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A review of guidelines on anticoagulation reversal across different clinical scenarios – Is there a general consensus?

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Abstract

Anticoagulation is key to the treatment/prevention of thromboembolic events. The primary complication of anticoagulation is serious or life-threatening hemorrhage, which may necessitate prompt anticoagulation reversal; this could also be required for nonbleeding patients requiring urgent/emergent invasive procedures. The decision to reverse anticoagulation should weigh the benefit–risk ratio of supporting hemostasis versus post-reversal thrombosis. We appraise the available guidelines/recommendations for vitamin K antagonist (VKA) and direct oral anticoagulant (DOAC) reversal in the management of major bleeding, and also assess recent clinical data that may not yet be reflected in official guidance. In general, available guidelines are consistent in their recommendations, advocating administration of vitamin K and 4-factor prothrombin complex concentrates (4F-PCCs) rather than fresh frozen plasma to patients with VKA-associated intracranial hemorrhage and life-threatening bleeding, and specific reversal agents as essential therapy for DOAC reversal in those same severe conditions. However, guidelines also recommend off-label use of PCCs for DOAC reversal when specific reversal agents are unavailable. Limited recent evidence generally support the latter recommendation, but guidelines are likely to evolve as more data become available.

Keywords

Anticoagulation reversal; Guidelines

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Ethics statement

TJM and CVP were both involved in conception of the idea for the review, development of the literature search strategy, interpretation of the literature and critical revision of the manuscript. Both authors read and approved the final version of the manuscript.

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1. Introduction

Anticoagulant therapy is fundamental for the prevention and treatment of thromboembolic diseases [1]. With an aging population, the number of people requiring chronic oral anticoagulation to manage conditions such as atrial fibrillation is increasing [2]. Options for anticoagulation have been increasing – currently available options include vitamin K antagonists (VKAs, primarily warfarin) and the newer direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban) [1,2]. However, several studies describe the risk of hemorrhage in patients taking anticoagulants. VKA use has been associated with more than double the risk of intracerebral hemorrhage (ICH) versus non-use [3], while patients receiving DOAC therapy have a lower or comparable risk of ICH or major bleeding compared with VKA therapy [4]. While DOACs have significantly changed the anticoagulation therapy landscape, DOAC-treated patients remain at some risk of major bleeding (up to 5% of patients, based on clinical trial data) [4].

Prompt anticoagulation reversal during severe/life-threatening bleeding events is a key component of multimodal therapy in these complex and fortunately rare clinical scenarios [3]. However, the decision to reverse anticoagulation should weigh the benefit–risk ratio of supporting hemostasis and potentially promoting post-reversal thrombosis. The advisability of administering reversal agents depends upon several clinical factors, including patient stability, timing of last anticoagulant dose, baseline coagulation assays (particularly international normalized ratio [INR] in the case of VKA-related hemorrhage), and product availability [5]. Reversal and other management strategies are often administered sequentially if required to obtain adequate control of bleeding.

VKA reversal can be achieved by various treatment approaches including fresh frozen plasma (FFP) and prothrombin complex concentrates (PCCs; including 3- or 4-factor PCC [3F-PCC or 4F-PCC] and activated PCC [aPCC]) [5,6]. Historically, clinicians used FFP for VKA reversal, but PCCs have taken precedence in this setting [3]. In contrast to FFP, PCCs require a lower infusion volume and shorter infusion time, are associated with a lower risk of pathogen transmission, and have a more rapid impact on INR [7]. Several clinical trials have found 4F-PCCs to be effective agents for urgent VKA reversal in patients with major bleeding or prior to emergency surgery [8-10]. The potential for increased post-treatment risk of thromboembolic events (TEEs) with 4F-PCCs is a concern, though several studies have shown this risk to be similar to that with FFP [8,10].

Since DOACs have shorter half-lives compared with warfarin, many non-life-threatening bleeding events are adequately controlled through supportive care (e.g. temporarily withholding DOAC therapy, blood product transfusion, etc) [11]. However, during a life-threatening bleed, DOAC reversal may become necessary in addition to supportive therapy and, in the recently dosed patient, oral activated charcoal administration. Vigorous resuscitation encompasses surgical control of bleeding when direct pressure cannot be applied, along with other stabilizing measures, such as FFP, 3F- or 4F-PCCs, and aPCCs [5,6,12]. Emergency hemodialysis may remove dabigatran from the circulation but is often

logistically challenging or not available; dialysis is not effective for anti-FXa anticoagulants [13,14].

Unlike VKA reversal, DOAC reversal has, until recently, been a clinical challenge due to limited availability of/access to specific reversal agents [15]. Two specific reversal agents are now available: idarucizumab for dabigatran [16], and andexanet alfa for apixaban and rivaroxaban [17]. Idarucizumab was approved in 2015 (US and Europe) [18,19]. Data from a large clinical study show that idarucizumab was associated with cessation of bleeding and normal periprocedural hemostasis in the majority of patients with major bleeding/requirement for urgent surgery, respectively [20]. Andexanet alfa (approved in the US in 2018 [21] and approved conditionally in Europe in 2019 [22]) is a relatively recent addition to the reversal agent armamentarium and is not mentioned in a majority of current guidelines. Limited availability and high cost may have constrained its use in clinical practice [23]. Clinical trial evidence suggests that andexanet alfa reduces anti-factor Xa activity by >90% in patients with major bleeding events [24].

In this narrative review, we appraise available guidelines and recommendations on bleeding management for VKA and DOAC reversal, and examine recent efficacy and safety data supporting use of reversal agents in this setting.

2. Methodology

This is a narrative review based on relevant US and international anticoagulation management and reversal guidelines published prior to April 2020; these were identified through PubMed and Internet searches, using the search terms “(anticoagulant reversal guidelines) OR anticoagulation reversal guidelines”. Where appropriate, the authors supplemented the searches according to their own understanding of the subject area. Clinical studies and reviews/meta-analyses published after January 1, 2018 were identified using similar search terms in PubMed: ((anticoagulant reversal) OR anticoagulation reversal) AND (“2018/01/01”[Date - Publication]: “3000”[Date - Publication]). Clinical studies and key reviews/meta-analyses focusing on the efficacy/safety of non-specific anticoagulation reversal agents in VKA and DOAC reversal were included, as were articles focusing on the efficacy/safety of idarucizumab in dabigatran reversal and the efficacy/safety of andexanet alfa in rivaroxaban/apixaban reversal. We selected the Jan. 1, 2018 cut-off, to capture recent important studies reported after the guidelines were published and thus not considered by those panels.

3. Consensus and divergence between the recommendations

3.1. Methodology of guideline development

Methodologies employed by guideline authors to generate recommendations on anticoagulant reversal strategies are summarized in Table 1. Most recommendations are based on a systematic review of the literature and acknowledge the lack of irrefutable evidence to fully support their recommendations, as specific reversal agents were either still in development or only recently approved at the time the guidance was developed. While clinical trial data support recommendations for PCC use in VKA reversal, recommendations

for PCC use in DOAC reversal were mainly based on expert opinion extrapolated from a small evidence base primarily in animal and in vitro models, healthy volunteers, and two small prospective cohorts of bleeding patients [25-27].

3.2. Anticoagulant reversal recommendations

3.2.1. Vitamin K antagonists—All guidelines recommend or suggest administering PCCs for VKA reversal only in cases of severe and life-threatening bleeding or prior to emergency surgery (Table 2).

3.2.1.1. Intracranial hemorrhage (ICH).: The European Stroke Organisation guideline recommends PCC at 30 IU/kg (along with vitamin K) for VKA reversal in ICH without distinguishing between 3- and 4-factor products [28]. The Neurocritical Care Society and the Society of Critical Care Medicine (NCS/SCCM), recommend discontinuation of VKAs and administration of vitamin K at a dose of 10 mg intravenously (IV) in cases of ICH [3]. Furthermore, these guidelines indicate the limited utility of FFP-based strategies in ICH due to the prolonged time to INR reversal, and acknowledge the low cost of FFP and its use in circumstances where PCCs are contraindicated (e.g. allergies or known adverse reaction to PCCs or their components) [3,29]. Treatment with FFP and vitamin K is recommended only if no other treatments are available. FFP should be administered at 10–20 mL/kg IV in combination with one dose of vitamin K 10 mg IV. The NCS/SCCM guidelines recommend 4F-PCC over 3F-PCC [3], with co-administration of vitamin K generally advised to ensure durable INR reversal. Initial reversal with PCCs alone rather than use in combination with FFP or recombinant Factor VIIa (rFVIIa) is also recommended. The dose of PCC should be weight-based and vary according to admission INR and type of PCC used.

Due to low-quality evidence and its association with thrombosis, rFVIIa is currently not recommended for VKA reversal in patients presenting with ICH (Table 2). Furthermore, American Heart Association/American Stroke Association (AHA/ASA) guidelines state that although rFVIIa administration rapidly reduces INR, it may not restore thrombin generation effectively as it does not replenish all of the vitamin-K dependent factors [30].

3.2.1.2. Life-threatening bleeding/surgery.: PCCs (primarily 4F-PCCs) are recommended or preferred for VKA reversal (Table 2), and several guidelines support usage of FFP for VKA reversal in life-threatening bleeding only if PCCs are unavailable [5,6,31,32]. The majority of guidelines also recommend co-administration of vitamin K. The European Society of Anaesthesiology (ESA) guideline recommends that patients on oral anticoagulant therapy should be given PCCs and vitamin K before any other coagulation management steps for severe perioperative bleeding. This guideline specifies 4F-PCC administration at a dose of 20–40 IU/kg for VKA reversal. Due to their thrombogenic profile, aPCCs are not indicated for VKA reversal, even in emergency bleeding situations [33]. Guidelines from the Association of Anaesthetists of Great Britain and Ireland also recommend against administration of rFVIIa in this setting (Table 2) [34].

3.2.2. Direct-acting oral anticoagulants—Most guidelines advocate using specific reversal agents as treatment, where available, and particularly in life-threatening situations.

Several guidelines recommend the use of PCCs for non-specific DOAC reversal when specific reversal agents are not available (Table 3).

3.2.2.1. ICH.: In patients with dabigatran-associated ICH and renal insufficiency, or dabigatran overdose, NCS/SCCM guidelines state that hemodialysis can be considered if idarucizumab is not available [3]. Hemodialysis is postulated to be ineffective for rivaroxaban and apixaban because of their high degree of protein binding, which can result in lower dialysis clearance. Charcoal can be considered as an option to diminish the effects of all DOACs in patients who present within 2 h of dosing (Table 3) [3]. The AHA and European Stroke Organisation guidelines describe FFP as having no clear utility for DOAC reversal in ICH [28,30]. The NCS/SCCM guidelines recommend administration of aPCC (50 IU/kg) or 4F-PCC (50 IU/kg) in patients with dabigatran- and direct factor Xa inhibitor-associated ICH [3]. These guidelines do not currently recommend rFVIIa for dabigatran-related ICH, but do recommend administering idarucizumab (5 g IV in two divided doses) with redosing of idarucizumab and/or hemodialysis during clinically significant bleeding [3]. Idarucizumab is generally recommended for dabigatran reversal in patients presenting with an ICH (Table 3). There are no recommendations in the NCS/SCCM guidelines regarding andexanet alfa use, as these documents were developed before its approval [3]; other guidelines have been appropriately updated to include these agents and are listed further on.

3.2.2.2. Life-threatening bleeding/surgery.: Similar to ICH management, hemodialysis may have a role for patients receiving dabigatran. Charcoal is generally recommended if the timing of the last DOAC dose is known (i.e. within ~2 h of last dose; Table 3), while FFP is not recommended for DOAC reversal by any of the guidelines included in this report. The Anticoagulation Forum (ACF) states that the volume of FFP required for the inhibition of thrombin or Factor Xa would likely cause adverse effects such as fluid overload, and states that the time taken to administer the high volume required would preclude its use in emergency/urgent settings [13]. If the patient needs volume support in the management of hemorrhagic shock, however, FFP can still be employed, though not explicitly as a reversal agent [35]. In the absence of a vitamin K deficiency or VKA treatment, none of the guidelines included here indicate a role for vitamin K administration in the management of DOAC-associated bleeding.

Despite being off-label, most guidelines suggest (or propose consideration of) aPCC or 3-/4F-PCC administration at doses 25–50 IU/kg in cases of serious or life-threatening bleeding when specific reversal agents are not available [5,6,13,14,31,35-42]. The mechanism of PCCs in DOAC reversal is not well understood, and studies of the effectiveness of PCCs in DOAC reversal have largely included healthy volunteers. However, recent clinical studies show that treatment with 4F-PCCs is associated with a low risk of TEEs and has similar efficacy to that shown for VKA reversal [42,43]. Some guidelines recommend the administration of rFVIIa for DOAC reversal; however, they note that rFVIIa should only be considered if other hemostatic measures have been ineffective, due to its relatively high risk of thrombosis [3,13,14,40].

Following the approval of idarucizumab and andexanet alfa, most guidelines recommend the use of these reversal agents in patients with severe or life-threatening bleeding events, or prior to emergency surgery (Table 3). For dabigatran reversal, idarucizumab 5 g IV is recommended [5,14,32,35,36,39,41,45,46]. Less guidance is available for andexanet alfa, but the American College of Cardiology recommends its usage in rivaroxaban/apixaban reversal and suggests the dose (high versus low) should be based on FXa inhibitor dose and time since last administration of FXa inhibitor [5]. This is supported by guidance from the ACF, which suggests treatment with andexanet alfa in patients with rivaroxaban- or apixaban-associated major bleeding, or prior to surgery in patients receiving these agents [46]; however, it should be noted that the FDA/Europe labels for andexanet alfa do not currently specify pre-surgical use [17]. There are significant uncertainties with andexanet alfa in periprocedural populations as it has not yet been extensively studied in urgent surgery, and optimal andexanet alfa infusion times during longer procedures are unknown [46]. As andexanet alfa is not indicated for edoxaban reversal, several guidelines still recommend using PCCs for this purpose [35,46,47]. However, the ACF recommends off-label treatment with either high-dose andexanet alfa or 4F-PCC in patients with edoxaban-associated major bleeding, or prior to surgery in patients receiving edoxaban [46].

4. Recent evidence for anticoagulant reversal

To identify any gaps between the available guidelines and currently available clinical evidence, we conducted a search to identify key clinical studies and reviews/metanalyses, focusing on efficacy/safety of non-specific and specific anticoagulation reversal agents for VKAs and DOACs. Key data for all articles are provided in Supplementary Table 1. There is recent evidence that 4F-PCCs effectively reduce INR in patients with VKA-associated bleeding, with TEE rates ranging from 1.8 to 6.5% [48,49] data from a meta-analysis of PCC use in VKA-associated ICH support these findings [50]. 4F-PCC was shown to reduce INR more effectively compared with 3F-PCC alone [48], but not compared with 3F-PCC + rFVIIa [49]; however, 4F-PCC has also been associated with a significantly lower rate of TEEs compared with 3F-PCC + rFVIIa [49]. In contrast, one recent retrospective study of emergency department data reported an increased rate of TEEs in patients on warfarin who received 4F-PCC compared with FFP [51]. aPCC appears to be similarly effective to 4F-PCC [52], and more effective than FFP [53], in reversing INR in patients with hemorrhage and traumatic ICH, respectively, with no significant different in TEE rate between treatments. One meta-analysis assessed the use of vitamin K for VKA reversal in patients with elevated INR (4.5–10) but no bleeding, concluding that vitamin K administration was not significantly associated with achieving the goal of timely INR reduction in this population [54].

Various studies have evaluated the safety and efficacy of 4F-PCCs in DOAC reversal, in settings including major bleeding and requirement for urgent surgery [27,44,55-61]. 4F-PCC was generally effective in achieving hemostasis in patients with major bleeding, with TEE rates ranging from 0% to 8% [27,44,56-60,62], and appeared to be associated with a mortality benefit versus no reversal treatment in patients with traumatic ICH [61]. However, one meta-analysis (including 10 case series) reported that it was difficult to assess whether the addition of 4F-PCCs was more effective in managing major bleeding

compared with cessation of DOAC therapy alone [63]. Another meta-analysis compared anticoagulant reversal rates for non-specific and specific reversal agents, reporting that patients on Factor Xa inhibitors generally experienced higher reversal rates compared with patients on dabigatran; reversal rates were highest in each case when a specific reversal agent was used [64]. Activated PCC was also shown to be effective in reversing DOAC anticoagulation due to bleeding or requirement for urgent surgical intervention, with TEE rates ranging from 8 to 10% [65,66].

A retrospective study investigated the safety and efficacy of 4F-PCC in patients with major bleeding, comparing outcomes according to baseline anticoagulation therapy (warfarin, rivaroxaban, or apixaban). Here, 4F-PCC effectively reversed warfarin, rivaroxaban, and apixaban anticoagulation, with <6% of patients experiencing TEEs; no between-group difference was observed in terms of either efficacy or safety for any treatment [55]. Another retrospective study of 4F-PCC in patients on warfarin or DOAC therapy with major bleeding/requiring emergent surgery supported these results, but reported a higher overall TEE rate (10.4%) [67]. Findings from a systematic review of studies including patients on VKA or DOAC therapy who received acute reversal management favored the use of PCC (particularly 4F-PCC) for VKA reversal, noting that TEE rates were higher in VKA patients receiving FFP versus those who received 4F-PCC; the authors did not recommend any particular therapy for DOAC reversal [68].

The safety and effectiveness of the specific reversal agents idarucizumab and andexanet alfa have been evaluated in several studies. The largest study (RE-VERSE AD; $n = 503$) reported that the majority of patients with uncontrollable/life-threatening bleeding experienced bleeding cessation within 24 h of idarucizumab administration, while >90% of patients requiring surgery reported normal hemostasis following idarucizumab administration [20]. These findings are supported by results from smaller studies in patients with bleeding or a requirement for urgent surgical procedure(s), along with a systematic literature review [69,70]. Other studies assessed the use of idarucizumab following acute ischemic stroke and immediately prior to thrombolysis treatment, reporting that idarucizumab effectively reversed the effects of dabigatran in this population [71,72].

The ANNEXA-4 study, which assessed the use of andexanet alfa in 352 patients with acute major bleeding within 18 h of rivaroxaban or apixaban administration, supported FDA and EMA approval of this reversal agent [24]. Treatment with andexanet alfa markedly reduced anti-factor Xa activity and was associated with good or excellent clinical hemostasis in 82% of cases with a 30-day TEE rate of 9.7% [24].

5. Discussion/summary

While VKAs have traditionally been the mainstay for anticoagulation, DOACs represent a major development in treating and preventing venous thromboembolic disease and in suppressing stroke risk in atrial fibrillation. Interest in DOAC therapy has increased significantly over time, with prescription claims rising from 15.4% to 31.0% of all oral anticoagulant claims between 2013 and 2015, according to US Medicare data [73]. Google Trend data also indicate an increasing global interest in DOAC therapy; the greatest

number of searches for dabigatran, rivaroxaban, and apixaban between 2012 and 2017 were conducted in North America, central/eastern Europe, and Australia. Interest in edoxaban was less pronounced and restricted to Germany, Japan, and the USA. Interest in warfarin therapy, in contrast to DOAC therapy, has decreased significantly over time [74].

A key issue with guidelines is that they become out of date as soon as they are published, due to the continuous publication of new clinical data. This is especially relevant for DOAC reversal, with several current guidelines published prior to the approval of andexanet alfa. Attempts are being made to update guidelines to address use of this agent. Recent clinical data support the use of 4F-PCC in VKA reversal and also DOAC reversal if specific agents are not available, while currently available clinical data on idarucizumab and andexanet alfa supports their use in specific DOAC reversal. It is likely that anticoagulation reversal guidelines will continue to evolve, particularly in the case of specific DOAC reversal agents, as more evidence becomes available on their appropriate use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

All authors had access to the data contained within this review (i.e. guidelines and research articles available online).

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Table 1

General overview of the guidelines and their development

Society/group (citation)	Aims	Evidence used and grading system	Format of guidelines
ICH			
European Stroke Organisation (Christensen et al. 2019) [28]	To provide clinically useful evidence-based recommendation on reversal of anticoagulant activity VKA, direct factor II (thrombin) inhibitors (dabigatran etexilat) and factor-Xa-inhibitors (apixaban, edoxaban and rivaroxaban) in patients with acute intracerebral hemorrhage.	The guideline was prepared following the Standard Operational Procedure for an ESO guideline document and according to GRADE methodology.	Recommendations separated into level of evidence (very low, low, moderate, high and very high) and strength of recommendation (weak versus strong)
American Heart Association (Raval et al. 2017) [46]	Review the literature and offer practical suggestions for providers who manage patients who are actively bleeding in the acute care and periprocedural setting, with specific clinical scenarios including ICH	Interprets available data rather than providing specific management recommendations in under-studied populations A systematic search of the literature was performed The group did not assign formal classes of recommendation/level of evidence	Practical suggestions are given by indication, including serious bleeding on DOAC protocol The strength of the recommendations and/or evidence quality are not indicated
Neurocritical Care Society; Society of Critical Care Medicine (Frontera et al. 2015) [3]	The aim was to develop evidence-based guidelines for counteracting the effects of commonly available antithrombotic agents in the setting of ICH	Formalized literature searches were conducted to end of November 2015 The writing committee reviewed articles selected from this database for inclusion in the treatment recommendations. The quality of evidence was analyzed and utilized the GRADE methodology; the committee developed recommendations VKA reversal, direct factor Xa antagonists, direct thrombin inhibitors, etc.	Evidence is appraised, followed by a list of recommendations for each antithrombotic agent, indicating the strength of the recommendation and quality of evidence supporting the recommendation
American Heart Association; American Stroke Association (Hemphill et al. 2015) [29]	To present current and comprehensive recommendations for the diagnosis and treatment of spontaneous ICH. An update of the 2010 guidelines	Literature search of PubMed was performed to end of August 2013 Recommendations follow the American Heart Association/American Stroke's Association's method of classifying the level of certainty of the treatment effect and the class of evidence	The guidelines consist of 10 sections (e.g. Emergency Diagnosis and Assessment, Hemostasis and Coagulopathy, Antiplatelet Agents, and DVT Prophylaxis, Blood Pressure), with classified recommendations and graded by level of evidence
Trauma			
Pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma (Spahn et al. 2019) [40]	This update is the fifth edition of a guideline first published in 2007 and updated in 2010, 2013 and 2016, with the aim of providing guidance for the management of bleeding following severe injury	Recommendations were generated using a structured, evidence-based consensus approach using the GRADE hierarchy of evidence and based on a systematic review of published literature (RCTs and non-RCTs, existing systematic reviews and guidelines) and expert opinion/ current clinical practice	Recommendations for managing bleeding following severe injury are given step by step in numerical order, with each recommendation graded on the strength of evidence supporting it
Severe or life-threatening bleeding			
Anticoagulation Forum, a North American organisation of anticoagulation providers (Cuker et al. 2019) [45]	Guidance on how the individual reversal agents should be administered, and to offer suggestions for stewardship at the health system level	Grade of evidence not mentioned; includes key questions regarding DOAC reversal through discussion and consensus among the authors. For each question, a summary of the evidence is provided, followed by guidance representing unanimous consensus of the authors	Guidelines are split into multiple questions, and an evidence summary is provided for each question
CHEST guideline and expert panel report (Lip et al. 2018) [30]	To provide guidance on stroke prevention and antithrombotic therapy, including management of bleeding	Electronic databases were searched systematically to identify relevant articles. The quality of the evidence was assessed using the GRADE approach.	The guideline is split into multiple sections, with the evidence discussed followed by a set of recommendations for each section

Society/group (citation)	Aims	Evidence used and grading system	Format of guidelines
		Graded recommendations and ungraded consensus-based statements were revised until consensus was reached	
American Society of Hematology (Witt et al. 2018) [31]	To provide evidence-based recommendations on the optimal management of anticoagulants for the prevention and treatment of VTE, including recommendations covering excessive anticoagulation and bleeding management	Guidance is based on reviews of evidence developed under the direction of the McMaster University GRADE Centre. This GRADE approach was used by the panel to assess evidence and make recommendations	Guideline includes 25 recommendations and two good practice statements Recommendations are presented, section by section along with supporting evidence, benefits, harms/burdens, other considerations and research needs
American College of Cardiology (Tomaselli et al. 2017) [5]	To provide guidance on the management of bleeding in patients treated with anticoagulants (both DOACs and VKAs) used for any indication	Guidance is based on the scientific evidence presented and expert opinions considered during the Anticoagulation Consortium Roundtable, and by subsequent review and deliberation on available evidence by the expert consensus writing committee	Provides guidance for temporary or permanent interruption of therapy, general approaches to bleeding management, decision support for treatment with a reversal agent, and indications and timing for reinstituting anticoagulant treatment Guidance is summarized by a series of decision pathway flow diagrams
Anticoagulation Forum (Burnett et al. 2016) [13]	To provide guidance on the practical VTE management of DOACs by answering a number of pivotal practical questions that apply to DOACs in real-world clinical scenarios, including managing bleeding complications in emergent situations	A literature search from the previous 10 years was conducted utilizing key words Guidance is based on the best available evidence wherever possible Guidance statements represent consensus opinion	Guidance statements around general DOAC management, including the management of DOAC-associated bleeding among other clinical scenarios are included
The Task Force for the management of atrial fibrillation of the European Society of Cardiology (Kirchhof et al. 2016) [6]	The second edition of the ESC guidelines on atrial fibrillation, developed to meet the growing need for effective care of patients with atrial fibrillation based on current state-of-the-art evidence. Specific guidance on the management of bleeding events is provided	External systematic reviews were commissioned to answer three Population, Intervention, Comparison, Outcome, Time (PICOT) questions on relevant topics, and these reviews informed specific recommendations Recommendations supported by >75% of the Task Force members were included in the guidelines. The level of evidence and the strength of the recommendations were weighed and graded according to predefined scales	Guidelines are split into multiple sections, one of which is the management of bleeding events in anticoagulated patients with atrial fibrillation. Sections provide a summary of the evidence with recommendations summarized in tables or decision pathway flow diagrams
Association of Anaesthetists of Great Britain and Ireland (Thomas et al. 2010) [33]	Guidelines developed to improve management of massive hemorrhage	Grade of evidence not mentioned in the text, but the Working Party believe the advice is consistent with European guidelines and current evidence published at the time	Consensus document
Surgery			
European Association of Cardiothoracic Anaesthesiology (Erdoes et al. 2018) [14]	To provide guidance for the monitoring and perioperative management of cardiac surgery patients on DOACs based on currently available literature and expert knowledge	Consensus statement developed based on an independent systematic review of peer-reviewed original research, review articles and case reports Recommendation/level of evidence was not graded	A series of 10 recommendations for best clinical practice are made, followed by a narrative review of the supporting literature
American College of Cardiology (Doherty et al. 2017) [74]	To provide guidance on the management of anticoagulation in patients with nonvalvular atrial fibrillation The guidance is primarily for elective planned procedures (the section on postprocedural anticoagulant management is also relevant for urgent/emergent procedures)	Narrative review of the literature to offer direct guidance where available. Areas in which clinical judgement is needed are highlighted	Guidance is in the form of statements and algorithms covering the decision of whether and how to interrupt anticoagulation; whether and how anticoagulant bridging should be performed; and when and how anticoagulant therapy should be restarted
European Society of Anaesthesiology (Kozek-Langenecker et al. 2017) [32]	An update of the 2013 ESA evidence-based guidelines on the management of severe perioperative bleeding to aid physicians to prepare for potential bleeding risks, plan for any	Electronic databases were searched from 2011 to 2015. The GRADE system was utilized	The report includes general recommendations, as well as specific recommendations in various fields of surgical intervention

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Society/group (citation)	Aims	Evidence used and grading system	Format of guidelines
	intraoperative bleeding and take any necessary action		
British Society for Hematology (Keeling et al. 2016) [75]	The guideline considers whether and when anticoagulants and antiplatelet agents should be stopped before elective surgery and invasive procedures, when agents can be restarted and how to manage patients on these drugs who require emergency surgery	Electronic databases were searched up to 2015. The GRADE system was used to evaluate levels of evidence and assess the strength of recommendations	Guidelines are broken down into sections with a review of the literature followed by a series of recommendations for each section
'Groupe d'Intérêt en Hémostase Périopératoire' (GIHP, working group on perioperative hemostasis; Faraoni et al. 2015) [36]	Updates to the management of DOACs. The article briefly reviews current evidence and proposes an algorithm based on published information for the perioperative management of patients treated with DOACs	Narrative review of literature of preoperative, intraoperative, and postoperative management of DOACs up to 2015	Recommendations on the perioperative management of patients treated with DOACs are formatted as an algorithm, largely based on expert opinion due to lack of good clinical studies available at the time
General			
American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (January et al. 2019) [76]	This is an update of the 2014 guideline for the management of patients with atrial fibrillation	This guideline reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the Institute of Medicine and on the basis of internal re-evaluation	This guideline follows Class of Recommendation and Level of Evidence
'Groupe d'Intérêt en Hémostase Périopératoire' (GIHP, working group on perioperative hemostasis; Albaladejo et al. 2018) [35]	This update of the 2013 guideline on the management of severe hemorrhages and emergency surgery applies to patients treated with dabigatran, with a bleeding complication or undergoing an urgent invasive procedure	Narrative review of literature covering management of hemorrhages and management of emergency invasive procedures in patients treated with dabigatran Guidance/recommendations/level of evidence are not graded	Recommendations are described within the text and summarized as algorithms displayed as figures
Canadian Cardiovascular Society (Andrade et al. 2018) [44]	The guidelines committee provides periodic reviews of new data to produce focused updates that address clinically important advances in atrial fibrillation management The 2018 update includes a section on the use of specific DOAC reversal agents	Recommendations were developed using the GRADE system. Individual studies and literature were reviewed for quality and bias	Details of the updated recommendations are presented, along with their background and rationale
European Heart Rhythm Association (Steffel et al. 2018) [34]	The third version of the original Practical Guide, published in June 2013 to unify a way of informing physicians on the use of the different DOACs in patients with atrial fibrillation	Evidence discussed narratively in the context of recommendations. Evidence includes in vitro, in vivo, and clinical studies	A total of 20 clinical scenarios are listed with practical answers based on available evidence One of the 20 topics focuses on the management of bleeding under DOAC therapy
Australasian Society of Thrombosis and Hemostasis (Tran et al. 2014) [41]	Development of local guidelines to manage patients receiving DOAC who present with bleeding or require urgent surgery	Recommendations on the administration of hemostatic agents are given based on the limited evidence General principles were drawn from existing guidelines	The practical guide comprises three sections: (1) selection of the most suitable patient groups to receive DOAC; (2) laboratory measurements of DOAC in appropriate circumstances; (3) management of patients taking DOAC in the peri-operative period, and strategies to manage bleeding complications or reverse the anticoagulant effects for urgent invasive procedures
'Groupe d'Intérêt en Hémostase Périopératoire' (GIHP, working group on perioperative	The guidelines were considered by the group to define the management basis around the management of major bleeding complications and	The method used was based on analysis of the literature reporting on the pharmacokinetic properties of the DOACs and their use in a surgical context	General recommendations are made, which consist of expert opinion The working group recognize that the

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Society/group (citation)	Aims	Evidence used and grading system	Format of guidelines
hemostasis; Pernod et al. 2013) [39]	emergency surgery that need to be evaluated and not an absolute guide for prescription	Due to the limited data available, the working group made extrapolations from existing data Members of the GIHP critically appraised the proposals until a consensus was reached	recommendations are of limited use for the 'specialized' centers
Thrombosis and Hemostasis Summit of North America (Kaatz et al. 2012) [77]	To develop guidance to help clinicians manage the reversal of DOACs in patients who are bleeding or require emergent surgery until more definitive and evidence-based guidelines became available	Narrative review of the evidence base, including in vitro, in vivo, and clinical studies	Different reversal strategies for DOACs, specifically dabigatran and rivaroxaban, are appraised based on the existing evidence base Recommendations are drawn from a final consensus among the authors
Grupo Catalán de Trombosis (Tromboc@t Working Group) (Olivera et al. 2018) [38]	Guidelines developed to establish clear recommendations for management of patients receiving DOAC treatment; includes advice on dabigatran reversal in cases of major or life-threatening hemorrhage or surgery OR urgent invasive procedures	A literature search was conducted using published literature (human studies only) in the EMBASE and MEDLINE databases from 2007 to 2016; published abstracts from the 2016 meeting of the American Society of Hematology were also searched using the same strategy. Bibliographic references were classified according to the level of evidence, following the criteria established by the US Agency for Health Research and Quality. The Working Group evaluated all compiled evidence and established recommendations based on the evidence; in cases where no evidence was found, consensus recommendations were made based on their clinical experience.	Consensus document

DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ICH, intracranial hemorrhage; RCT, randomized controlled trial; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 2

Summary of guidelines for the reversal of vitamin K antagonists

Guidelines	Indication	PCC	FFP	rFVIIa	Plus Vitamin K
ICH					
European Stroke Organisation (Christensen et al. 2019) [28]	ICH	PCC (30 IU/kg) in adults with ICH during use of VKA over no treatment to decrease mortality and normalise INR. Very low/Strong	PCC (30 IU/kg) in patients with ICH during use of VKA over FFP (20 mL/kg) to decrease mortality and normalise INR. Moderate/Strong	Recommend against using rFVIIa to improve outcome, decrease haematoma expansion or increase normalisation of INR. Very Low/Strong	Vitamin K (10 mg IV) in addition to fast reversal strategies including PCC to prevent re-increase of INR to decrease haematoma expansion and decrease mortality. Very low/Strong
Neurocritical Care Society; Society of Critical Care Medicine (Frontera et al. 2015) [3]	ICH	✓ 3F-PCC or 4F-PCC PCC to patients with ICH and INR ≥1.4. Proposed initial reversal with PCC alone rather than combined with FFP or rVIIa 4F-PCC recommended over 3F-PCC	✓ FFP may be considered in patients over no treatment when PCCs are unavailable or when PCCs are contraindicated Patients who have already received a full dose of PCC but do not have adequate INR correction may also receive FFP as re-dosing of 4F-PCCs (i.e. Kcentra®) is not recommended	✗ Low-quality evidence	✓ One dose of vitamin K 10 mg IV as soon as possible to ensure durable INR reversal
American Heart Association; American Stroke Association (Hemphill et al. 2015) [29]	ICH	✓ PCCs might be considered over FFP, as the former may have fewer complications and correct the INR more rapidly than FFP	✓ Guidelines acknowledge that FFP and vitamin K have been the mainstay of anticoagulation reversal but PCCs may be considered over FFP	✗ rFVIIa does not replenish all the vitamin K-dependent factors and may not restore thrombin generation as effectively as PCCs	✓ Intravenous vitamin K
Trauma					
Pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma (Spahn et al. 2019) [40]	Trauma	✓ Recommend early use of PCC for emergency VKA reversal (Grade 1A) Thromboprophylaxis as early as possible is prudent in patients who have received PCC	–	–	✓5 mg IV phytomenadione (vitamin K1) (Grade 1A)
Severe or life-threatening bleeding					
CHEST guideline and expert panel report (Lip 2018) [30]	Severe or life-threatening bleeding	✓ PCCs preferred over FFP	✓	–	✓

Guidelines	Indication	PCC	FFP	rFVIIa	Plus Vitamin K
American Society of Hematology (Witt et al. 2018) [31]	Life-threatening bleeding	✓ In patients with elevated INR, 4F-PCCs suggested Guidelines state 4F-PCC preferred over FFP	✓ 4F-PCC preferred over FFP	–	✓ IV vitamin K supplemented by 4F-PCC
American College of Cardiology (Tomaselli et al. 2017) [5]	Major bleeding	✓ Only 4F-PCC are licensed for rapid VKA reversal (aPCC not indicated) PCC preferred over FFP Dosed based on INR and body weight (INR 2–4 25 U/kg; INR 4–6 35 U/kg; INR >6 50 U/kg; max dose 5000 U capped at 100 kg body weight). Or low fixed-dose option, 1000 U for any major bleed; 1500 U for ICH	✓ 10–15 mL/kg recommended but only if 4F-PCC unavailable	–	✓ 1 −10 mg by slow IV administration (in 25–50 mL normal saline over 15–30 min) Must be supplemented by PCC/FFP for major bleed
The Task Force for the management of atrial fibrillation of the European Society of Cardiology (Kirchhof et al. 2016) [6]	Moderate-severe and severe or life-threatening bleeding	✓ Consider for severe or life-threatening bleeding (restores coagulation quicker than FFP)	✓ Consider for severe or life-threatening bleeding (restores coagulation quicker than vitamin K)	–	✓ Vitamin K 1–10 mg IV for moderate-severe bleed
Association of Anaesthetists of Great Britain and Ireland (Thomas et al. 2010) [33]	Massive hemorrhage	✓ PCC recommended Dose based on INR: 2–3.9 25 U/kg; 4–5.9 35 U/kg; >6 50 U/kg	–	–	✓ IV vitamin K (5–10 mg) coadministered with PCC
Surgery					
European Society of Anaesthesiology (Kozek-Langenecker et al. 2017) [32]	Severe perioperative bleeding	✓ 4F-PCC 25–50 IU/kg recommended	If PCC unavailable, plasma 15–20 mL/kg (plus IV vitamin K 5–10 mg) recommended	–	✓ IV vitamin K (5–10 mg) coadministered with PCC
British Society for Hematology (Keeling et al. 2016) [75]	Emergency surgery	✓ If surgery cannot wait 6–8 h, reverse warfarin with 25–50 U/kg 4F-PCC, with a preference for a lower dose and checking INR	–	–	✓ If surgery can wait 6–8 h, reverse warfarin with 5 mg IV vitamin K

✓ Recommended; ✗ Not recommended; — Not mentioned in guidelines.

3F-PCC, three-factor prothrombin complex concentrate; 4F-PCC, four-factor prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate; DOAC, direct oral anticoagulant; DTI, direct thrombin inhibitors; FFP, fresh frozen plasma; ICH, intracranial hemorrhage; INR, international normalized ratio; IU, international unit; IV, intravenous; PCC, prothrombin complex concentrate; rVIIa, recombinant factor VIIa; unit; VKA, vitamin K antagonist.

Table 3

Summary of guidelines for the reversal of the effects of direct oral anticoagulants

Guidelines	Indication	Specific reversal agents	PCC	FFP	rFVIIa	Vitamin K	Adjunctive therapy		
							Oral activated charcoal	Hemodialysis	Hemoperfusion with activated charcoal
ICH									
European Stroke Organisation (Christensen et al. 2019) [28]	ICH	andexanet alfa for (FXaI). Low/Weak idarucizumab for dabigatran. Low/Strong	For FXaIs 4-factor PCC (37.5–50 IU/kg) Very Low/Weak	Secondary to PCC	–	–	–	–	–
American Heart Association (Raval et al. 2017) [46]	ICH	Idarucizumab for dabigatran	✓ With rivaroxaban, apixaban, or edoxaban, should receive PCC until more specific reversal agents become available	–	–	–	–	–	–
Neurocritical Care Society; Society of Critical Care Medicine (Frontera et al. 2015) [3]	ICH	DTI: recommend administering idarucizumab (5 g IV in two divided doses) to reverse dabigatran	✓ Xa inhibitors: 4F-PCC (50 U/kg) or activated PCC (50 U/kg) if ICH occurred within 3–5 terminal half-lives of drug exposure or in the context of liver failure DTI: for dabigatran if idarucizumab is unavailable	✗	✗ 4F-PCC or aPCC is recommended over rFVIIa because of the lower risk of thrombotic events	–	✓ 50 g of activated charcoal to intubated ICH patients with enteral access and/or those at low risk of aspiration who present within 2 h of dosing	✓ DTI: if idarucizumab is not available and the patient has renal insufficiency or overdosed on dabigatran OR clinically significant bleed apparent despite idarucizumab or PCC treatment	
American Heart Association; American Stroke Association (Hemphill et al. 2015) [29]	ICH	– In development at the time	✓ Consider FEIBA/ PCCs for dabigatran, rivaroxaban, or apixaban on an individual basis in cases with elevated INR	✗ Unclear utility	✓ Consider on an individual basis in cases with elevated INR	–	✓ May be used if the most recent dose of dabigatran, apixaban, or rivaroxaban was taken <2 h earlier	✓ May be considered for dabigatran reversal	–
Trauma									
Pan-European, multidisciplinary Task Force for	Trauma	For life-threatening bleeding in patients on dabigatran,	✓ Factor Xa inhibitors: For life-threatening	–	–	–	–	–	–

Guidelines	Indication	Specific reversal agents	PCC	FFP	rFVIIa	Vitamin K	Adjunctive therapy		
							Oral activated charcoal	Hemodialysis	Hemoperfusion with activated charcoal
Advanced Bleeding Care in Trauma (Spahn et al. 2019) [40]		idarucizumab 5 g IV (Grade 1B) and suggest TXA (15 mg/kg [or 1 g] IV) (Grade 2C)	bleeding, suggest TXA (15 mg/kg [or 1 g] IV) and consider use of PCC (25–50 U/kg) until specific reversal agents are available (Grade 2C)						
Severe or life-threatening bleeding									
Anticoagulation Forum (Cuker et al. 2019) [45]	Major and life-threatening bleeding	Dabigatran: consider idarucizumab 5 g IV Rivaroxaban or apixaban: consider andexanet alfa (dosing according to US FDA label) Edoxaban: consider high-dose andexanet alfa (800 mg bolus followed by a continuous infusion of 8 mg/min for up to 120 min)	✓ Dabigatran: If idarucizumab is unavailable, consider aPCC 50 U/kg IV Rivaroxaban or apixaban: If andexanet alfa unvailable, consider 4F-PCC (2000 U) Edoxaban: 4F-PCC (2000 U)	–	–	–	✓ DOAC overdose along with bleeding	–	–
American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society (Januaryet al. 2019) [76]	Life-threatening bleeding Surgery	✓ Life-threatening bleeding or surgery For dabigatran: Consider idarucizumab Life-threatening or uncontrolled bleeding Rivaroxaban and apixaban: Consider andexanet alfa	–	–	–	–	–	–	–
CHEST guideline and expert panel report (Lip et al. 2018) [30]	Severe or life-threatening bleeding	Specific reversal agent recommended first-line if available	✓ PCCs are the preferred non-specific reversal agent if a specific reversal agent is unavailable, but data are limited	–	–	–	✓ For overdose or if last dose within 2–4 h	–	–
American Society of Hematology (Witt et al. 2018) [31]	Life-threatening bleeding	Dabigatran: idarucizumab FXa inhibitors: andexanet alfa	✓ FXa inhibitors: 4F-PCC (guideline does not recommend either	–	–	–	–	–	–

Guidelines	Indication	Specific reversal agents	PCC	FFP	rFVIIa	Vitamin K	Adjunctive therapy		
							Oral activated charcoal	Hemodialysis	Hemoperfusion with activated charcoal
			4F-PCC or andexanet alfa over the other)						
American College of Cardiology (Tomaselli et al. 2017) [5]	Major bleeding	Dabigatran: idarucizumab 5 g IV Apixaban and rivaroxaban: andexanet alfa (according to DOAC dose and timing of last administration)	✓ Dabigatran: 4F-PCC or aPCC 50 U/kg IV (if idarucizumab unavailable) Edoxaban: 4F-PCC 50 U/kg IV; consider aPCC 50 U/kg IV (if 4F-PCC unavailable) Apixaban and rivaroxaban: 4F-PCC or aPCC 50 U/kg (if andexanet alfa unavailable)	✗	–	–	✓ If DOAC ingestion was within the last 2–4 h	–	–
Anticoagulation Forum (Burnett et al. 2016) [13]	Major bleeding	–	✓ 4F-PCC (KCentra®) 50 U/kg or aPCC 80 U/kg for Xa inhibitors and direct thrombin inhibitors, respectively	✗	✗ Not as a first-line reversal agent	–	✓ If DOAC ingestion was within the last 6 h	✓ For dabigatran patients, especially if renally impaired	–
The Task Force for the management of atrial fibrillation of the European Society of Cardiology (Kirchhof et al. 2016) [6]	Moderate-severe and severe or life-threatening bleeding	Dabigatran: idarucizumab FXa inhibitors: andexanet alfa	✓ For severe/life-threatening bleeding, consider PCC if no specific reversal agent available	–	–	–	✓ For moderate-severe bleeding, consider if DOAC recently ingested (<2–4 h)	✓ Dialysis clears dabigatran but less effective for other DOACs	–
Surgery									
European Association of Cardiothoracic Anaesthesiology (Erdoes et al. 2018) [14]	Moderate or severe bleeding during cardiac surgery	Dabigatran: idarucizumab IV two doses of 2.5 g Rivaroxaban, apixaban, edoxaban: andexanet alfa	✓ PCC (25–50 U/kg)/ aPCC (50 U/kg)	✓ ✓ Consider for moderate/ severe bleeding	✓ Consider for severe bleeding	–	–	✗ May not be applicable in the hemodynamically unstable bleeding patient	–
American College of Cardiology (Doherty et al. 2017) [74]	Urgent/emergent procedure with high bleeding risk	Dabigatran: idarucizumab	–	–	–	–	–	–	–

Guidelines	Indication	Specific reversal agents	PCC	FFP	rFVIIa	Vitamin K	Adjunctive therapy		
							Oral activated charcoal	Hemodialysis	Hemoperfusion with activated charcoal
European Society of Anaesthesiology (Kozek--Langenecker et al. 2017) [32]	Severe perioperative bleeding	Dabigatran: idarucizumab	✗ There is limited evidence that 4F-PCC and aPCC provide clinical benefit and there is a lack of evidence regarding optimal dosing and possible thrombotic risk	–	✗ There is limited evidence that rFVIIa provides clinical benefit and there is a lack of evidence regarding optimal dosing and possible thrombotic risk	–	✓ For apixaban 20 mg	✓ For dabigatran	–
British Society for Hematology (Keeling et al. 2016) [75]	Emergency surgery	Dabigatran: idarucizumab FXa inhibitors: andexanet alfa	✗ PCCs should not be routinely used prior to emergency surgery but could be considered in the event of diffuse coagulopathic bleeding	–	–	–	–	✓ For dabigatran (but rarely practical)	–
Groupe d'Intérêt en Hémostase Périopératoire' (GIHP, working group on perioperative hemostasis; Faraoni et al. 2015) [36]	Major intraoperative bleeding	–	✓ 4F-PCCs 25–50 U/kg FEIBA 30–50 U/kg (maximum 200 U/kg) in case of life-threatening bleeding	–	Limited evidence to support its use	–	–	–	–
General									
'Groupe d'Intérêt en Hémostase Périopératoire' (GIHP, working group on perioperative hemostasis; Albaladejo et al. 2018) [35]	Severe or life-threatening bleeding or ICH (patients on dabigatran)	Dabigatran: idarucizumab administered according to the SmPC	✓ Second-line if idarucizumab unavailable, PCC (50 U/kg) or aPCC (30–50 U/kg)	–	–	–	✓ Usually only in rare clinical cases of overdose	✓ Not clearly established in the management of hemorrhages and emergency invasive procedures	–
Canadian Cardiovascular Society (Andrade et al. 2018) [44]	Uncontrollable or life-threatening bleeding/urgent surgery	Dabigatran: idarucizumab 5 g IV as soon as possible FXa inhibitors: insufficient data to recommend andexanet alfa at this time	–	–	–	–	–	–	–

Guidelines	Indication	Specific reversal agents	PCC	FFP	rFVIIa	Vitamin K	Adjunctive therapy		
							Oral activated charcoal	Hemodialysis	Hemoperfusion with activated charcoal
Grupo Catalán de Trombosis (Tromboc@t Working Group) (Olivera et al. 2018) [38]	Major or life-threatening hemorrhage or surgery OR urgent invasive procedures	Dabigatran: idarucizumab if available (2 × 2.5 g vials)	✓ Dabigatran: PCC 25–50 IU/kg (if idarucizumab unavailable)	–	–	–	–	–	–
European Heart Rhythm Association (Steffel et al. 2018) [34]	Severe, life-threatening bleeding, surgery	For non-life-threatening major bleeding Dabigatran: consider idarucizumab (see below) First-line for life-threatening bleeding (or immediate surgical procedures – dabigatran) Dabigatran: idarucizumab 5 g IV in two doses of 2.5 g IV no >15 min apart FXa inhibitors: andexanet alfa if available and approved (dose based on FXa inhibitor and timing of last administration)	✓ May be considered second-line for life-threatening bleeding (and first-line for immediate surgical procedures for patients on FXa inhibitors) PCC 50 U/kg (with additional 25 U/kg if clinically needed) aPCC 50 U/kg; max 200 U/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC, if available	✗ Not as reversal agent but may be considered as plasma expander	✗ PCCs are preferred given the absence of outcome data and pro-coagulant effect	–	–	✓ Dabigatran: consider for severe but non-life-threatening bleeding	–
Australasian Society of Thrombosis and Hemostasis (Tran et al. 2014) [41]	Life-threatening bleeding or urgent surgery[a]	–	✓ 3F-PCC 25–50 IU/kg aPCC 25–100 IU/kg	–	✓ Administration of rFVIIa 90 μ/kg every 2 h	–	✓ Patients with moderate and severe bleeding who present within 4 h of the last dose of dabigatran or rivaroxaban	✓ For dabigatran users, especially if renally impaired or dabigatran is present in excess No role for dialysis in rivaroxaban and apixaban-related basis as they are highly protein bound	–
'Groupe d'Intérêt en Hémostase Périopératoire' (GIHP, working group on	Urgent surgery/ severe bleeding or ICH	–	✓ Urgent surgery (for rivaroxaban and dabigatran): PCC 25–50 U/kg or	–	✗ Not considered first line	–	–	–	–

Guidelines	Indication	Specific reversal agents	PCC	FFP	rFVIIa	Vitamin K	Adjunctive therapy		
							Oral activated charcoal	Hemodialysis	Hemoperfusion with activated charcoal
perioperative hemostasis; Pernod et al. 2013) [39]			FEIBA 30–50 U/kg [applies primarily to emergency situations where you cannot wait] ICH or severe bleeding (for rivaroxaban and dabigatran): PCC 25–50 U/kg (severe bleeding); 50 U/kg (ICH) or FEIBA 30–50 U/kg						
Thrombosis and Hemostasis Summit of North America (Kaatzet al. 2012) [77]	Critical bleeding or emergency surgery	–	✗ Consensus was not reached regarding PCC due to absence of data	✗	✗	✗ No role in reversing the effect of DOACs	✗ If DOAC intake was within 2 h of presentation	✗	✗ To be considered in patients with impaired renal function in dabigratan users Use of dialysis is not likely effective for apixaban or rivaroxaban users

✓ Recommended; ✗ Not recommended; — Not mentioned in guidelines.

3F-PCC, three-factor prothrombin complex concentrate; 4F-PCC, four-factor prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate; DOAC, direct oral anticoagulant; DTI, direct thrombin inhibitors; FFP, fresh frozen plasma; ICH, intracranial hemorrhage; INR, international normalized ratio; IU, international unit; IV, intravenous; PCC, prothrombin complex concentrate; rVIIa, recombinant factor VIIa; TXA, tranexamic acid; U, unit.

[a]No published data were available at the time; therefore, specific advice was not given on managing bleeding in patients on this agent.