

MANAGEMENT OF BLEEDING UNDER NOAC THERAPY

GENERAL ASPECTS

- ❖ THE PHASE III TRIALS HAVE CONSISTENTLY SHOWN THAT NOACS CAUSE LESS INTRACRANIAL AND LESS LIFE-THREATENING BLEEDS THAN WARFARIN
- ❖ DESPITE THE ABSENCE OF SPECIFIC REVERSAL AGENTS IN THESE TRIALS. NOT ONLY WAS THERE A SIMILAR OR EVEN A REDUCED BLEEDING INCIDENCE, BUT PATIENTS EXPERIENCING A MAJOR (PARTICULARLY EXTRACRANIAL) BLEED UNDER NOACS WERE ALSO SHOWN TO HAVE A MORE FAVOURABLE OUTCOME THAN FOR BLEEDING UNDER VKA TREATMENT.
- ❖ THIS IS UNDERLINED BY THE REDUCTION IN ALL-CAUSE MORTALITY AS WELL AS LIFE-THREATENING/FATAL BLEEDS WHICH WAS OBSERVED WITH NOACS VS. WARFARIN
- ❖ NEVERTHELESS, AS MORE PATIENTS ARE BEING TREATED WITH NOACS, THE ABSOLUTE NUMBER OF NOAC-RELATED BLEEDING EVENTS INCREASES. IMPORTANTLY, ANY BLEED IS AN OPPORTUNITY TO REVIEW THE CORRECT CHOICE AND DOSING OF THE NOAC AND TO EVALUATE MODIFIABLE BLEEDING RISK FACTORS INCLUDING SUBOPTIMALLY TREATED HYPERTENSION, EXCESSIVE ALCOHOL INTAKE AND CONCOMITANT ANTIPLATELET THERAPY, NSAIDS, GLUCOCORTICOIDS ETC.

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- ❖ To optimally manage NOAC-treated patients who present with a bleed we strongly suggest developing a hospital-wide policy in an interdisciplinary manner among cardiologists, hemostasis experts, emergency physicians/intensive care specialists, surgeons, and others.
 - ❖ This protocol should describe the availability, timing, and indications of specific coagulation tests as well as the availability and use of specific and nonspecific reversal agents. Such a policy needs to be communicated well and be easily accessible (e.g. on an intranet site, in the emergency room, in pocket-sized leaflets etc.). In addition, a regular interdisciplinary review and discussion of patients experiencing severe bleeding complications (as well as strokes) is encouraged in order to share different subspecialty experiences as well as perception of such events and subsequent preferences.

STRATEGIES TO MANAGE BLEEDING COMPLICATIONS IN PATIENTS TREATED WITH NOACS RELY ON A PRECISE ANALYSIS OF THE CLINICAL SITUATION

- ❑ The type of bleeding: nuisance/minor, major non-life threatening, or life-threatening. Based on clinical judgement—including location, extents, patient's age, comorbidities, . . .
- ❑ Potentially supported by 'official' bleeding definitions International Society of Thrombosis and Hemostasis (ISTH)
The patient and his/her treatment, including:
 - The exact time of last NOAC intake
 - Prescribed dosing regimen
 - Renal function
 - Other factors influencing plasma concentrations (e.g. hepatic function, co-medications etc.)
 - Other factors influencing haemostasis (e.g. concomitant use of antiplatelet drugs).
- The patient's thromboembolic risk Particularly when considering the use of prothrombotic agents, and regarding the necessity of (early) re-initiation of anticoagulant therapy

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- Both routine coagulation tests and assays that specifically measure NOAC plasma levels are important adjuncts in the assessment of NOAC related bleeds
 - Normal results of dTT/ecarin clotting time (for dabigatran) or anti-Xa activity (for anti-FXa treated patients) exclude relevant levels of the respective anticoagulants. Importantly, conventional coagulation tests may be abnormal not only due to the effect of the NOAC itself, but for a variety of other reasons, particularly in the setting of severe bleeding and consumption coagulopathy.
 - Conversely, it needs to be kept in mind that restoration of coagulation alone does not necessarily result in improved clinical outcome (e.g. in the context of intracranial haemorrhage).

LIFE-THREATENING BLEEDING OR BLEEDING INTO A CRITICAL SITE

- ❖ Patients with a life threatening bleed or bleeding into a critical site while treated with NOACs may benefit from its reversal in addition to the standard measures outlined above and in Figure 9.
- ❖ Although laboratory values (including a full coagulation panel) should be taken prior to any reversal measures in order to guide further treatment during the course, immediate actions are guided by clinical assessment without waiting for the results of laboratory measurements.
- ❖ Conversely and importantly, normalization of coagulation in itself is not necessarily sufficient to stop a bleed but may allow for more invasive interventions to control the bleeding source.
- ❖ Furthermore, even after direct reversal, significant NOAC concentrations may reappear in some patients and contribute to recurrent or continued bleeding (particularly after andexanet alpha due to its shorter half-life, less after idarucizumab administration), underlining the necessity for continued clinical and laboratory monitoring.

Continuing / Restart NOAC?

Consider factors favouring withholding vs. (re-)starting anticoagulation, e.g.:

- Unidentifiable site of bleeding
- Multiple angiodysplasias in the GI tract
- No reversible / treatable cause?
- Bleeding during treatment interruption
- Chronic alcohol abuse
- Older age
- Careful re-assessment of stroke and bleeding risk

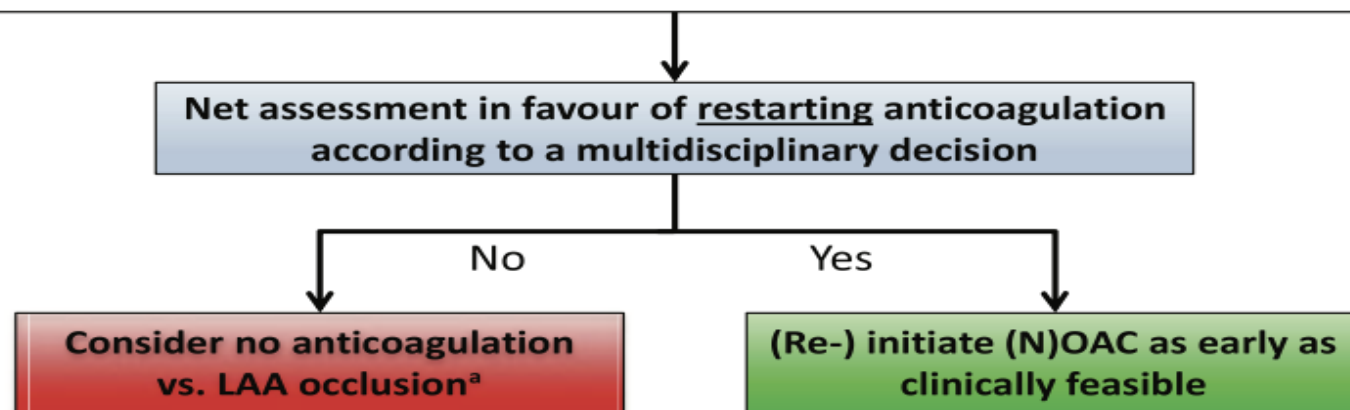
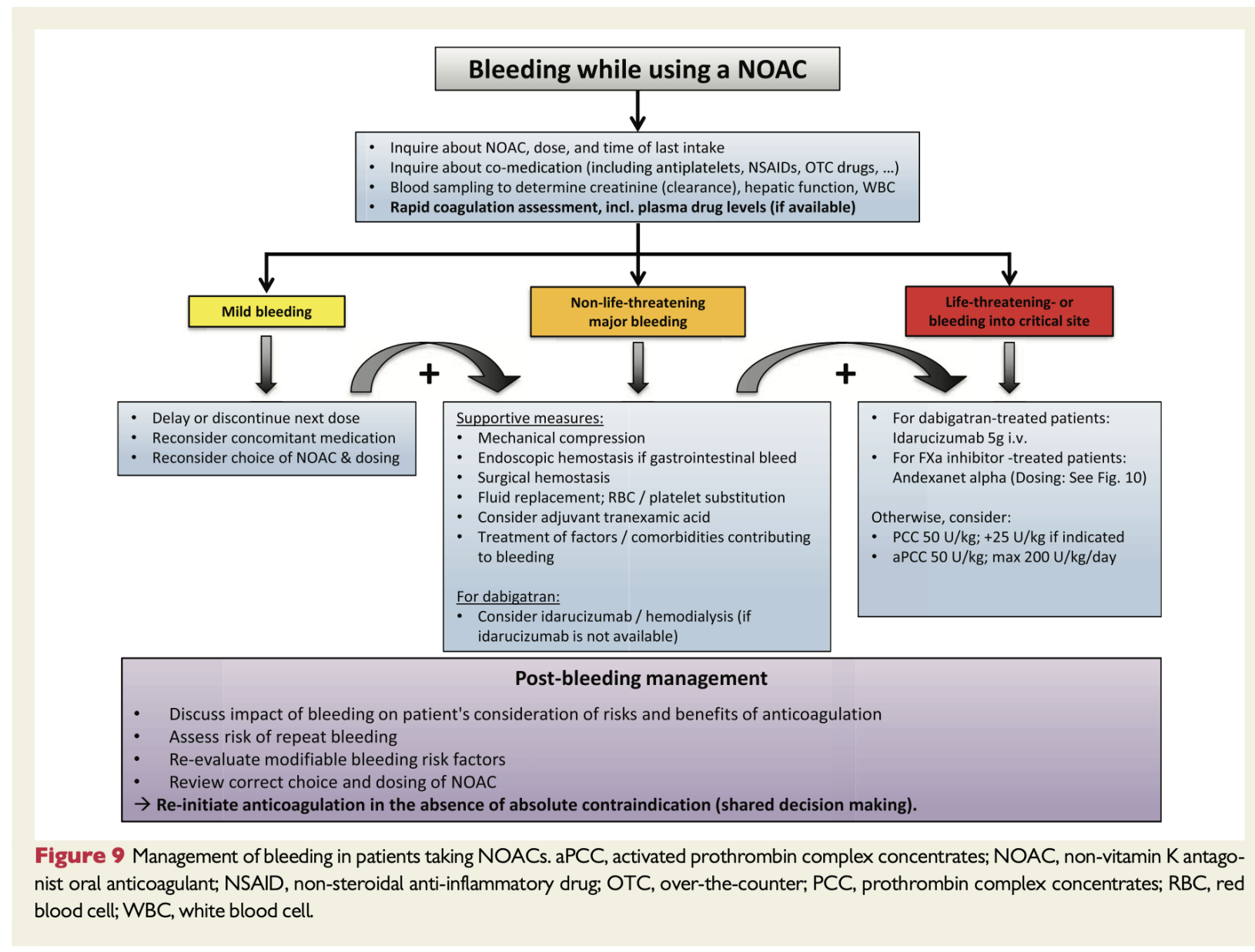


Figure 11 (Re-) initiation of anticoagulation after GI bleeding.

^aWithout RCT evidence; ideally include patient in ongoing trial. GI, gastrointestinal; LAA, left atrial appendage; NOAC, non-vitamin K antagonist oral anticoagulant.



Idarucizumab

- ✓ Idarucizumab is a humanized antibody fragment that specifically binds dabigatran. In the 'Reversal Effects of Idarucizumab in Patients on Active Dabigatran' (RE-VERSE-AD) study the drug was successfully used in patients on dabigatran presenting with major or life-threatening bleeding, or with the necessity of emergency surgery.
- ✓ This was confirmed in the observational RE- VECTO registry. Idarucizumab completely reversed the anti- coagulant activity of dabigatran within minutes in almost all patients and is hence considered first-line therapy in such situations. A total of 5 g idarucizumab is administered intravenously in two ready-to-use doses of 2.5 g i.v., administered as two consecutive infusions over 5–10 min each or as a bolus injection.
- ✓ Continued clinical and laboratory monitoring is strongly advised, since a 5 g dose of idarucizumab may not completely neutralize an exceptionally high level of dabigatran (e.g. in case of overdose or CKD). Also, low levels of dabigatran may reappear after 12– 24 h.
- ✓ After 24 h, dabigatran can be re-started if clinically indicated and feasible, with normal kinetics. Other anticoagulants, including heparins, are not affected by idarucizumab.
- ✓ If idarucizumab is not available, dialysis may be used to partially eliminate dabigatran from the circulation. However, starting and performing dialysis in a patient with a severe (potentially life-threatening) bleed may be challenging and may only be advisable if idarucizumab is not readily available.

DIRECT REVERSAL OF APIXABAN, EDOXABAN, OR RIVAROXABAN (FXA-INHIBITORS)

- Andexanet alfa is a recombinant, inactive human FXa analogue that non-specifically binds FXa inhibitors thereby preventing all FXa inhibitors (including low-molecular weight- and UFHs) from inhibiting FXa.
- In the 'Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors 4' (ANNEXA-4) study, andexanet alpha was successfully used in major or life-threatening bleeding; in contrast to REVERSE-AD the trial did not include patients undergoing emergency surgery.
- The drug comes as a lyophilized powder which needs to be reconstituted before use. It is administered as a bolus over 15–30 min, followed by a 2-h infusion depending on the NOAC and on the timing since last intake.

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- In the EU Andexanet alpha is only approved for the reversal of life-threatening or uncontrollable bleeding in patients taking apixaban or rivaroxaban. In view of the very similar mode of action and preliminary subanalyses from the ANNEXA-4 trial (Benz et al., presented at the International Stroke Conference meeting 2021) it can be assumed that it will have a similar effect in patients on edoxaban.
 - Since anticoagulant activity may reappear after cessation of the infusion it is currently less clear at what point in time and with which anticoagulant effect FXa inhibitors or heparin can be (re-)administered following andexanet alpha administration.

COAGULATION FACTORS

- ❖ Clinical trials and registry data with NOACs have shown that administration of coagulation factors is rarely needed.
- ❖ Indeed, any NOAC-antagonizing effect of a procoagulant has to be balanced carefully against the potential prothrombotic effect.
- ❖ Animal experiments as well as studies in healthy volunteers have indicated the potential usefulness of prothrombin complex concentrate (PCC) and activated PCC (aPCC) for the normalization of coagulation parameters under NOAC treatment as a surrogate for haemostatic support.
- ❖ As indicated above, data from the large phase III trials demonstrated that outcomes of bleeds under NOACs were similar (if not better) than in the VKA arm (with diverse bleeding treatments applied, including PCC/aPCC).
- ❖ The efficacy on clinical outcomes of PCCs or aPCCs in patients taking NOACs who are actively bleeding has not been firmly established in an RCT. However, several observational studies in patients with major bleedings have been published (with some inherent limitations including the retrospective, non-controlled setting as well as absence of a control group) indicating that (a)PCCs appeared to be efficacious in supporting haemostasis. Its usefulness in intracranial Haemorrhage, on the other hand, is uncertain.

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- The administration of PCCs or aPCCs can hence be considered in a patient with a life-threatening bleed if immediate haemostatic support is required, especially in situations where a specific reversal agent is not available or too costly.
 - The choice between PCC and aPCC may depend on their availability and the experience of the treatment centre. As indicated, aPCC induces a strong procoagulant effect and should only be used by physicians experienced in their use.
 - PCC and aPCC are preferred over recombinant activated factor VIIa (90 mg/kg) given the absence of any outcome data and the latter's pronounced procoagulant effect.

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- Fresh frozen plasma (FFP) is no longer considered a useful reversal strategy, primarily due to the plasma abundance of NOACs which will inhibit newly administered coagulation factors upon administration of FFP and the resulting large volume of FFP that would need to be administered to have any impact on coagulation.
 - Vitamin K and protamine administration have no role in the management of a bleeding under NOACs; these may only be useful in the management of bleeding under NOACs when vitamin K deficiency is suspected or in case of concomitant treatment with heparins, respectively

