1) the procedure cannot be delayed and 2) the procedure cannot be safely performed while anticoagulated [6]. Considering the relatively short half-life of DOACs (4–26 h) compared to warfarin (20–60 h) [10–15], simple interruption of DOACs before an elective or urgent procedure may be all that is required to allow a safe intervention. Such brief periods of interruption were demonstrated in the PAUSE study to be associated with a low risk of both bleeding and thrombosis [16]. This recommendation is in line with other guidance documents. For instance, the 2017 ACC Consensus Decision Pathway for Periprocedural Anticoagulation also supports evaluation of bleeding risk and interruption of anticoagulation if there is a risk of clinically important bleeding [17].

In circumstances where there is a substantial risk for bleeding such as DOAC overdose or trauma, not initiating a DOAC reversal strategy unless bleeding is found is recommended [6]. Evidence for this was largely indirect and came from small single center studies that found the overall prevalence of bleeding in patients after trauma or overdose was low and generally had favorable outcomes without DOAC reversal. Clinicians should always first follow standard trauma evaluation protocol, comprehensively assess for possible bleeding and determine the patient's risk for bleeding. If a DOAC was taken recently, gastrointestinal sequestration with activated charcoal is a viable option [6]. As always, supportive measures and ongoing monitoring for new evidence of bleeding are required.

The guidance recommended using dosing recommended by the US FDA except for expanding to include off-label use for correction of the anticoagulant effect of edoxaban and betrixaban [1,2]. If clinicians feel that an attempt to counteract an anticoagulant effect is warranted and andexanet alfa is not available for use, 4-Factor PCC is recommended; aPCC can be considered if idarucizumab is not available [6].

Cuker et al. also strongly encouraged hospitals and hospital-systems to optimize logistics which will improve DOAC reversal time and prevent medical errors. Strategies included centralization and controlled distribution of reversal agents, strict access and rapid order processing, standardized protocols for administration and reporting measures to ensure accountability [6]. At the time of writing, 77% of US hospitals surveyed did not have andexanet alfa on formulary and the most cited rationale was the product's cost. Given that 84% of US hospitals belong to a system or network [18], strategies to transport patients or drugs to ensure access could be widely implemented. Furthermore, clinicians and hospitals should be aware of emerging evidence regarding DOAC

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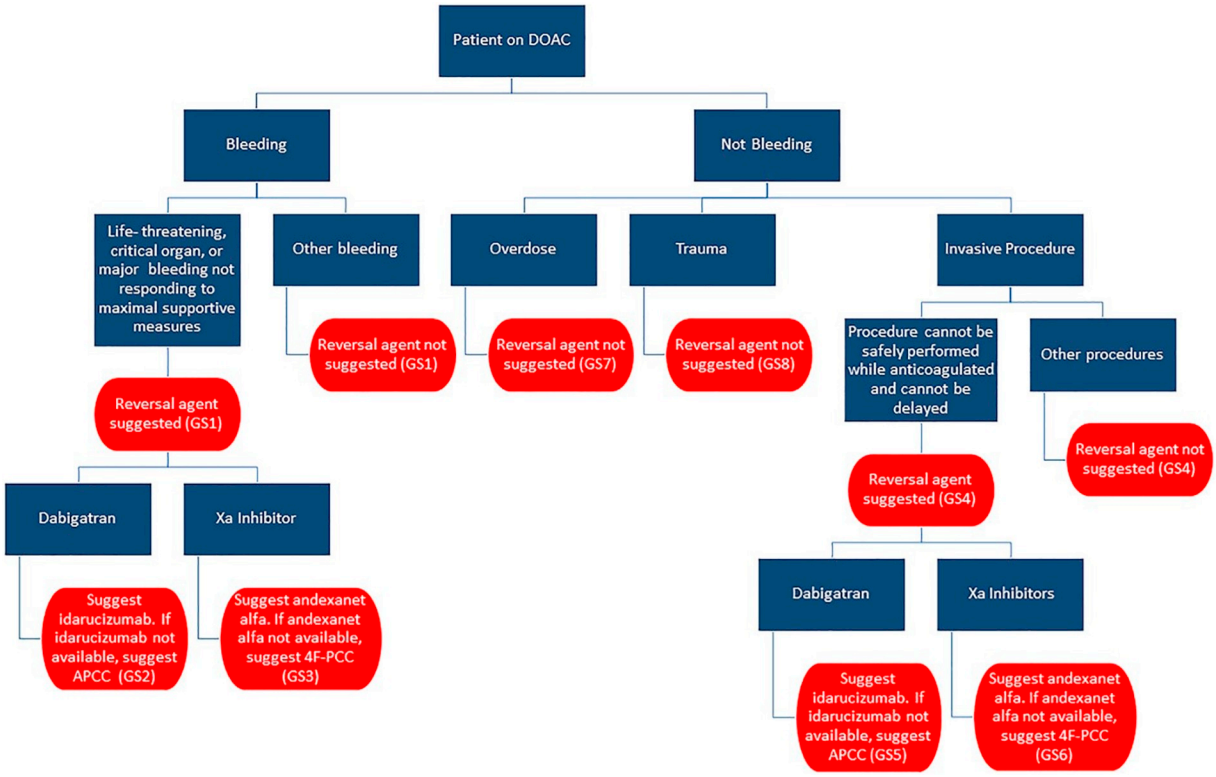

Fig. 1. Summary of DOAC reversal guidelines from the Anticoagulation Forum [6].

reversal and adjust their strategies accordingly.

There are important limitations to the Anticoagulant Forum guidance document; foremost amongst them is the lack of high-quality evidence supporting the clinical effectiveness of any of the interventions discussed. Further, given the complexities of studies in this clinical area, it is unlikely that such evidence will become available. Other areas where guidance will be required is intraoperative management of bleeding in patients whose anticoagulant status is unclear and recommendations for development and testing of rapid laboratory or point of care assays to detect the presence and/or amount of coagulation inhibitor present.

Since the approval of andexanet alfa in May 2018, specific DOAC reversal is now possible for all the DOACs. The DOAC reversal guidance by the Anticoagulation Forum offers clinicians a useful reference on the use of the new specific DOAC reversal agents, idarucizumab and andexanet alfa. The key principles outlined in this guidance are summarized here and in Fig. 1.

1) Supportive measures should be first line management and specific DOAC reversal should only be indicated if there is major bleeding (life threatening or bleeding not responding to support) or reasonable expectation of major bleeding (emergent, undelayable procedure).
2) Hospitals should implement strategies to optimize use of DOACs.
3) Dosing of specific reversal agents should follow the FDA labels.

Declaration of Competing Interest

Mark Crowther reports that his institution has received research funding on his behalf from Bayer, Pfizer, Heart and Stroke Foundation and Leo pharma; that he has received personal fees from Shionogi, Alexion, Octtapharma, BMS Canada, CSL Behring, Servier Canada, Diagnostica Stago and Asahi Kasei; that he has sat on data safety monitoring boards for Daiichi; and that he holds stocks in Alnylam. William Shi reports that he does not have any conflict of interest.

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