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ISTH SSC COMMUNICATIONS

Reversal of direct oral anticoagulants: guidance from the SSC of the ISTH

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Abstract

The currently approved direct oral anticoagulants (DOACs) are increasingly used in clinical practice. Although serious bleeding risks are lower with DOACs than with vitamin K antagonists, bleeding remains the most frequent side effect. Andexanet alfa and idarucizumab are the currently approved specific reversal agents for oral factor (F) Xa inhibitors and dabigatran, respectively. Our prior guidance document was published in 2016, but with more information available on the utility and increased use of these reversal agents and other bleeding management strategies, we have updated this International Society on Thrombosis and Haemostasis guidance document on DOAC reversal. In this narrative review, we compare the mechanism of action of specific and nonspecific reversal agents, review the clinical data supporting their use, and provide guidance on when reversal is indicated. In addition, we briefly discuss the reversal of oral FXIa inhibitors, a new class of DOACs currently under clinical development.

KEYWORDS
andexanet, bleeding, direct oral anticoagulants, factor XI inhibitors, idarucizumab, prothrombin complex concentrates

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1 | INTRODUCTION

The currently approved direct oral anticoagulants (DOACs) include apixaban, edoxaban, and rivaroxaban, which inhibit factor (F)Xa, and dabigatran, which inhibits thrombin (FIIa). These drugs have been licensed for 15 years, and with generic formulations now available in many countries, their use is likely to increase further.

The risk of serious bleeding, particularly intracranial hemorrhage (ICH), is lower with DOACs than with vitamin K antagonists, but bleeding remains the most frequent side effect. Andexanet alfa (andexanet) and idarucizumab are the currently approved specific reversal agents for oral FXa inhibitors (FXaIs) and dabigatran, respectively. With more information now available on the utility and increased use of these reversal agents, an updated International Society on Thrombosis and Haemostasis guidance document on DOAC reversal is timely. In this narrative review, we compare the mechanism of action of specific and nonspecific reversal agents, review the clinical data supporting their use, and provide guidance on when reversal is indicated. In addition, we briefly discuss the reversal of oral FXIa inhibitors, a new class of DOACs currently under clinical development.

2 | DOAC REVERSAL AGENTS

2.1 | Specific reversal agents

2.1.1 | Idarucizumab

Idarucizumab is a monoclonal antibody Fab fragment with a high affinity for dabigatran that rapidly reverses its anticoagulation effects. Idarucizumab has a half-life of ~45 minutes that is prolonged with renal dysfunction [1]. Idarucizumab was approved by the US Food and Drug Administration in 2015 based on the results of an international multicenter single-arm cohort study (RE-VERSE AD) that evaluated the efficacy of idarucizumab as a reversal agent for dabigatran-treated patients with life-threatening bleeding or requiring urgent surgery [2]. Patients received an intravenous 5 g idarucizumab bolus infusion over 30 minutes. The primary endpoint was the maximum percentage reversal of the anticoagulant effects of dabigatran as determined by the ecarin clotting time or diluted thrombin time. In the final analysis, there were 503 participants, including 301 (mean age, 79 years; 57.1% males) with life-threatening bleeding and 202 (mean age, 77 years; 50.5% males) needing urgent surgery [3]. The median time to hemostasis for patients with life-threatening bleeding was 2.5 hours. Periprocedural hemostasis was rated as normal in 93% of the patients requiring urgent surgery, and none had severely abnormal hemostasis. The duration of idarucizumab reversal was ~24 hours. The 30-day risk of thromboembolic complications after reversal was 4.8%. Most of these events occurred in patients whose baseline anticoagulation had not been restarted [3].

Idarucizumab is the only agent evaluated and approved for reversal before urgent surgery or interventions in nonbleeding patients. A separate analysis of such patients included 49 abdominal, 45 orthopedic, 34 vascular, 8 neurologic, and 4 genitourinary surgical procedures; 29 catheter-based cases, including 20 cases for drainage; and 8 diagnostic procedures [4]. Dabigatran reversal occurred within minutes in most patients, with normal hemostasis in 92%. The median time from idarucizumab administration to surgery or intervention was within 2 hours except for neurosurgery (3.3 hours). The 30-day mortality was 12.6%, without reported adverse safety signals. The absence of a control group limits the interpretation of these safety findings.

2.1.2 | Andexanet alfa

Andexanet alfa (andexanet) is a recombinant FXa variant without enzymatic activity or capacity to incorporate into the prothrombinase complex because of the substitution of the active site serine residue with an alanine residue and deletion of the gamma-carboxyglutamic acid (Gla) domain, respectively [1]. In individuals treated with oral FXaIs, andexanet rapidly decreased anti-FXa activity and free drug levels and increased thrombin generation [5,6]. In the andexanet alfa (ANNEXA)-A and ANNEXA-R randomized clinical trials, which compared andexanet with a placebo, an intravenous andexanet bolus followed by an infusion significantly reduced anti-FXa activity for up to 4 hours in healthy volunteers dosed to steady-state with apixaban (94% vs 21% reduction) or rivaroxaban (92% vs 18% reduction) and increased thrombin generation for up to 12 hours [5,6]. Andexanet alfa was approved by the US Food and Drug Administration in 2019 based on these reported clinical studies.

The prospective, open-label, single-cohort ANNEXA-4 study examined andexanet for the treatment of major bleeding in patients receiving FXaI rivaroxaban, apixaban, edoxaban, or enoxaparin within 18 hours of their most recent dose [7]. Andexanet was administered as an intravenous loading dose followed by a 2-hour infusion, with the dose depending on the type of FXaI taken and the timing of the most recent intake. The coprimary outcomes were the percentage change in anti-FXa activity and the percentage of patients with excellent or good hemostatic efficacy 12 hours after the infusion adjudicated using prespecified criteria that differed depending on the bleeding site. Patients with ICH and a Glasgow coma score less than 7 or a hematoma volume greater than 60 mL were excluded. A total of 479 patients were enrolled in the final analysis set (mean age, 78 years; 46% female), most of whom were receiving apixaban (51%) or rivaroxaban (37%) for atrial fibrillation (81%) [8]. Efficacy was analyzed in 342 patients with baseline anti-FXa activity levels above predefined thresholds (≥75 ng/mL for apixaban and rivaroxaban, ≥40 ng/mL for edoxaban, and ≥0.25 IU/mL for enoxaparin; reported in the same units used for calibrators). Bleeding was predominantly intracranial (69%) or gastrointestinal (GI; 23%). After treatment with andexanet, the median anti-FXa activity decreased by 93%, and 80% of evaluable participants were adjudicated as having excellent or good hemostatic efficacy at 12 hours. Thrombotic events occurred in 10% of participants, none of whom had resumed oral anticoagulation; 16 occurred

despite parenteral anticoagulant thromboprophylaxis [8]. The absence of a control group limits the interpretation of these safety findings [9].

In the ANNEXA-I trial, individuals with ICH presenting within 6 hours of symptom onset and 15 hours after the last dose of apixaban, edoxaban, or rivaroxaban were randomized to andexanet or usual care [10]. The primary efficacy endpoint was effective hemostasis at 12 hours, defined as meeting all the following criteria: (i) ≤35% hematoma volume expansion at 12 hours, (ii) National institutes of Health Stroke Scale score increase of <7 at 12 hours, and (iii) no rescue therapy, either surgical or prothrombin complex concentrates (PCCs), administered between 3 and 12 hours after randomization. The trial was stopped early after a preplanned interim analysis of data from 450 patients met the criteria for efficacy ($P < .031$). The final analysis included 530 patients (mean age, 79 years; 46% female), 87% of whom were treated for atrial fibrillation [10]. PCCs were administered to 85.5% of patients in the usual care group. A higher proportion of patients receiving andexanet than usual care had excellent or good hemostatic efficacy (67% vs 53.1%; adjusted difference, 13.4 percentage points; 95% CI, 4.6-22.2; $P = .003$). A lower proportion had hematoma increase ≥12.5 mL or death within 12 hours after randomization occurred in 24 of 216 patients (11.1%) receiving andexanet alfa and in 36 of 214 (16.8%) receiving usual care. At 30 days, the proportion of patients who died (27.8% vs 25.5%) and the proportion of survivors with favorable functional status (modified Rankin scale score, ≤3; 28.0% vs 30.9%) were not statistically different in the andexanet and usual care groups, respectively. Thromboembolic events were significantly more frequent in the andexanet group (10.3% vs 5.6%; absolute increase of 4.6 per 100 patients; 95% CI, 0.1-9.2; $P = .048$), particularly ischemic stroke (6.5% vs 1.5%; absolute difference, 5.0; 95% CI, 1.5-8.8). Important methodological limitations of the study include the open-label design, which can bias the use of cointerventions, and the lack of standardized treatment within the usual care group [10].

2.2 | Nonspecific reversal agents

2.2.1 | PCCs

PCCs are concentrates purified from plasma that contains FII (prothrombin), FIX, FX, and FVII in various concentrations. Four-factor (4F) PCCs contain all 4 of the vitamin K–dependent coagulation proteins and small amounts of protein C and S, whereas 3-factor PCCs have little or no FVII and were originally developed for hemophilia B management [11]. 4F-PCCs are the most studied and clinically used PCCs for DOAC reversal and/or associated bleeding management. PCCs are likely to overcome the anticoagulant effects of DOACs by increasing thrombin generation via the provision of high levels of coagulation proteins [12]. 4F-PCCs can be given as a weight-based dose (typically 25-50 IU/kg) or as a fixed dose (eg, a single dose of 2000 IU) [13].

Volunteer studies have demonstrated the capacity of 4F-PCCs to partially correct thrombin generation after DOAC administration and emerged as an off-label treatment for DOAC-related bleeding. *In vitro* and volunteer studies report that 4F-PCCs can restore thrombin generation in DOAC-treated subjects, although the effect may depend on circulating DOAC concentrations [14,15]. The risk of thromboembolic complications with PCCs in this setting appears to be low. Pooled and meta-analysis have confirmed these findings with a global efficacy of 80% and a maximum thromboembolism rate of 4% based on available data [16,17].

4F-PCCs also appear to be effective when used preemptively in DOAC-treated nonbleeding patients scheduled to undergo an emergency invasive procedure [18,19], but prospective studies comparing 4F-PCCs with placebo in this setting have not yet been reported. A retrospective study evaluating the use of PCCs compared to andexanet alfa reported a 31% reduced in-hospital mortality rate compared to 4F-PCC. Of note is that ANNEXA-I is the only randomized trial that compares a specific reversal agent head-to-head with "usual care," which mostly involved 4F-PCC administration. Despite the limitations of large retrospective studies, they provide the bulk of the current information on differences in outcomes with various reversal strategies for FXaIs.

The optimal dosing regimen of 4F-PCCs is uncertain for DOAC reversal. In a meta-analysis of 25 studies that included 1760 patients, there were no significant differences in hemostatic effectiveness, thromboembolic events, or mortality rates between fixed and weight-based dosing strategies, but the average total weight-based dose was lower with a fixed-dosed strategy of 2000 IU [13].

2.2.2 | Activated PCC

Activated PCC (APCC) contains FVIIa and FX, FIX, and FII in their zymogen state. The only currently available APCC is FEIBA (factor eight inhibitor bypassing activity-Takeda), which is licensed to treat bleeding in patients with hemophilia A or B who have inhibitors [11]. *In vitro* analyses suggest that APCC increases thrombin generation more than either PCCs or recombinant FVIIa (rFVIIa) [12]. A retrospective study on the use of APCC in 82 DOAC-treated patients with bleeding or requiring urgent surgery reported moderate to good hemostasis in 56% of patients with major bleeding, and surgical hemostasis was normal in 84% of patients receiving APCC for urgent surgery. The 30-day risk of thromboembolism was 6% [20].

2.2.3 | Recombinant FVIIa

rFVIIa binds to tissue factor at sites of vascular injury and initiates thrombin generation. Like APCC, rFVIIa is approved for the management of bleeding in hemophilia A or B patients with inhibitors. In studies where thrombin generation was measured after DOACs were added to plasma, rFVIIa addition shortened the lag time and the time to peak thrombin but did not affect the peak thrombin concentration or the endogenous thrombin potential [12]. There is no evidence

supporting the use of rFVIIa for treating DOAC-associated bleeding, and its safety is unknown.

2.3 | Comparisons among reversal agents

As noted from ANNEXA-I, there was improved hemostatic efficacy (67% [150/244] vs 53.1% [121/228] for usual care) [9,10]. Observational cohort studies have reported outcomes of patients who were given andexanet or PCCs for bleeding in routine clinical practice. Several of these suggest comparable effectiveness but numerically higher rates of thromboembolic complications with andexanet than with 4F-PCCs [21,22]. In a retrospective analysis that included data on 4395 patients from 354 US hospitals, the odds of in-hospital mortality in the overall cohort were lower among individuals receiving andexanet than among those receiving 4F-PCCs (128/2122 [6.0%] vs 241/2273 [10.6%], respectively; odds ratio [OR], 0.50; 95% CI, 0.39-0.65) with similar results for intracranial and GI bleeding [23]. Another study reported lower 30-day mortality among 322 patients treated with andexanet in the ANNEXA-4 trial compared with a propensity-score matched cohort of 88 patients treated with 4F-PCCs in routine clinical practice (14.6% vs 34.1%, respectively; relative risk, 0.43; 95% CI, 0.29-0.63) [24]. Interpretation of these findings is limited by the retrospective design, absence of some baseline patient-specific and bleed-related characteristics, and limited adjustment for potential confounders that could lead to prognostically significant differences in the groups at baseline. Other indirect comparisons also suggested decreased mortality with andexanet than with 4F-PCCs [25,26].

In a retrospective cohort study that included 232 patients with DOAC-associated ICH, 116 (50%) received conservative treatment and 102 (44%) received 4F-PCCs [27]. Good neurologic recovery occurred in 74 patients (31%), but 92 patients (39%) died within 90 days. Baseline median hematoma volume was 21.7 mL with an IQR of 3.6 to 66.1 mL. The use of 4F-PCCs were not associated with improved neurological recovery (adjusted odds ratio [aOR], 0.62; 95% CI, 0.33-1.16; $P = .14$), mortality at 90 days (aOR, 1.03; 95% CI, 0.70-1.53; $P = .88$), in-hospital mortality (aOR, 1.11; 95% CI, 0.69-1.79; $P = .66$), or hematoma expansion reduction (aOR, 0.94; 95% CI, 0.38-2.31; $P = .90$). Higher hematoma volumes, decreased Glasgow coma scale scores, and intraventricular bleeding were associated with lower odds of good neurologic outcomes but not hematoma expansion [27]. Additional reports include a retrospective evaluation of 3030 FXaI-related US hospitalizations for major bleeding from FXaI use [28]. They noted that hospital mortality was 23% ($n = 507$) for ICH, 4% ($n = 1453$) for GI bleeding, 4% for andexanet alfa treatment ($n = 342$), 10% for 4F-PCC treatment ($n = 733$), 11% for fresh frozen plasma (FFP) treatment ($n = 925$), 8% for other agents ($n = 794$), and no agents ($n = 438$) [28].

Three ongoing clinical trials are evaluating 4F-PCCs for the optimization of hemostasis. One is a randomized noninferiority study evaluating center-specific PCCs dosing for patients needing urgent high-bleed-risk surgery within 15 hours from the last dose of FXaI [29]. Another is a phase 3 randomized prospective multicenter trial comparing low- and high-dose 4F-PCC (Octaplex-Octapharma) regimens in patients taking FXaI who present with major bleeding [30]. The third study is an observational study examining the effect of 4F-PCCs on thrombin generation in patients taking oral FXaI who present with significant bleeding or require urgent surgery [31]. However, these 3 PCC studies do not have comparator groups. A multinational, observational study of hospitalized patients with FXaI-associated major bleeds evaluating 2 cohorts of 2000 patients each is planned [32]. The study will include a historic cohort of medical chart data to discharge for FXaI patients with major bleeds and later enroll patients receiving any reversal or replacement therapy.

2.4 | Reversal strategies under investigation

2.4.1 | Ciraparantag

Ciraparantag (PER977) is a synthetic cationic molecule originally developed to reverse heparin but was subsequently found to bind DOACs [1]. Ciraparantag also binds citrate, making monitoring reversal with plasma-based coagulation assays impossible. Instead, a whole blood clotting time (WBCT) test was developed. In healthy volunteers given a single dose of edoxaban, ciraparantag doses of 100 to 300 mg fully reversed the WBCT [33,34]. Compared with placebo in volunteers given apixaban or rivaroxaban, ciraparantag reversed the WBCT at 60 mg and 180 mg, respectively [35]. A clinical trial with ciraparantag is being planned [36].

2.4.2 | FXa variants

Novel FXa variants under development include zymogen-like molecules with procoagulant activity but do not bind to FXaI. VMX-C001 (VarmX) is an FX variant that has an active site mutation based on the FX sequence of the eastern common brown snake venom. VMX-C001 is insensitive to oral FXaI when activated and converts prothrombin to thrombin [37]. The mutant FXa is inhibited by antithrombin. Clinical studies of VMX-C001 are underway [38].

2.4.3 | Extracorporeal hemadsorption

Hemadsorption of oral FXaI using a styrene copolymer column with sorbent beads has been proposed as a reversal strategy in patients undergoing cardiac surgery. Proof of concept was demonstrated using an *in vitro* benchtop recirculation model with bovine whole blood spiked with clinically relevant concentrations of DOACs. Removal rates of 99% for apixaban and rivaroxaban were observed after 6 hours of recirculation [39]. For cardiac surgical patients, the system can be used in line with the cardiopulmonary bypass circuit; however, in anticoagulated patients without preexisting vascular access, a

dialysis catheter with a large bore cannula would need to be placed, adding to the potential bleeding risk.

2.5 | Adverse effects of reversal agents and bleeding management

In DOAC-treated patients with serious bleeding, reversal agents are associated with a reported rate of thromboembolic complications ranging from 4% to 10%, depending on the reporting timeframe, the population studied, and which reversal agent is used [7,16]. However, the potential incremental harm of different therapies is uncertain in the absence of controlled or comparative randomized studies. In healthy volunteer studies of DOAC reversal, no thromboembolic complications were reported following andexanet, idarucizumab, or PCCs [5,40,41]. In patients, the risk of thromboembolic complications is impacted by their underlying risk of thrombotic complications if anticoagulation therapy is withheld during or after a bleeding episode or after major surgery [12]. When used for warfarin reversal, the risk of thrombotic complications with PCCs is ~8%, whereas the risk with FFP is ~6%, likely reflecting the baseline risk [42]. Whether observed thromboembolic events are due to a direct prothrombotic effect from the products used for anticoagulation reversal or due to delayed anticoagulation resumption after major bleeding in patients with underlying thrombotic risk is unclear as none of the phase 3 clinical studies had a control arm. For example, similar rates of thromboembolism were seen among patients receiving PCC's 7.8% or plasma 6.4% for warfarin-related bleeds. Most thrombotic events occur before restarting therapeutic anticoagulation, emphasizing the importance of restarting anticoagulation as soon as clinically acceptable to mitigate the risk of thrombosis after anticoagulation reversal [3,8]. Thromboembolic events appear to be more common with andexanet than with PCCs. This may reflect better reversal efficacy or that andexanet forms a nonproductive complex with tissue factor pathway inhibitor, thereby attenuating its antithrombotic effects [43].

3 | REVERSAL OF ORAL FXIa INHIBITORS

The next generation of anticoagulation agents is the oral FXIa inhibitors. These agents are being developed with the expectation that FXI will be a safer target for new anticoagulants than FXa or thrombin because FXI is essential for thrombosis but mostly dispensable for hemostasis and may have a lower rate of associated bleeding [44]. Asundexian and milvexian are the oral FXIa inhibitors in the most advanced stages of development. Asundexian is given once daily and has a half-life of 14 to 17 hours, whereas milvexian is given twice daily and has a half-life of 9 to 12 hours. There is no specific reversal agent for either drug.

In patients requiring urgent surgery, intravenous tranexamic acid may reduce the risk of bleeding. For patients with serious bleeding, tranexamic acid and low-dose rFVIIa are suggested, therapies related to experience with FXI deficiency management. If rFVIIa is unavailable or if there is ongoing bleeding despite rFVIIa administration, APCC is an option [44,45]. There is no evidence supporting the use of PCC or FFP to reverse oral FXIa inhibitors [44].

4 | POTENTIAL INDICATIONS FOR REVERSAL

Potential indications for reversal are listed in the Table. These include major bleeding, the need for urgent surgery that cannot be delayed, or invasive procedures at increased bleeding risk. Idarucizumab has been licensed for both indications since 2016. Andexanet is only licensed for the reversal of rivaroxaban or apixaban in patients with major bleeding. Even in countries where formal regulatory approval has been granted, the use and availability of andexanet is limited, possibly because of its high cost.

Despite the availability of andexanet, nonspecific reversal agents, particularly 4F-PCCs, are frequently used in patients taking oral FXaI who present with serious bleeding or undergoing emergency surgery or high-bleeding risk invasive procedures. Guidelines recommend APCC use for dabigatran reversal if idarucizumab is unavailable and PCCs for reversal of oral FXaI when andexanet is unavailable [46]. With the results of the ANNEXA-I trial, the hemostatic efficacy of andexanet alfa was mainly driven by hematoma expansion reduction that was superior to usual care that included mostly PCCs although the mortality between groups was unchanged. Further studies are needed to optimize the risk-to-benefit ratio of andexanet alfa along with well-designed rigorous trials to establish the efficacy of PCCs in DOAC-associated bleeding.

It should be noted that FFP has no role as a "reversal agent" and should only be used to manage dilutional coagulopathy in the case of massive bleeding as part of a massive transfusion protocol [47]. Likewise, tranexamic acid has no formal role in DOAC reversal, although it may be a useful adjunct in DOAC-treated patients with major bleeding or requiring urgent surgery.

5 | LABORATORY TESTING

Laboratory testing can guide hemostatic management but should not take precedence over clinical assessment of life-threatening bleeding. Initial laboratory testing should include creatinine for assessment of renal function, particularly in patients taking dabigatran.

Although the activated partial thromboplastin time, prothrombin time, and thrombin time can be prolonged with high concentrations of DOACs, these tests lack sufficient sensitivity to guide reversal decisions for oral FXaI. In contrast, a normal thrombin time rules out the presence of dabigatran, and a normal activated partial thromboplastin time rules out the presence of asundexian or milvexian.

For quantification of dabigatran levels, the diluted thrombin time or the ecarin clot time using dabigatran calibrators is the preferred assay. This is due to their linear correlation with drug concentrations, as assessed by mass-spectroscopy [48]. Although ecarin chromogenic assays can be used, they are not widely available.

TABLE Guidance on indications for use or nonuse of specific antidotes and other therapies.

Guidance on indications for use of specific antidotes and other therapies	Idarucizumab[a] Licensed for reversal of dabigatran in major hemorrhage and emergency surgery since 2016	Andexanet alfa[a] Licensed for reversal of rivaroxaban and apixaban in major hemorrhage since 2019	PCC[b] Not licensed for specific DOAC reversal	Tranexamic acid[c] Not licensed for specific DOAC reversal
Guidance on indications for use	• Life-threatening bleeding: intracranial hemorrhage, expanding or uncontrollable bleeding • Bleeding in a critical organ or closed space • Urgent or emergency surgery or intervention that cannot be delayed in patients with a high risk for procedural bleeding, ie, neurosurgery	• Life-threatening bleeding: intracranial hemorrhage, expanding or uncontrollable bleeding • Bleeding in a critical organ or closed space • Urgent relief surgery for intracranial hemorrhage	• Life-threatening bleeding: intracranial hemorrhage, expanding or uncontrollable bleeding • Bleeding in a critical organ or closed space • Urgent or emergency surgery or intervention that cannot be delayed in patients with a high risk for procedural bleeding, ie, neurosurgery • Might be useful in trauma patients with dilution coagulopathy due to massive blood loss	• Life-threatening bleeding: intracranial hemorrhage, expanding or uncontrollable bleeding • Bleeding in a critical organ or closed space • Urgent or emergency surgery or intervention that cannot be delayed in patients with a high risk for procedural bleeding, ie, neurosurgery • Might be useful in trauma patients with dilution coagulopathy to prevent hyperfibrinolysis
Guidance on indications in which the antidote or other therapies should not be used	• Elective surgery • Gastrointestinal bleeds that can be stopped by local supportive measures • High DOAC drug levels without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance	• Urgent or emergency surgery or intervention (not licensed, will interfere with perioperative heparin treatment) • Elective surgery • Gastrointestinal bleeds that can be stopped by local supportive measures • High DOAC drug levels without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance	• Elective surgery • Gastrointestinal bleeds that can be stopped by local supportive measures • High DOAC drug levels without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance	• Elective surgery • Gastrointestinal bleeds that can be stopped by local supportive measures • High DOAC drug levels without associated bleeding • Need for surgery or intervention that can be delayed long enough to permit drug clearance

DOAC, direct oral anticoagulant; PCC, prothrombin complex concentrate.

[a] When quantitative DOAC measurements are available, the use of specific antidotes should only be considered when the residual DOAC concentration is >50 to 75 ng/mL depending on the type of surgery.

[b] Should only be used when a specific antidote is not available and/or in case of dilution coagulopathy due to a massive blood loss.

[c] Should only be used when hyperfibrinolysis is suspected and other hemostatic therapies could not stop bleeding.

For FXaI, the drug levels of apixaban, rivaroxaban, or edoxaban are best quantified using calibrated chromogenic anti-FXa assays. Heparin-calibrated anti-FXa assays show an approximately linear relationship for FXaI levels of 30 to 100 ng/mL with acceptable sensitivity and specificity, but the relationship is nonlinear with concentrations <30 ng/mL or >150 ng/mL [49,50]. Heparin-calibrated anti-FXa assays are therefore not recommended to exclude concentration thresholds of 30 to 50 ng/mL without a rigorous and well-defined in-house laboratory validation process [6].

DOAC concentrations of 30 ng/mL and 50 mg/mL are considered clinically relevant thresholds [12,51,52]. A threshold of 50 ng/mL is reasonable for consideration of reversal in patients with major bleeding, although a threshold of 30 ng/mL can be considered if bleeding is life-threatening [12]. 4F-PCCs, APCC, and rFVIIa have no effect on DOAC levels, whereas andexanet and idarucizumab reduce circulating DOAC levels by acting as drug antidotes rather than reversal agents [12]. Specific assays may be required to assess reversal after andexanet administration because the high sample dilution required for conventional calibrated chromogenic anti-FXa assays can lead to *in vitro* dissociation of andexanet from its FXaI target and overestimation of circulating FXaI levels after reversal [53]. As a result, calibrated commercially available chromogenic anti-FXa assays should not be used to assess reversal of FXaI after andexanet administration.

6 | PERIOPERATIVE MANAGEMENT FOR URGENT SURGERY

DOAC-treated nonbleeding patients who need urgent surgery are at higher risk for perioperative bleeding (17%-23% vs 1%-2%) and thromboembolism (7%-16% vs 0.5%-1.0%) than those undergoing elective surgery [52]. Mitigating these risks is based on empiric management that involves active reversal or passive elimination of the DOAC anticoagulant effect preoperatively and timely resumption of anticoagulation postoperatively [54].

Preoperative DOAC management involves 4 considerations. First is determining the urgency of surgery, whether emergency (ie, within 6 hours), urgent (ie, between 6 and 24 hours), or semiurgent (ie, between 24 and 48 hours). Second, when possible, the timing of the last DOAC dose must be ascertained, and the residual anticoagulant effect must be determined at clinical presentation. Third is determining the need for reversal based on residual circulating drug. Fourth, is determining whether the procedure even requires reversal since some procedures can be performed safely without interruption of anticoagulation.

Emergency surgery includes surgery for a ruptured or obstructed viscus or surgery for bleeding that is life-threatening and/or at a critical site (eg, intracranial, spinal, aneurysm rupture). If testing is available, a DOAC level ≥50 ng/mL may necessitate reversal, whereas surgery without reversal would be feasible with a level <50 ng/mL. If a DOAC level is not available or if the time of the last dose is unknown, reversing any potential ongoing anticoagulant effect of prior DOAC therapy would be reasonable, especially in patients having an urgent surgery or emergency surgery associated with high-bleeding or in specific anatomical sites that require normal hemostasis such as neurosurgical interventions.

Urgent surgery includes lower limb fractures, acute limb ischemia, and emergent surgery in clinically stable patients. Hip fracture is important because it is common, is associated with considerable morbidity and mortality, and requires, ideally, surgical repair within 24 hours [55]. DOAC levels can help inform the need for reversal and the timing of surgery. In elderly patients who need emergency surgery, the half-life of DOACs can be prolonged [56]. This should be taken into consideration when planning surgery. For example, patients with a hip fracture and a DOAC level at presentation of <50 ng/mL could proceed to surgery within the next 6 to 8 hours, whereas a DOAC level of 50 to 100 ng/mL would suggest the need to defer surgery for 20 to 24 hours as this added time interval is likely to result in a decrease in DOAC level to 50 ng/mL at the time of surgery. If a DOAC level is not available or if the time of the last dose is not known, reversal may be warranted to allow surgical repair to proceed within 24 hours. Another potential option would be to forgo reversal and allow sufficient time of at least 48 hours for elimination of the anticoagulation effect.

Semiurgent surgery may involve patients with acute cholecystitis or diverticulitis, nonseptic abscess, or stable malignant or nonmalignant effusion that can initially be treated medically, followed by surgery or percutaneous interventions. If available, a DOAC level can help inform the optimal timing for the procedure and inform management when surgery can be safely done.

Although DOAC level testing may not be universally available, we suggest the need for more widespread testing availability with rapid turnaround times. Although such testing may add to healthcare costs, the assays are likely to be less expensive than reversal agents. Further, there are no cost-effectiveness studies to inform the cost-to-benefit ratio of reversal agents beyond direct costs, and differences in the acquisition costs of these agents vary depending on the country.

7 | HOSPITAL USE AND ADMINISTRATION

Despite the availability of guidelines and other published information, each hospital should consider developing its own care pathways for use of agents to manage bleeding in patients taking DOACs and other oral anticoagulants. In addition to balancing benefits and risks, cost, availability, and indications need to be considered. A recent study suggests from an implementation pathway perspective that a door-to-treatment time for ICH bleeding of 60 minutes or less is optimal to reduce in-hospital mortality [57]. Similar to a hospital stroke code is an evolving concept of an ICH code as a multidisciplinary rapid response team that deals with ICH in a rapid fashion using standardized

protocols [58]. A recent study of a large health system's clinical pathway for DOAC reversal noted the importance of including timing considerations of door-to-treatment times of DOAC reversal pathways [59]

8 | AVAILABILITY AND STORAGE

Availability and storage logistics are important considerations for optimizing care pathways. Anticoagulation reversal usually occurs in the emergency department or the operating room. Idarucizumab and andexanet require refrigeration, andexanet requires reconstitution, and both are often stored in the pharmacy. Storage in the emergency department may facilitate rapid administration to patients with ICH or other life-threatening bleeds. The ordering of reversal agents is often restricted to specific prescribers, including emergency medicine physicians, hematologists, critical care physicians, and pharmacists. PCCs are maintained at room temperature but require reconstitution before use. PCCs may be stored in the pharmacy, blood bank, or emergency department at room temperature. Development of policies surrounding provider-specific access and center-specific approval pathways for releasing reversal agents is essential.

9 | CONCLUSIONS AND FUTURE DIRECTIONS

Specific reversal agents for dabigatran and oral FXaI are now available. However, there are still many unanswered questions since most phase 3 trials were open-label and not randomized, with endpoints based on surrogate coagulation test results.

The utility of andexanet for the reversal of oral FXaIs in patients requiring urgent surgery remains unknown. Head-to-head comparisons of andexanet with 4F-PCCs are needed, particularly after current data focused on ICH reversal but further studies to define the risk-to-benefit ratio of andexanet in optimal patient populations are needed, including well-powered longitudinal studies to assess mortality and functional outcomes in these patients. It remains uncertain whether the reduction in hematoma expansion observed with andexanet results in improved patient outcomes despite the increase in thrombotic events, particularly ischemic stroke. Well-designed rigorous trials are needed to establish efficacy of PCC in DOAC-associated bleeding as this has not been examined. There also has been no direct comparison between idarucizumab and nonspecific reversal strategies (ie, PCCs) in dabigatran-associated bleeding.

Unintended reversal of unfractionated and low molecular weight heparin in patients receiving FXaI-directed andexanet reversal before urgent cardiac surgery requiring cardiopulmonary bypass or vascular surgery is problematic but data are needed to determine if PCCs would be better for this indication. Additional randomized clinical trials evaluating 4F-PCCs for surgical interventions for patients receiving DOACs are underway. Alternately, do we need additional reversal strategies such as VMX-C001 or hemadsorption?

Thrombin generation assays and viscoelastic testing methods may represent promising future modalities for managing bleeding patients and surrogate biomarkers of efficacy and safety. Thrombin generation assays are increasingly used as a research tool for managing bleeding and anticoagulation but are not routinely available in clinical practice [26]. Viscoelastic testing may be more useful as a dynamic, rapid, point-of-care test to be implemented at the bedside when managing patients with life-threatening bleeding [55]. Point-of-care assays that can be performed without laboratory expertise and specifically measure residual DOAC concentrations in whole blood within 5 to 10 minutes at bedside are under clinical development.

Finally, it remains to be determined whether DOACs that target FXIa will be safer than currently available DOACs, thereby obviating the need for reversal. The DOACs are here to stay, and their use will increase as generic versions become more widely available. Although we have made much progress in DOAC reversal, we still have a long way to go.

AUTHOR CONTRIBUTIONS

J.H.L. developed the initial outline in collaboration with all the authors and wrote and edited the initial and subsequent drafts. Each author wrote their respective sections, and the manuscript was critically reviewed by J.I.W. and B.R. All of the included authors contributed to the development of the document, reviewed the versions, and approved the manuscript.

DECLARATION OF COMPETING INTERESTS

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