

Managing reversal of direct oral anticoagulants in emergency situations

Anticoagulation Education Task Force White Paper

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Background on Anticoagulation Education Task Force

- Publication based, in part, on findings from the Anticoagulation Education Task Force (held in Mainz, Germany in October 2015)
 - Meeting chaired by internist with interest in thrombosis and bleeding disorders, Walter Ageno, and cardiologist, A John Camm
 - A broad range of medical professional societies, patient groups, healthcare providers invited to nominate physicians and lay members with interest and expertise in anticoagulation and reversal agents
- Aim of the meeting: to discuss the current status of anticoagulation reversal and the fundamental changes in the management of bleeding associated with DOACs occasioned by the approval of idarucizumab, a novel, specific reversal agent for dabigatran, as well as recent clinical data on specific reversal agents for factor Xa inhibitors
- Meeting funded by Boehringer Ingelheim

Background on Anticoagulation Education Task Force (continued)

- Paper describes the main results of the discussion and the recommendations for the correct use of the reversal agents proposed by the members of the task force
 - No formal consensus strategies were applied
 - After the meeting, a white paper was drafted by the two chairmen together with one of the invited experts, Peter Verhamme, and shared with other participants for input
 - No formal endorsement was sought from national or international scientific societies, so the content of this white paper solely reflects the opinion of the members of the Task Force

Need for DOAC reversal

- Bleeding in case of vitamin K antagonists has been managed for decades with the administration of vitamin K and repletion of a variety of coagulation factors
- A limitation of the DOACs, to date, has been the lack of clinically proven reversal agents

“To address the clinical need for specific reversal agents, a number of compounds have been recently developed, one, idarucizumab, has been approved for clinical use and a second, andexanet alfa, is under evaluation by regulatory agencies.”

**Recommendations:
Operationalising anticoagulant
reversal in clinical practice**

Candidates: Who should receive reversal agents?

Table 2: Situations in which to consider use of a reversal agent

Clinical situation	Definite need for a reversal agent	Reversal agent possibly helpful (patient-dependent)	Reversal agent generally not needed
Life-threatening bleeding (e.g., intracranial haemorrhage, symptomatic or expanding extradural haemorrhage, or uncontrollable haemorrhage)	X		
Bleeding in a closed space or critical organ (e.g., intracranial, intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome)	X		
Persistent major bleeding despite local haemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose	X		
Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance	X		
Emergency surgery or intervention in patients at high risk for procedural bleeding: neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac, or vascular surgery (aortic dissection/aneurysm repair), hepatic, or other major organ surgery	X		
Need for urgent surgery or intervention in patients with acute renal failure		X	
Elective surgery			X
Gastrointestinal bleeds that respond to supportive measures			X
High drug levels or excessive anticoagulation without associated bleeding			X
Need for surgery or intervention that can be delayed long enough to permit drug clearance			X
DOACs, non-Vitamin K oral anticoagulants. Adapted from Levy et al. 2015 (31).			

Protocol development

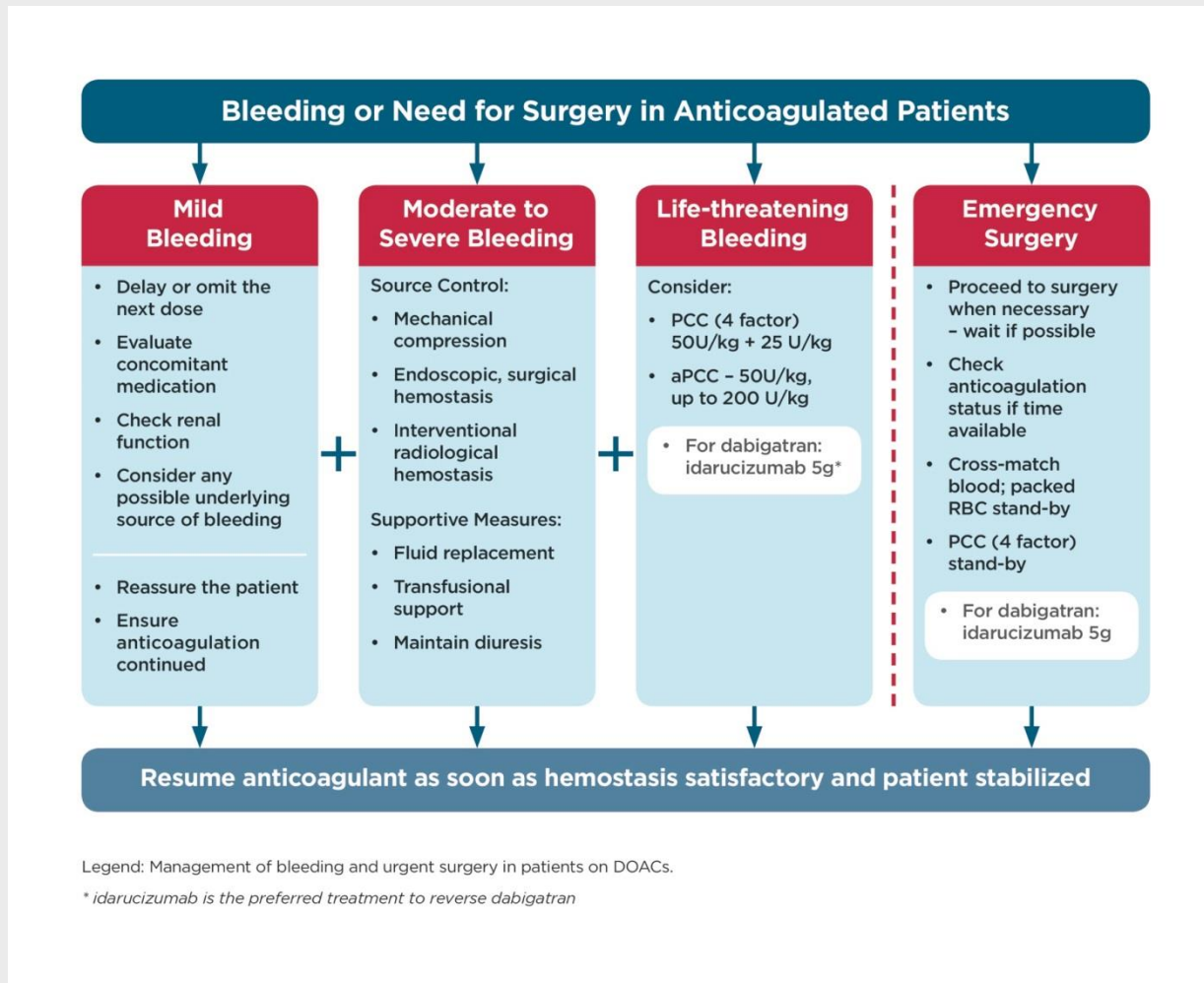
Table 3: Who should control access to reversal agents?

- Investigate whether there is a hospital bleeding management protocol – if not contact relevant departments: haematology, cardiology, neurology, etc.
- Check that the reversal agent has been incorporated into the hospital formulary – if not take steps for the reversal agent to be considered by the appropriate committee.
- Redraft the policy and flow chart(s) regarding the management of bleeding related to DOACs.
- Discuss with relevant staff where the reversal agent should be stored ([accident and] emergency department, pharmacy, etc).
- Arrange a supply of the reversal agent via the pharmacy or contact with the pharmaceutical company.
- All appropriate hospital staff members should be made aware of the availability of specific reversal agent therapy.
- Where applicable, a patient prescribed DOAC therapy should be informed of the availability of a specific reversal agent.
- After use of the reversal agent inform the pharmacy (and the pharmaceutical company) that a new supply is needed.
- Maintain a log on the use of the reversal agent and consider joining a local, national or international registry of post-marketing experience with the reversal agent.

DOAC, direct oral anticoagulant.

How should reversal agents be used in clinical practice?

Figure 1: An algorithm for management of patients treated with a DOAC who present with mild, moderate to severe, or life-threatening bleeding or who require emergency surgery. DOAC, direct oral anticoagulant.



Patient education: How should patients be educated about anticoagulation?

- Education should focus on the index conditions and the serious consequences of non-adherence
- Patient should be clearly informed about:
 - treatment indication, dosing schemes, dosing instructions in case one or more doses are missed, risks associated with non-adherence and risks associated with drug intake
- Patient should receive adequate instructions for detecting and proper reporting of adverse reactions and should therefore receive contact information of the prescribing clinic

“Question of reversal when initiating a DOAC should also be addressed with patients.”

Conclusions

- Reversal agents for the DOACs may reduce concerns regarding the use of DOACs by facilitating ready control of bleeding in emergency situations
- Certain situations (e. g. life-threatening or persistent bleeding, bleeding into a closed space, and urgent interventions) warrant prompt use of reversal agents; other situations should be decided on a case-by-case basis
- Rapid reversal of anticoagulation per se will never solve bleeding until the source of bleeding has been appropriately managed and treated
- Entry of these agents into clinical practice requires consideration of access and operationalization that must be clearly elucidated on an institutional level to prevent over- and misuse of reversal agents