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NARRAGTIVE REVIEW

Clinical protocols for oral anticoagulant reversal during high risk of bleeding for emergency surgical and nonsurgical settings: a narrative review

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Idarucizumab;
Andexanet alfa

Abstract

Background and objectives: Oral anticoagulants prevent thromboembolic events but expose patients to a significant risk of bleeding due to the treatment itself, after trauma, or during surgery. Any physician working in the emergency department or involved in the perioperative care of a patient should be aware of the best reversal approach according to the type of drug and the patient's clinical condition. This paper presents a concise review and proposes clinical protocols for the reversal of oral anticoagulants in emergency settings, such as bleeding or surgery.

Contents: The authors searched for relevant studies in PubMed, LILACS, and the Cochrane Library database and identified 82 articles published up to September 2020 to generate a review and algorithms as clinical protocols for practical use. Hemodynamic status and the implementation of general supportive measures should be the first approach under emergency conditions. The drug type, dose, time of last intake, and laboratory evaluations of anticoagulant activity and renal function provide an estimation of drug clearance and should be taken into consideration. The reversal agents for vitamin K antagonists are 4-factor prothrombin complex concentrate and vitamin K, followed by fresh frozen plasma as a second-line treatment. Direct oral anticoagulants have specific reversal agents, such as andexanet alfa and idarucizumab, but are not widely available. Another possibility in this situation, but with less evidence, is prothrombin complex concentrates.

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Conclusion: The present algorithms propose a tool to help healthcare providers in the best decision making for patients under emergency conditions.

Introduction

Oral anticoagulants are broadly used in the prevention of thromboembolic events and stroke in patients with atrial fibrillation and mechanical heart valves, those undergoing treatment for deep venous thrombosis, and patients with pulmonary embolism, as well as in the prevention of venous thromboembolism in medical and orthopedic surgery patients.[1,2] Oral anticoagulants have been used for more than 60 years, and its use is tending to increase worldwide as the population ages.

The vitamin K antagonist (VKA) warfarin was the pioneer oral anticoagulation drug and still has clinical importance. Its prescription has increased by 3.6 times in a 15-year period.[3] Warfarin is a VKA that inhibits the synthesis of factors II, VII, IX, X and the anticoagulant proteins C and S.[1] Warfarin has a very high bioavailability and a long half-life, and its elimination is almost entirely via hepatic metabolism[4,5] (Table 1).

More recently, direct oral anticoagulants (DOACs) have become available as an alternative to warfarin. They provide direct, selective, and reversible inhibition of the coagulation factors showing similar efficacy and a safer bleeding profile with a faster onset of action, shorter duration after discontinuation, fewer food and drug interactions, easier administration with a fixed dose, and no need for routine laboratory monitoring of the anticoagulant effect.[6–9] The drugs available are factor Xa inhibitors (rivaroxaban, apixaban, betrixaban, and edoxaban) and direct thrombin inhibitors (dabigatran). Rivaroxaban, apixaban, and edoxaban have high bioavailability, short half-lives, and a high plasma protein binding ability (54–95%).[10–12] The direct thrombin inhibitor dabigatran is rapidly absorbed after oral administration, and it has low bioavailability, a longer half-life than Xa inhibitors, and low protein-binding ability[13] (Table 1).

Nonetheless, warfarin continues to be the most commonly used anticoagulant in the world because DOACs are not globally accessible, are expensive, and have not yet been extensively studied with regard to their use for all VKA indications.[14]

Patients taking oral anticoagulants could face situations in which the acute reversal of therapy is necessary, such as life-threatening bleeding due to treatment or acute injury, prior to invasive procedures, or other emergency circumstances with a high risk of bleeding. Coagulation factor replacement with prothrombin complex concentrates (PCCs), which consist of 3-factor PCC (II, IX, and X), 4-factor PCC (II, VII, IX, and X), and activated PCC (aPCC) with four coagulation factors (in inactive and activated forms), as well as fresh frozen plasma (FFP), are well-known nonspecific reversal agents for oral anticoagulants.[15] Recently, specific reversal agents for DOACs were approved, including andexanet alfa for the reversal of apixaban and rivaroxaban, and idarucizumab for dabigatran.[16]

Clinicians and surgeons working in emergency departments or involved in the perioperative care of a patient taking oral anticoagulants must know the best approach to the rapid reversal of anticoagulant activity and should choose the safest and most efficient protocol according to the type of drug, its pharmacokinetic profile, and the patient's medical history and clinical condition. This paper provides a concise narrative review regarding the reversal of anticoagulants and recommends clinical algorithms for patients taking oral anticoagulants who need urgent reversal of the therapy. These protocols include emergency surgical and nonsurgical scenarios and provide algorithms for both VKA and DOAC reversal.

Methods

In this review, the authors searched national and international literature to identify currently available data on the main points of the management of oral anticoagulant reversal for the development of this clinical protocol.

The authors included systematic and nonsystematic literature reviews, randomized clinical trials, prospective and retrospective cohort studies with or without a control group, case reports, case series, and guidelines addressing the reversal of oral anticoagulation in humans under emergency circumstances. The studies were written in Portuguese or English, and published in the last 12 years up to September 2020. They excluded in vitro investigations as well as studies using animals.

The PubMed, LILACS, and Cochrane Library databases were used with the following search terms (keywords and delimiters): oral anticoagulant and reversal, warfarin and reversal, nonvitamin K antagonists, direct oral anticoagulants and reversal, prothrombin complex concentrates, idarucizumab, and andexanet alfa.

Results

The authors chose 82 articles jointly according to their relevance, with full agreement among the reviewers. Table 2 summarizes the most relevant evidence identified on the reversal of anticoagulants: clinical trials, systematic reviews, cohorts, and case series studies. A flow chart documenting the process of selecting the studies is presented in Figure 1.

Table 1 Pharmacological properties of oral anticoagulants.

	Warfarin[4,5]	Rivaroxaban[10]	Apixaban[11]	Edoxaban[12]	Dabigatran[13]
Target	Vitamin K-dependent factors	Factor Xa	Factor Xa	Factor Xa	Thrombin
Prodrug	No	No	No	No	Yes
Bioavailability (%)	79-100	63-79	66	50	3-7
Tmax (hrs)	3-9	2-4	1-2	1-2	1-3
T½ (hrs)	36-42	7-13	8-15	9-11	12-17
Protein binding (%)	99	95	87	54	35
Dialysis	No	No	14%	No	50-60%
Renal elimination (%)	80	33	25	35	80
Reversal agents	Vitamin K PCC FFP	Andexanet alfa PCC	Andexanet alfa PCC	Andexanet alfa PCC	Idarucizumab PCC
Laboratory	INR PT	Anti-factor Xa	Anti-factor Xa	Anti-factor Xa	ECT DTT

Tmax, time to maximum plasma concentration; T½, half-life; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma; INR, International Normalized Ratio; PT, prothrombin time; ECT, ecarin clotting time; DTT, diluted thrombin time.

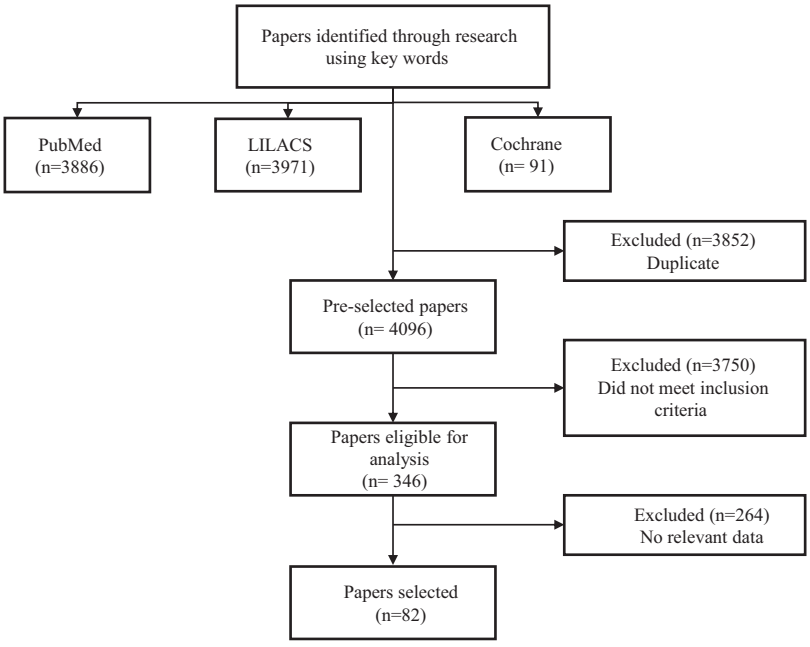

Figure 1 Study selection process.

Emergency anticoagulation reversal: general considerations

In an emergency scenario, the strategy for oral anticoagulant reversal depends on the type of drug; the presence, location, and level of bleeding; and the need for and type of invasive procedure.

Patients taking oral anticoagulants have a higher risk of spontaneous bleeding due to treatment or trauma. Attention should be given to head injuries; most anticoagulated patients are elderly, with a high risk of intracerebral hemorrhage (ICH).[17]

The first approach in a bleeding situation in anticoagulated patients is the identification of the bleeding source and severity of bleeding (Fig. 2). Evaluation of the patient's hemodynamic status should be performed and must be closely monitored.

General measures providing supportive care with hemostatic procedures (mechanical compression, use of topical hemostats, sutures, vessel clipping, etc.), volume replacement and/or transfusions should be established, with an evaluation of the necessity for an invasive procedure as treatment (surgery/embolization) and the risk of bleeding due to the procedure on its own versus the thrombotic risk due to anticoagulant withdrawal.

Concomitant medications, such as antiplatelet therapy, could interfere with anticoagulant activity. Patients taking warfarin should be questioned about the use of antibiotics,

Table 2 Summarized evidence regarding the reversal of warfarin and DOACs.

References	Study design	Population	Reversal agents	Results
Warfarin studies				
Steiner, 2016[40]	Prospective, randomized, open-label, blinded-endpoint clinical study	50 VKA-ICH patients	4F-PCC vs FFP	67% of PCC group vs 9% of FFP group, $p = 0.0003$
Goldstein, 2015[30]	Prospective, randomized, open-label, clinical study	181 VKA-treated patients needing urgent surgical or invasive procedures	4F-PCC vs FFP	90% of the PCC group vs 75% of the FFP group. Rapid INR reduction in 55% of the PCC group vs 10% of the FFP group
Kerebel, 2012[37]	Prospective, randomized, open-label study	59 VKA-associated intracranial hemorrhage	4F-PCC	40 IU.kg^{-1} of 4F-PCC significantly decreased the INR compared to that of the 25 IU.kg^{-1} group ($p = 0.001$).
Demeyere, 2010[55]	Prospective, randomized, open-label, clinical study	40 cardiac surgery patients	4F-PCC vs FFP	Faster target INR with PCC ($p = 0.007$), and less additional dose ($p < 0.001$)
Burburry 2011[33]	Prospective single-arm clinical study	178 presurgical patients under warfarin	Vitamin K	94% with INR levels 1.5 or less on the day of surgery
Chausson, 2018[41]	Pilot clinical study	26 acute ischemic stroke patients	4F-PCC and vitamin K	No symptomatic ICH or thrombotic events
Pautas, 2011[34]	Prospective, observational study	239 elderly hospitalized patients with over-anticoagulation	Vitamin K	Decrease in INR levels, achieving 2.7 $\pm$ 1.3 on Day 1 ($p < .0001$)
Bhatia, 2010[32]	Prospective, observational study	45 proximal hip fracture patients	Vitamin K	INR levels decreased to 1.5 or less in 2 days (mean, 38 h; range, 15–64 h
Rimsans, 2018[42]	Prospective, observational study	37 patients with continuous flow left ventricular assistive devices	4F-PCC	Efficient reversal, no case of thromboembolism, mean INR from 2.9 to 1.7 ($p < 0.0001$)
Yank, 2011[62]	Systematic review	64 studies included	rFVIIa vs placebo or usual care	No mortality reduction Increased thromboembolism risk
Dentalli, 2011[38]	Systematic review	27 studies included	3F-PCC and 4F-PCC	Incidence of thromboembolic complications: 1.8% (95% CI 1.0-3.0) with 4F-PCC and 0.7% (95% CI 0.0-2.4) with 3F-PCC
Matino, 2015[63]	Systematic review	2 studies, with 69 patients	rFVIIa vs aPCC	Similar hemostatic effect No increase in thromboembolic risk
Chai-Adisaksopha, 2016[35]	Systematic review	13 studies included	PCC vs FFP	PCC: significant reduction in mortality, more rapid INR reduction, less volume overload. No statistically significant difference in VTE risk
Milling, 2016[39]	Post hoc analyses of pooled data	2 randomized trials, with 388 patients	4F-PCC vs FFP	Incidence of thromboembolic complications: 7.3% in the 4F-PCC group and 7.1% in the FFP group

Table 2 (*Continued*)

References	Study design	Population	Reversal agents	Results
				Risk difference 0.2%; 95% CI -5.5% to 6.0%
Barton, 2018[60]	Retrospective cohort study	195 patients with life-threatening bleeding	4F-PCC vs 3F-PCC and rFVIIa	Faster and longer duration of reversal with 4F-PCC ($p < 0.01$) Higher mortality and VTE with 3F-PCC and rFVIIa ($p < 0.01$)
Rowe, 2016[51]	Retrospective cohort study	158 patients with warfarin-associated hemorrhage	aPCC vs 4F-PCC	No difference in effectiveness and safety between treatments
Holt, 2018[48]	Retrospective cohort study	134 patients with warfarin-associated bleeding	4F-PCC vs 3F-PCC	INR normalization: 84.2% with 4F-PCC vs. 51.9% with 3F-PCC, $p = 0.0001$
Mattisson, 2018[44]	Retrospective case-control study	Patients with hip fractures: 99 taking warfarin and 99 controls	4F-PCC and vitamin K	No significant differences in blood loss, adverse events or mortality
Hedges, 2015[45]	Retrospective chart review	193 patients taking warfarin and DOACs	PCC, 4F-PCC	65.8% achieved target INR in 8.03 h (IQR 3.38–34.07) 4.1% with acute VTE
Voils, 2015[49]	Retrospective chart review	165 patients requiring emergency reversal	4F-PCC vs 3F-PCC	No difference in VTE events. Higher mortality in 3F-PCC group ($p < 0.01$)
Mehringer, 2018[61]	Retrospective chart review	129 cardiac surgery patients with significant bleeding	rFVIIa vs 4F-PCC	No difference in bleeding, thromboembolic events, or re-exploration
Chapman, 2014[58]	Retrospective chart review	106 patients needing emergency reversal	3F-PCC vs low-dose rFVIIa	71.9% rFVIIa patients achieved target INR vs. 33.8% 3F-PCC, $p = 0.001$ No difference in VTE risk
Carothers, 2018[50]	Retrospective chart review	89 patients with traumatic ICH	aPCC vs FFP	Reversal achieved in 90.3% with aPCC vs 69.7% with FFP, $p = 0.029$ Faster reversal with aPCC, $p = 0.003$. No difference in mortality and VTE risk
Woo, 2014[57]	Retrospective chart review	63 VKA-ICH patients	FFP vs rFVIIa vs PCC	PCC and rFVIIa reached target INR faster than FFP ($p < 0.05$). More rebound with FFP and rFVIIa ($p = 0.001$)
Sarode, 2012[59]	Retrospective chart review	46 VKA-ICH patients	3F-PCC and rFVIIa	Rapid and effective reversal
Astrup, 2018[47]	Retrospective chart review	37 patients with urgent reversal	Single fixed dose of 1500 IU of 4F-PCC	75% achieved INR $\leq$ 1.5 100% achieved INR $\leq$ 2
Mačiukaitienė, 2018[43]	Retrospective chart review	35 VKA-ICH requiring urgent neurosurgical procedures	4F-PCC and vitamin K	Decrease in INR ($p < 0.01$), PT ($p < 0.01$), and PTT ($p = 0.02$), no adverse effect
Scott, 2018[46]	Retrospective cohort study	31 VKA-ICH patients	4F-PCC	No significant difference between the fixed and weight-based doses of 4F-PCC
DOACs studies				
Pollack, 2017[91]	Multicenter, prospective, open-label study	503 patients under dabigatran with bleeding or urgent surgical intervention	Idarucizumab	100% of median maximum percentage reversal
Siegal, 2015[68]	Prospective, randomized, double-blind, placebo-controlled study	101 healthy older volunteers taking Xa inhibitors	Andexanet alpha	Efficient reversal within minutes after administration

Table 2 (*Continued*)

References	Study design	Population	Reversal agents	Results
Connolly, 20196[69]	Prospective, open-label, single-group study	352 patients who had acute major bleeding within 18 hours after administration of a factor Xa inhibitor	Andexanet alpha	92% reduction in anti-factor Xa activity.
Eerenberg, 2011[71]	Prospective, randomized, double-blind, placebo-controlled study	12 healthy volunteers taking rivaroxaban or dabigatran	4F-PCC	Immediate and complete reversal of rivaroxaban anticoagulation activity (p = 0.0001) No effect on dabigatran
da Luz, 2017[72]	Systematic review and meta-analysis	12 studies included DOAC reversal	PCC	PCC reversed the prothrombin time and endogenous thrombin potential (p < 0.01)
			Andexanet alfa Idarucizumab	Andexanet alfa, idarucizumab: completed reversal was achieved
Piran, 2019[80]	Systematic review and meta-analysis	10 case series with 340 patients presenting direct Xa inhibitor–related major bleeding	4F-PCC	Effective management of bleeding: 0.69 (95% CI 0.61-0.76). Mortality: 0.16 (95% CI: 0.07-0.26), VTE: 0.04 (95% CI: 0.01-0.08)
Majeed, 2017[74]	Prospective cohort study	84 patients under Xa inhibitors presenting major bleeding events	4F-PCC	Efficacy in 69.1% of patients
Dybdahl, 2019[79]	Retrospective cohort study	62 patients taking factor Xa inhibitors with traumatic ICH	4F-PCC vs no reversal	No difference in mortality, functional recovery, hospitalization duration or thromboembolic events
Allison, 2018[36]	Retrospective, observational study	33 patients taking Xa inhibitors with major bleeding requiring emergent reversal	4F-PCC	83.8% achieved hemostasis No VTE event
Green, 2019[82]	Retrospective chart review	421 patients with DOAC-related major bleeding	4F-PCC	Low-dose PCC: lower mortality (hazard ratio: 0.5; 95% CI: 0.02–1.19; p = 0.07)
Piran, 2018[73]	Retrospective chart review	247 Xa inhibitors patients undergoing emergency surgery or an invasive procedure	4F-PCC	85.7% achieved good hemostasis. No VTE events occurred.
Dager, 2019[81]	Retrospective analysis	64 patients with DOAC-related bleeding	aPCC	Thromboembolic complications: 8%.
Tao, 2018[77]	Retrospective chart review	43 patients under Xa inhibitors needing emergency reversal	4F-PCC	VTE: 2.1%, 95% CI: 0.1-12.3
Harrison, 2018[76]	Retrospective chart review	42 factor Xa inhibitor anticoagulant and VKA-ICH	4F-PCC	No difference in the mortality, rates of hemorrhagic expansion, VTE, between Xa inhibitors and VKA patients receiving 4F-PCC
Engelbart, 2019[84]	Retrospective case series study	42 patients with emergent reversal of DOAC for life-threatening hemorrhage or urgent surgical interventions	aPCC	Thrombotic events: 10%; hemorrhage progression: 10%; mortality: 29%

Table 2 (*Continued*)

References	Study design	Population	Reversal agents	Results
Sheikh-Taha, 2019[75]	Retrospective chart review	29 patients taking factor Xa inhibitors with major bleeding	4F-PCC	72.4% patients achieved clinical hemostasis
Grandhi, 2015[78]	Retrospective chart review	18 patients with Xa inhibitors-ICH	4F-PCC	No hemorrhagic complications after surgery. One VTE event
Senger, 2016[81]	Retrospective chart review	17 patients under dabigatran or rivaroxaban with ICH	4F-PCC	Of 6 patients who underwent immediate surgery, 50% presented severe intraoperative hemorrhage
Dibu, 2016[87]	Prospective observational study	127 patients with spontaneous ICH under DOAC: 5 patients receiving aPCC	aPCC	No ICH expansion, hemorrhagic, or thrombotic complications
Schulman, 2014[92]	Case series	4 patients under DOAC with a major bleeding episode	aPCC	Recovery, no effect on hemostatic parameters

VKA, vitamin K antagonist; ICH, intracerebral hemorrhage; INR, international normalized ratio; IVT, intravenous thrombolysis; DOACs, direct oral anticoagulants; VTE, venous thromboembolism; CI, confidence interval.

nonsteroidal anti-inflammatory drugs, acetaminophen, metronidazole, amiodarone, antiepileptic drugs, and selective serotonin reuptake inhibitors and the ingestion of foods that prolong the international normalized ratio (INR).[1] Patients taking DOACs have fewer drug interactions, but a pharmacokinetic study showed that azole-antimycotics, HIV protease inhibitors, phenytoin, rifampin, and amiodarone could interfere with drug activity.[18–20]

Laboratory evaluations help guiding the management of patients during emergencies by detecting and quantifying the remaining anticoagulant activity, and are essential for the assessment of hemostasis before surgery. These evaluations must include the coagulation status, blood cell count, blood group, and hepatic and renal function. Abnormal renal and liver functions affect the metabolism and elimination of the drug. Renal perfusion and urine output should be maintained to help eliminate anticoagulant drugs. Laboratory evaluation of anticoagulation activity will be further discussed in this paper.

The type, dosage, and time of the last intake of an oral anticoagulant provide the time for elimination according to its half-life and patient renal function. The drug must be suspended immediately after a bleeding episode. At the time of reintroduction of the drug, the need for dose adjustment must be evaluated in cases of spontaneous bleeding.

The anticoagulant should not be suspended in cases of a small invasive procedure with minimal bleeding risk, such as blood tests, dental extraction, dermatological biopsies, and gastrointestinal endoscopic procedures without the risk of bleeding.[21] However, in cases of moderate to major bleeding or surgical indication, the balance between the risk of bleeding and the risk of a thromboembolic event must be considered, and withdrawal of the drug is recommended in cases of a high-risk scenario such as ICH; neuraxial anesthesia; and abdominal, cardiothoracic, intracranial, orthopedic operations.[22–24] The possibility of postponing surgery should be evaluated, with a delay long enough to promote drug clearance. Surgery with a high risk of bleeding must be postponed as long as possible. In patients taking VKAs, drug withdrawal is necessary for at least 5 days prior to surgery for drug clearance.[24] The withdrawal of DOACs will vary according to the risk of bleeding, and it is recommended 2 days before a high-risk procedure and 1 day before a low-risk procedure.[25] For patients under dabigatran with a clearance of creatinine less than 50 $mL.min^{-1}$, the withdrawal is 4 days before surgery with a high-risk of bleeding and 2 days for low-risk procedures.[25]

A reversal agent should be used in cases of bleeding not responding to supportive measures, uncontrolled, major, life-threatening bleeding, bleeding located in critical organs (central nervous system, abdominal, thoracic), trauma, or urgent surgery.[26] Urgent surgery requires immediate reversal, clotting factor supplements (provided by PCCs), and intensive care support.[26]

The use of tranexamic acid (TXA) as a hemostatic agent significantly reduces mortality in bleeding trauma patients,[27] and it is inexpensive with few side effects.[28] TXA can be used in cases of major bleeding in patients taking oral anticoagulants and/or trauma patients within 3 hours. Its mechanism of action is based on competitive inhibition of the activation of plasminogen to plasmin, preventing clot lysis.

The reversal of warfarin

The reversal of warfarin is based on the clinical scenario and the evaluation of INR, with a therapeutic range of 2 to 3. For these patients, the prothrombin time (PT) and INR provide the status of VKA activity.[29] Warfarin reversal is accomplished with the administration of PCCs, preferably 4-factor PCC, and vitamin K.[30] If those are not available, fresh frozen plasma (FFP), 3-PCC, or aPCC could also be used (Fig. 3).

Patients at very high risk of a thromboembolic event should use low molecular weight heparin (LMWH) after warfarin discontinuation as a bridging anticoagulation strategy.[24]

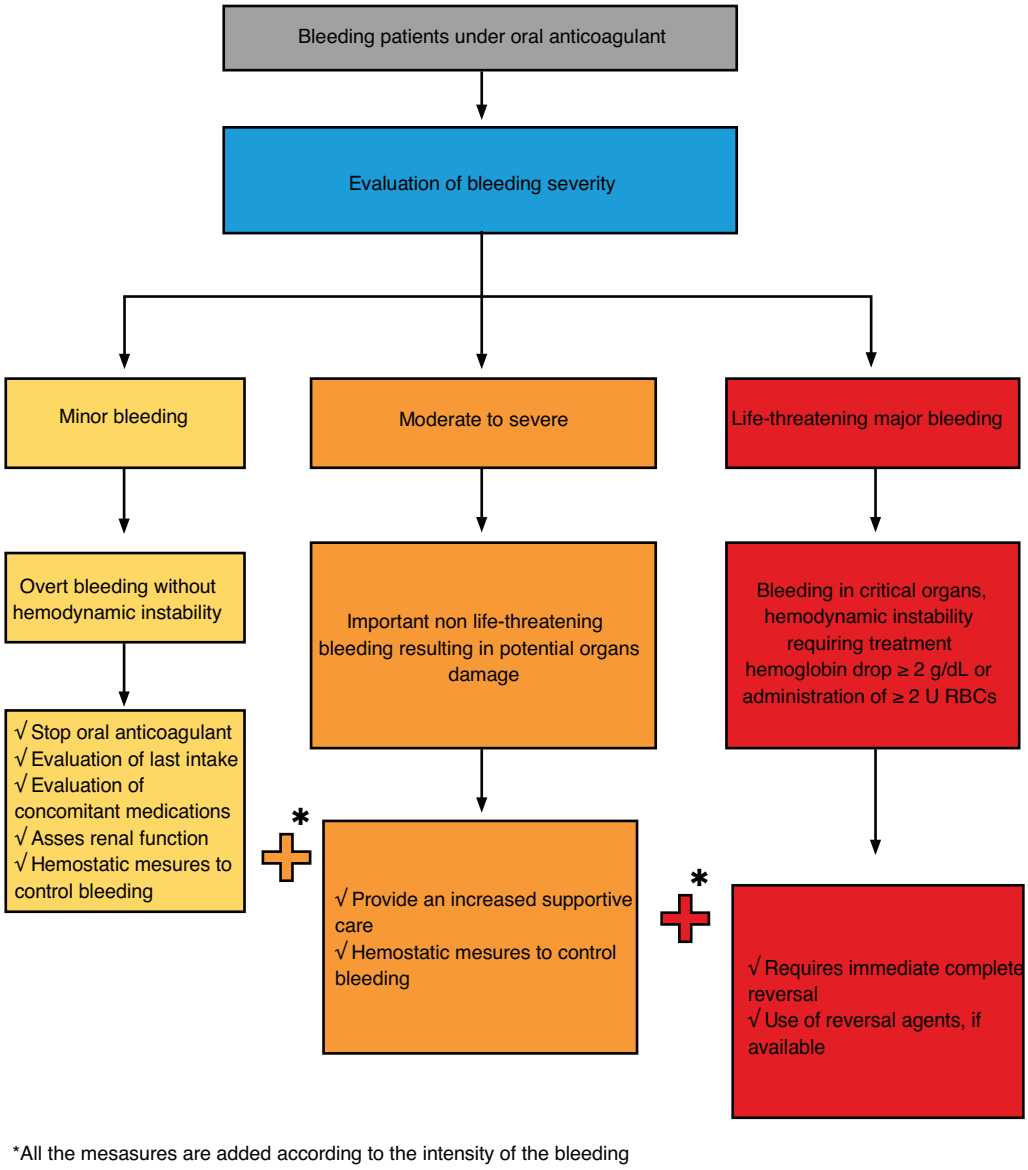

Figure 2 Assessment of bleeding in patients taking oral anticoagulants. * All the measures are added according to the intensity of the bleeding.

Vitamin K is not a direct hemostatic agent but rather a cofactor for the activation of factors II, VII, IX, X, and the anticoagulant proteins C and S.[31] The usual dose of vitamin K varies from 5 to 10 mg or an even lower dose (1 to 3 mg) via the intravenous route, and it should be combined with coagulation factor administration in an emergency setting because, alone, it could take from 4 to 24 hours to normalize coagulation.[32–34]

PCCs are considered the treatment of choice for VKA reversal in emergency settings, such as in patients with significant bleeding.[35] Four-factor PCC is a plasma-derived product that restocks the vitamin K-dependent proteins, factors II, VII, IX, X, and proteins C and S. It is used for warfarin reversal, and it shows efficacy in factor Xa inhibitor reversal but limited evidence for thrombin inhibitor reversal.[36]

The administration of 4-factor PCC is performed intravenously with rapid infusion and low volume, promoting reversal of warfarin in 10 minutes.[37] The risk involved in the use of PCCs is mainly allergic reactions, heparin-induced thrombocytopenia (HIT, for preparations containing heparin), and thromboembolic complications;[38,39] however, proteins C and S in 4-factor PCC may improve its safety profile as they are coagulation inhibitors, decreasing the risk of thromboembolic events after reversal.

Prospective, randomized clinical trials show the clinical efficacy of 4-factor PCC in the reversal of warfarin as being superior to that of FFP in patients presenting VKA-related ICH[40] and achieving faster homeostasis in patients needing reversal for surgical interventions.[30] A retrospective observational study demonstrated the efficacy and safety of warfarin reversal using 4-factor PCC and vitamin K in acute ischemic stroke patients before undergoing

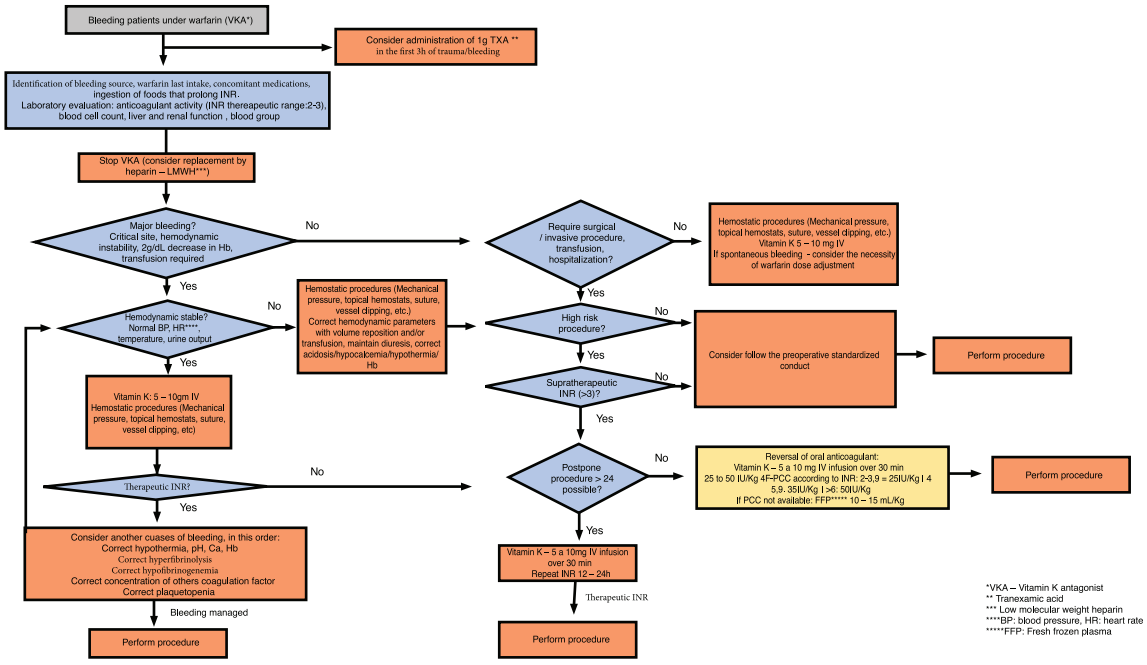

Figure 3 Reversal due to bleeding after trauma, due to spontaneous bleeding and/or before surgery in patients taking warfarin. VKA, Vitamin K antagonist; BP, Blood pressure; HR, Heart rate; FFP, Fresh frozen plasma.
** Tranexamic acid.
*** Low molecular weight heparin.

intravenous thrombolysis;[41] in patients with continuous flow left ventricular assistive devices presenting bleeding or the need for urgent surgery, with no thromboembolic event observed;[42] in patients with intracranial bleeding requiring urgent neurosurgical intervention;[43] and in patients undergoing early orthopedic surgery (within 24 hours) due to hip fractures.[44] In an observational study of 143 patients on warfarin, the use of 4-factor PCC was safe as a reversal agent mainly for bleeding and prior to surgery, with 5 cases of thromboembolic complications.[45] Evidence regarding fixed doses of 1000 units and 1500 units of 4-factor PCC showed a similar efficacy compared to weight-based dosing.[46,47]

Four-factor PCC is preferred over 3-factor PCC because 4-factor PCC leads to a more significant reduction in the INR,[48] and the survival rate is higher.[49] aPCC proved to be more effective and faster than FFP for warfarin reversal in patients with traumatic ICH,[50,51] but it is not indicated for all patients because it may present a higher thrombotic risk compared to 4-PCC due to a high content of both prothrombin and thrombin; however, no comparative safety study has been identified.

Although FFP is much less expensive than 4-PCC, current guidelines recommend the use of 4-factor PCC over FFP.[52–54,70] Four-factor PCC has a safer profile and faster action than FFP in patients undergoing cardiopulmonary bypass surgery.[55] A systematic review and meta-analysis of 13 studies showed that PCC significantly reduces all-cause mortality, reduces the INR faster and is effective in smaller volumes compared to FFP, without an increased risk of thromboembolic events.[35] FFP is a human product that contains all coagulation factors, including fibrinogen, and it should be administered with Vitamin K.[31] To use FFP, it is essential to verify ABO compatibility. A larger infused volume is required (15 mL.kg^{-1}), increasing the risk of transfusion-associated circulatory overload and worsening renal function in patients with renal impairment.[35] All the characteristics of FFP, including long defrosting time and long infusion time, show that it is not an ideal therapy for urgent or emergency settings. Additionally, the use of FFP requires consideration of the risk of venous thromboembolism, allergic reactions, anaphylactic reactions, transfusion-related acute lung injury (TRALI), hemolysis, and infections.[56]

Recombinant activated factor VII (rFVIIa) is a hemostatic agent that increases thrombin generation by activating factor X at the site of vascular injury. It should not be used as a single agent to reversal because it is usually not capable of restoring hemostasis. The actual recommendation is not to use rFVIIa for warfarin reversal unless no other option is available, or in case of failure with previous treatments. A review of 63 patients with warfarin-ICH showed that both rFVIIa and PCC, in addition to vitamin K, are more effective with faster reversal than FFP but are associated with more INR rebound with rFVIIa.[57] rFVIIa seems superior to 3-factor PCC for warfarin reversal,[58] and their joint administration could be an option because 3-factor PCC has a lack of adequate levels of factor VII; however, their efficacy remains inferior to 4-factor PCC alone.[59,60] rFVIIa is more expensive than PCCs and has a rapid but short duration of action. Data from a literature review show that the use of rFVIIa as a prothrombotic agent could result in an increased risk of thromboembolic events, especially in elderly patients and when used for off-label indications such as the reversal of anticoagulant agents.[61–64]

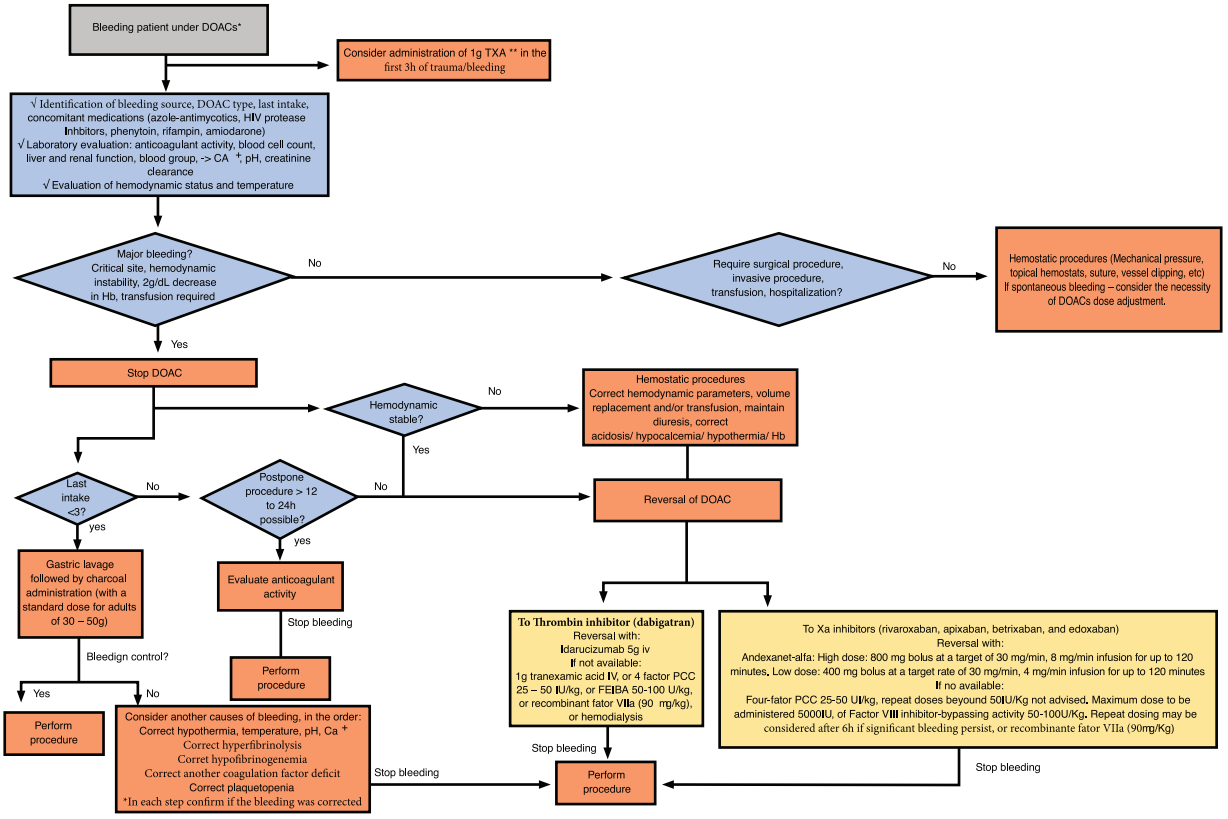

Figure 4 Reversal due to bleeding after trauma, due to spontaneous bleeding and/or before surgery in patients taking DOACs. BP, Blood pressure; HR, Heart rate; Hb, Hemoglobin.
* Direct oral anticoagulant.
** Tranexamic acid.

The reversal of DOACs

Active charcoal could be useful by helping reduce the absorption of DOACs (if the last dose was less than 2 hours before an emergency).[65] Hemostatic strategies using specific DOACs reversal agents should always be considered for patients with major bleeding, if available.[70]

The factor Xa inhibitors

Rivaroxaban, apixaban, and edoxaban anticoagulant action can be monitored by anti-FXa activity.[18] The factor Xa inhibitors at on-therapy or above on-therapy levels may not affect PT values or may induce a significant prolongation of the PT.[66,67]

Andexanet alfa is the specific Xa inhibitor that is currently on the market. Literature reports the use of 4-factor PCC or aPCC as non-specific, off-label, Xa inhibitor reversal agents, if andexanet alfa is not available (Fig. 4).

Andexanet alfa binds Xa inhibitors competitively with high affinity. It is indicated only for patients with severe, life-threatening bleeding, 18 hours within the last dose of anticoagulant.[68] The administration is performed intravenously, as a bolus and via infusion, and the effect is observed 5 minutes after intravenous administration, up to 2 hours after administration of the bolus and 1 to 2 hours after a 2-hour infusion.[68] The efficacy of andexanet alfa regarding the reversal of rivaroxaban and apixaban was first evaluated in 101 healthy volunteers, showing at least 80% reversal of anti-factor Xa activity.[68] This effect started 2 to 5 minutes after the bolus and lasted 2 hours after the bolus. In patients receiving Xa inhibitors (n = 352) presenting with major acute bleeding (mostly gastrointestinal or intracranial), treatment with andexanet alfa in a bolus followed by a 2-hour infusion showed that effective hemostasis was achieved in 82% of patients after 12 hours of reversal administration, and 10% of patients presented thromboembolic events within 30 days.[69]

High cost, limited availability, and the lack of clinical experience limit the use of andexanet alfa and other specific reversal agents. Anti-factor Xa is almost all protein bound; therefore, it is not possible to remove it by dialysis. Four-factor PCC is the non-specific agent most commonly used for reversal and guidelines support its use despite low evidence level.[22,70,71] Data on the use of PCC for anti-factor Xa are still limited. A single bolus of 50 IU.kg^{-1} of 4-factor PCC completely reversed the effect of rivaroxaban in 12 healthy subjects, with normal PT in 12.8 $\pm$ 1.0 seconds and maintained this effect for 24 hours.[72] In a meta-analysis, PCCs efficiently reversed the factor Xa inhibitors, represented by a significantly decreased PT and increased endogenous thrombin potential.[73] Four-factor PCC promoted hemostasis without any thromboembolic event in trauma patients (n = 33) presenting major bleeding using direct factor Xa inhibitors, mostly rivaroxaban,[36] and in 21 patients undergoing emergency surgery/procedures.[74] The use of a fixed dose of 2000 IU (approximately 25 IU.kg^{-1}) of 4-factor PCC

in 84 patients with major bleeding, mostly ICH and gastrointestinal bleeding, was effective in 69.1% of patients for the reversal of rivaroxaban and apixaban, with a low incidence of thromboembolic events and death (3 ischemic strokes leading to death).[75] In a prospective cohort of 66 patients on rivaroxaban or apixaban with major bleeding, 65% achieved good hemostasis with 2000 IU 4-factor PCC, but 8% presented thromboembolic events.[76] A dose-weight-based 50 IU.kg^{-1} to a maximum of 5000 IU of 4-factor PCC was evaluated in the reversal of apixaban and rivaroxaban action in 29 bleeding patients (most of them exhibiting ICH and gastrointestinal bleeding)[77] and 14 ICH patients,[78] with no thromboembolic events observed. Forty-three patients received 25 to 50 IU.kg^{-1} 4-factor PCC for the reversal of rivaroxaban or apixaban due to major bleeding or invasive emergency procedures, with only one thromboembolic event.[79] The efficacy and safety of 4-factor PCC for the reversal of Xa inhibitors were demonstrated in 18 patients presenting with traumatic ICH, hemorrhage stroke, subarachnoid hemorrhage, and tumoral hemorrhage, with one thromboembolic event.[80] In a retrospective cohort, reversal of direct factor Xa inhibitors with 4-factor PCC did not increase mortality or thromboembolic events in patients with traumatic ICH.[81] A meta-analysis with ten case series including 340 patients receiving 4-factor PCC showed that it was safe and effective for the reversal of factor Xa inhibitor in patients with major bleeding. However, the authors classified this meta-analysis as low-quality evidence because they did not identify comparative studies.[82] The use of PCCs for the reversal of factor Xa inhibitors before immediate neurosurgery was reported in six cases, but 50% of the cases presented severe bleeding during the operation, with three deaths due to bleeding.[83] In the observation of the reversal of DOACs using PCC to manage bleeding, the dose of 25 IU.kg^{-1} seemed to result in a better outcome than did a higher dose.[84] Preference should be given to nonactivated PCC because it presents more data available in the literature and probably has lower prothrombotic activity. Reports of case series studies and retrospective analyses show that aPCC was effective for the reversal of rivaroxaban in a patient with subdural hematoma[85] and in the setting of hemorrhage or the need for urgent surgical procedures.[86–89]

The thrombin inhibitor

The diluted thrombin time (DTT) and the ecarin clotting time (ECT) are the assays suitable for quantification of dabigatran.[66,67,90] The ECT test provides a consistent direct measurement of thrombin inhibitor activity, but it is not widely available. Patients under dabigatran may present normal or increased aPTT and TT. A normal range of these parameters does not rule out the anticoagulation effect, and an increased range may not indicate a more imminent bleeding risk.[90]

Removal through dialysis is possible, taking at least 4 hours to eliminate approximately 60 to 70% of the drug.[91,92] Therefore, patients who are hemodynamically unstable due to bleeding are not candidates for dialysis.

Reversal of dabigatran is achieved with idarucizumab. If this drug is not available, limited evidence supports the use of aPCC or PCC at 50 U.kg^{-1} (maximum dose 4000 units) (Fig. 4). Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran and acts as a specific reversal agent in cases of emergency surgery or urgent procedures, or major bleeding, life-threatening bleeding, or uncontrolled bleeding.[93] It takes 2.5 hours for bleeding cessation after the intravenous administration of 5 g and 24 hours for complete reversal.[93] However, some patients, especially those with comorbid renal failure, may rebound and need a repeated dose.[93] Idarucizumab was evaluated for the reversal of dabigatran in a clinical study with 461 patients exhibiting uncontrolled bleeding or presenting before an urgent procedure.[93] The results showed 100% of the median maximum percentage reversal, assessed by either DTT or ECT. Of 203 patients assessed for bleeding, 67.7% had confirmed bleeding cessation within 24 hours, and periprocedural hemostasis was normal in 93.4%.

The literature shows controversial results for the use of PCCs as a reversal agent for dabigatran. Limited evidence of efficacy was observed in reported case series in which aPCC reversed dabigatran, controlled bleeding, with no thromboembolic events.[94,95] One patient was reported to have a rapid response after the administration of aPCC during cardiac ablation,[96] and one patient responded to PCCs and FFP.[97] Other reported cases showed the inefficacy of PCCs and aFVII.[72,98]

Conclusion

Emergency situations, such as trauma, bleeding, and urgent surgery, involve the reversal of anticoagulants. Reversal is achieved by the administration of hemoderivatives such as PCCs and FFP, and specific agents for DOACs. PCCs and vitamin K have the highest benefit-risk ratio for warfarin reversal in emergency settings; the preferred choice is 4-factor PCC. Patients taking DOACs should receive specific reversal agents (andexanet alfa, idarucizumab). In cases of non-availability of specific reversal agents, PCC or aPCC could be considered based on limited evidence.

Conflicts of interest

Carlos Galhardo Jr received honoraria for consulting and lecture fees from ASPEN Pharma and CSL Behring. Dr Hugo Dantas has received honoraria for lecture fees from CSL Behring and Merck Sharp & Dohme. Luiz Henrique Ide Yamauchi and Dr João Carlos de Campos Guerra declare that they have no conflicts of interest relevant to the manuscript submitted to the Brazilian Journal of Anesthesiology.

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