Other Options for Anticoagulation Reversal: Dialysis, Charcoal, CytoSorb®

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Introduction

Accidental or intentional ingestion of inappropriate doses of direct oral anticoagulants (DOAC) might result in overdosing and potential risk of spontaneous bleeding. In addition, correct intake of DOAC in combination with rapidly decreasing renal or hepatic function or by interactions with newly added drugs might result in higher-than-expected DOAC concentrations and even overdosing.

Overdosing is a concern, as the risk of major bleeding gradually increases with increasing DOAC concentrations in these drugs due to increasing anticoagulant effect. The latter has been clearly shown for dabigatran and edoxaban.[1-3] However, a gradually increased bleeding risk with the higher DOAC concentrations with rivaroxaban and apixaban seems very likely.

Further, it has been shown that, after overdosing of DOACs, patients are more likely to develop any bleeding (relative risk (RR), 6.68; 95% CI, 2.63 to 17.1) and major bleeding (RR, 18.1; 95% CI, 3.85 to 85.0) as compared to patients with overdose ingestion of antiplatelet agents.[4] However, due to the short elimination half-lives of DOACs, high plasma concentrations usually decrease over a short period of time. Of note, the rapid reversal by specific antagonists or by administration of prothrombin complex concentrates (PCC) with the intention to reduce bleeding risk might lead to thromboembolic events in patients anticoagulated due to increased thromboembolic risk. In agreement, the European Society of Anaesthesiology and Intensive Care (ESAIC) 2024 guidelines suggest not to reverse overdoses of dabigatran or FXa inhibitors in the non-bleeding patients who are not scheduled for urgent or emergent surgery.[5] In addition, the ESAIC 2024 guidelines pointed out that such interventions without need might increase the risk of systemic thromboembolism.[5]

Potentially, non-pharmacological interventions aiming to lower DOAC levels or to reverse anticoagulant effects might be considered. Among them, the use of hemodialysis, charcoal, and hemoabsorption systems (CytoSorb®) will be discussed in the following sections.

Hemodialysis

The ESAIC 2024 guidelines suggest that general measures to eliminate dabigatran and FXa inhibitors should be applied in non-bleeding patients with accidental or intentional DOAC overdose.[5] Measures to eliminate the FXa inhibitors include the stimulation of diuresis, as all DOAC have a relevant renal elimination.

The indication for hemodialysis, in contrast, must be carefully evaluated in DOAC patients with overdosing. In general, hemodialysis is indicated in drug overdose when the substance is dialysable. Premises for good dialysability are a low protein binding and relevant proportion of renal elimination (**Table 1**).

Table 1. Renal elimination, protein binding und clearance by dialysis in different DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Kidney elimination (%)	80-85	35	27	50
Plasma protein binding (%)	26-28	>90	87	55
Drug clearance by dialysis (%)	62-68	Negligible	Negligible	Negligible

(modified after Elenjickal et al.[6])

According to Elenjickal et al., drug clearance of dabigatran by dialysis is high (about 62-68%), whereas the effects of hemodialysis in direct FXa inhibitors is rated to be negligible.[6] In some contrast, Aursulesei et al. stated that apixaban is at least partially dialysable.[7] However, the use of hemodialysis might be clinically most effective in patients with dabigatran overdose.[8] In agreement, the ESAIC 2024 guidelines stated that in patients with dabigatran overdose, the use of hemodialysis in the hemodynamically stable non-bleeding patient is an option to rapidly reduce plasma levels.[5]

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The clinical use of hemodialysis in drug overdose or intoxication is justified if drug overdose causes severe complications that cannot be managed with other treatments. Most evidence for the effects of hemodialysis comes from studies that were published more than 10 years ago. At that time, the direct reversal of DOACs was not feasible due to the missing availability of specific antagonists (i.e., idarucizumab and andexanet alfa). Thus, the use hemodialysis in dabigatran overdosing might today only be indicated when idarucizumab is not available.

Charcoal

In patients with recent intentional overdosing with DOAC, the administration of charcoal and the endoscopic removal of residual pills in the stomach can be considered. Specific recommendations were made in the ESAIC 2024 guidelines to consider activated charcoal for early dabigatran overdose (2C recommendation).[5] Similarly, in early apixaban overdose, the administration of activated charcoal might be considered.[5,9] **Table 2** lists the suggested time frames after ingestion of DOACs within which charcoal and gastroscopic removal might be considered.

Table 2. Application of charcoal in different DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Activated charcoal	when ingestion within 2 hours	when ingestion within 8 hours	when ingestion within 6 hours	when ingestion within 2 hours
Gastroscopic removal	may be considered	may be considered	may be considered	may be considered

(modified after Neumann et al.[10])

Hemoabsorption/CytoSorb®

CytoSorb® is one of the most commonly used blood purification devices. It consists of a 300 mL cartridge containing small styrene copolymer beads with a diameter of 425-1000 µm and surface area of 850 m^2/g.[11-13] These beads preferably bind and remove hydrophobic substances of about 10 to 55 kDa. The CytoSorb® hemoabsorber can be easily integrated into extracorporeal circuits including cardiopulmonary bypass systems or hemofilters.[12]

The CytoSorb® hemoabsorber has been proposed in various clinical settings including sepsis, ARDS, hyperinflammatory syndrome, cardiac surgery, or recovery after cardiac arrest.[14] In addition, the use of CytoSorb® has been suggested for the removal of anticoagulant drugs including DOACs and ticagrelor.

The use of CytoSorb® hemoabsorber for managing DOACs in the setting of emergent cardiac surgery has recently completed fundamental preclinical investigations.[12,15] The available clinical results are limited and most evidence stemmed from one German clinical center.[16,17] Given that the technology is still under clinical investigation and the limited evidence of benefits, any definitive conclusions are prevented from being made at the moment.[16]

Accordingly, there are no recommendations in the recent patient blood management guidelines of the European Association for Cardio-Thoracic Surgery and the European Association of Cardiothoracic Anaesthesiology and Intensive Care (EACTS/EACTAIC).[16] However, there is a 2C recommendation in the recent ESAIC 2024 guidelines.[5]

In conclusion, the use of the CytoSorb® hemoabsorber might be an option in patients with recent intake of anti-Xa inhibitors scheduled for emergent cardiac surgery when andexanet alfa is not an option. However, given the costs of such absorbers and the questionable benefits, the use of CytoSorb® hemoabsorber should be individualized to patients who might benefit most and with proven relevantly elevated DOAC levels (e.g., ≥ 80-100 ng/mL).

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