REVIEW ARTICLE

Direct Oral Anticoagulants in Emergency Trauma Admissions

Perioperative Management, and Handling Hemorrhage

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SUMMARY

Background: Direct (non-vitamin-K-dependent) oral anticoagulants (DOAC) are given as an alternative to vitamin K antagonists (VKA) to prevent stroke and embolic disease in patients with atrial fibrillation that is not due to pathology of the heart valves. Fatal hemorrhage is rarer when DOACs are given (non-valvular atrial fibrillation: odds ratio [OR] 0.68; 95% confidence interval [95% CI: 0.48; 0.96], and venous thromboembolism: OR 0.54; [0.22; 1.32]). 48% of emergency trauma patients need an emergency operation or early surgery. Clotting disturbances elevate the mortality of such patients to 43%, compared to 17% in patients without a clotting disturbance. This underscores the importance of the proper, targeted treatment of trauma patients who are taking DOAC.

Methods: This review is based on articles retrieved by a selective search in PubMed and on a summary of expert opinion and the recommendations of the relevant medical specialty societies.

Results: Peak DOAC levels are reached 2–4 hours after the drug is taken. In patients with normal renal and hepatic function, no drug accumulation, and no drug interactions, the plasma level of DOAC 24 hours after administration is generally too low to cause any clinically relevant risk of bleeding. The risk of drug accumulation is higher in patients with renal dysfunction (creatinine clearance [CrCl] of 30 mL/min or less). Dabigatran levels can be estimated from the thrombin time, ecarin clotting time, and diluted thrombin time, while levels of factor Xa inhibitors can be estimated by means of calibrated chromogenic anti-factor Xa activity tests. Routine clotting studies do not reliably reflect the anticoagulant activity of DOAC. Surgery should be postponed, if possible, until at least 24–48 hours after the last dose of DOAC. For patients with mild, non-life threatening hemorrhage, it suffices to discontinue DOAC; for patients with severe hemorrhage, there are special treatment algorithms that should be followed.

Conclusion: DOACs in the setting of hemorrhage are a clinical challenge in the traumatological emergency room because of the inadequate validity of the relevant laboratory tests. An emergency antidote is now available only for dabigatran.

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Direct or non-vitamin-K-dependent oral anticoagulants (apixaban, dabigatran, edoxaban, and rivaroxaban) offer an alternative to vitamin K antagonists for the prevention of stroke and systemic embolus formation in patients who have non-valvular atrial fibrillation and at least one risk factor for stroke (1–6, e1–e8). They are claimed to be characterized by both easier handling and a more favorable benefit–risk profile, particularly with regard to intracranial and other life-threatening hemorrhages, and increasing numbers of patients are being treated with these new substances. Direct oral anticoagulants have also been licensed for treating and preventing recurrence of venous thromboembolisms, for the perioperative prevention of venous thromboembolisms in hip and knee replacement surgery (apixaban, dabigatran, and rivaroxaban), and for the treatment of acute coronary syndrome (rivaroxaban with acetylsalicylic acid, with or without clopidogrel or ticagrelor). The benefits and risks of direct or non-vitamin-K-dependent oral anticoagulants versus vitamin K antagonists depend essentially on successful calibration of the International Normalized Ratio (INR).

The advantage of direct or non-vitamin-K-dependent oral anticoagulants is that they achieve comparable efficacy and an improved safety profile while dispensing with the need for regular monitoring of laboratory parameters (2–6, e1–e3, e8). Disadvantages arise from the limited availability of antidotes and the lack of laboratory confirmation by means of the coagulation tests available in the routine and emergency situations (e8). Demonstration of direct or non-vitamin-K-dependent oral anticoagulants and negation of their effect constitute a challenge, particularly in an emergency scenario with immediate surgical consequences and bleeding (7). Fully one fourth of patients on anticoagulants have to suspend their treatment for a time within 2 years, usually because of operations/interventions (e9). Owing to the introduction of the CHA₂DS₂-VASc score, together with demographic change, increasing numbers of elderly persons at higher risk of falls and fractures are receiving direct or non-vitamin-K-dependent oral anticoagulants. The above-mentioned challenge for hospital staff dealing with emergency trauma admissions is thus growing in importance (6, e10, e11). The data of the TraumaRegister® of the

German Society for Trauma Surgery (*Deutsche Gesellschaft für Unfallchirurgie*) show that the number of elderly patients with comorbidities admitted to emergency trauma facilities has been on the increase for years (e12). Emergency operations and early surgical treatment are necessary in 5.5% and 42.5%, respectively, of (severely) injured patients, the most frequently performed procedures being laparotomy (50%), craniotomy (20%), thoracotomy (10%), and pelvic interventions (e13). Retrospectively, coagulation disorders, either congenital or acquired (e.g., due to anticoagulants), were associated with elevated mortality in trauma with or without head injury (43% versus 17%; e10, e11, e14, e15). Combining data from three large meta-analyses, *Table 1* shows the rates of spontaneous bleeding, including fatal hemorrhage, for direct or non-vitamin-K-dependent oral anticoagulants versus the standard vitamin K antagonists in patients being treated for venous thromboembolism and atrial fibrillation (8–10).

Methods

This review is based on data derived from a selective survey of the MEDLINE/PubMed and Cochrane Library databases using appropriate search terms, together with expert opinion and recommendations issued by the following professional bodies: American College of Cardiology (ACC)/American Heart Association (AHA) and Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA), European Society of Cardiology (ESC), Association of Scientific Medical Societies in Germany (AWMF), National Institute for Health and Care Excellence (NICE).

Pharmacokinetics/pharmacodynamics

The pharmacokinetic/pharmacodynamic characteristics of the direct or non-vitamin-K-dependent oral anticoagulants are summarized in the *eTable*. Peak concentrations are attained 2 to 4 hours after intake. In the presence of normal renal function, levels decrease over a period of 12 to 24 hours, first rapidly and then more slowly. Renal function is of crucial significance for the plasma concentration and duration of action of direct or non-vitamin-K-dependent oral anticoagulants, because they are eliminated to a varying extent via the kidneys; the risk of accumulation in the case of renal failure is highest for dabigatran, followed in descending order by edoxaban, rivaroxaban, and apixaban (11–13, e16). Concentrations of rivaroxaban are increased in severe disorders of renal function (creatinine clearance [CrCl] 15–29 mL/min); moderate renal failure (CrCl 30–49 mL/min) led to an increase in the rate of severe bleeding from 3.4% to 4.5% in patients on rivaroxaban (5, 6). Cumulation effects requiring dose adjustment have been reported for apixaban from CrCl <30 mL/min and for dabigatran and edoxaban from CrCl ≤ 50 mL/min. Moderate to severe impairments of hepatic function must be taken into account (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] >2 × upper reference value / total

bilirubin 1.5 × upper reference value). A scoring system has been developed to check anticoagulation and assess the risk of hemorrhage during treatment with vitamin K antagonists:

- Albumin 2.5–3.49 g/dL and/or creatinine 1.01–1.99 mg/dL = 1 point
- Albumin <2.5 g/dL and/or creatinine ≥ 2 mg/dL = 2 points.

With an overall score of 4 points or more the bleeding risk is high (e17). Details of the various dose adjustments for individual direct or non-vitamin-K-dependent oral anticoagulants in the presence of impaired renal and hepatic function can be found in the respective summaries of product characteristics.

The bioavailability of dabigatran is lower than for any of the other substances, so even small fluctuations in absorption lead to considerable differences in the steepness of the rate of increase in plasma (14) (*eTable*). The intestinal absorption of dabigatran is pH-dependent and may be lower with parallel intake of proton pump inhibitors. Due to its low protein binding, dabigatran (and edoxaban) is the only substance that is dialyzable in appreciable amounts (15, e18). Apixaban and rivaroxaban are partly metabolized via cytochrome CYP3A3; comedication with amiodarone, carbamazepine, clarithromycin, dronedarone, verapamil, quinidines, ketoconazole, fluconazole, ciclosporin, erythromycin, or diltiazem can lead to variations in plasma concentration with a significant increase in the risk of hemorrhage (5, 6). The dosage of direct or non-vitamin-K-dependent oral anticoagulants varies depending on the indication.

Monitoring/coagulation testing

Treatment with direct or non-vitamin-K-dependent oral anticoagulants is currently not routinely monitored (5, e8), but monitoring may improve the benefit–risk profile if the specific characteristics of the individual patient are taken into account (e19). All of these substances attain their peak concentrations and thus their maximal anticoagulatory effect 2–4 h after intake of the last dose (5). For estimation of the current plasma concentration it is important to know:

- Which direct or non-vitamin-K-dependent oral anticoagulant was taken how long before blood sampling
- The dosage
- Whether there is any impairment of renal/hepatic function and/or relevant comedication (5, 6).

For all direct or non-vitamin-K-dependent oral anticoagulants, the time course of plasma concentrations and anticoagulatory effects can be approximately projected: 24 h after last intake of a substance with a half-life of 10–12 h the plasma concentration will no longer be a significant risk factor for hemorrhage, provided there is no kidney/liver function impairment, relevant interaction with comedication, or accumulation (5, 6).

To date there is no universally available validated (rapid) test system for any of the direct or non-vitamin-K-dependent oral anticoagulants that possesses

TABLE 1

Rates of spontaneous bleeding including fatal bleeding in patients on direct or non-vitamin-K-dependent oral anticoagulants versus standard vitamin K antagonists being treated for venous thrombembolism or atrial fibrillation (relative risk and [95% confidence interval])

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Venous thrombembolism				
Major bleeding	0.31 [0.17; 0.55]	0.55 [0.38; 0.82]	0.85 [0.60; 1.21]	0.76 [0.49; 1.18]
Intracranial bleeding	0.50 [0.13; 2.01]	0.40 [0.11; 1.47]	0.08 [0.00; 1.37]	0.28 [0.07; 1.13]
Fatal bleeding	0.50 [0.05; 5.54]	0.20 [0.02; 1.70]	0.20 [0.04; 0.91]	0.62 [0.08; 5.05]
Mortality	0.79 [0.53; 1.19]	0.95 [0.64; 1.42]	1.05 [0.83; 1.33]	1.00 [0.67; 1.42]
Atrial fibrillation				
Major bleeding	1.25 [0.64; 2.4]	0.68 [0.15; 3.04]	0.70 [0.49; 1.00]	0.79 [0.44; 1.43]
Fatal bleeding*	0.88 [0.44; 1.76]	0.48 [0.30; 0.76]	0.45 [0.31; 0.65]	0.69 [0.37; 1.27]
Mortality	0.50 [0.34; 0.74]	0.69 [0.45; 1.04]	Not documented	0.56 [0.36; 0.86]

(Modified from [8–10]). Results of two meta-analyses on acute treatment of venous thrombembolism, each covering six phase-III studies with a total of >27 000 patients, and one meta-analysis on treatment of atrial fibrillation covering five studies with a total of >43 000 patients.

* Including intracranial bleeding

satisfactory sensitivity and specificity (e20). *Figure 1* shows the range of results displayed by the available means of measurement (6, 16).

The factor IIa (thrombin) inhibitor dabigatran

The thrombin time and the ecarin clotting time can be used to confirm a dabigatran concentration sufficient to achieve an anticoagulatory effect (12, e8, e21). The ecarin clotting time is based on the action of ecarin (a metalloprotease), which in the absence of thrombin inhibitors converts prothrombin to meizothrombin and then, following fibrinogen cleavage, to fibrin. Ecarin clotting time is measured proportionally to thrombin inhibitor concentration. The thrombin time ratio shows a linear dose–effect relationship at therapeutic concentrations. The activated partial thromboplastin time shows a limited dose–effect relationship; the variable sensitivity means that the results have to be interpreted with caution and not without knowledge of the reagents used (16). Particularly at higher concentrations of dabigatran the curve flattens and offers no correlation with activated partial thromboplastin time (12). The so-called diluted thrombin time offered by many coagulation testing facilities demonstrates thrombin inhibition directly with a linear relationship to previously measured plasma concentrations and serves as a quantitative measure (5, 16). In the event that the time and amount of the most recent dose of dabigatran are unknown, normal values for thrombin time, ecarin clotting time, and diluted thrombin time indicate the absence of dabigatran in any clinically relevant concentration (16, 17).

Factor Xa inhibitors

Chromogenic anti-factor-Xa activity tests can be used to estimate the plasma concentrations of factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban), but

require calibration with substance-specific reagents (16, 18, e21). No calibration standard is available for the emergency scenario. Lacking anti-factor-Xa activity in plasma with or without specific calibration indicates the absence of an active anticoagulatory level of factor Xa inhibitors (16). After intake of factor Xa inhibitors, peak concentrations at 2–4 h are accompanied by prolongation of prothrombin time and activated partial thromboplastin time to levels 1.2 (1.6) to 2 times the upper reference values. Thrombin time is not suitable for determining the anticoagulatory effect of factor Xa inhibitors.

Owing to the slight and/or variable increases within the therapeutic range, the routinely performed coagulation tests (activated partial thromboplastin time/partial thromboplastin time and prothrombin time) do not permit confident estimation of anticoagulatory effect (16). For both tests, results in the reference range beyond 3 h (dabigatran) or 4 h (factor Xa inhibitors) after intake of a direct or non-vitamin-K-dependent oral anticoagulant broadly rule out therapeutic concentrations with a clinically relevant danger of hemorrhage (16, 18). Urine test strips for qualitative assessment without clinical validation have been developed (rivaroxaban) or are in the process of development (apixaban and dabigatran) (19); the usefulness of viscoelastic test procedures and endogenous thrombin potential is unclear (e22, e23).

Perioperative management of emergency trauma

The perioperative management of patients who have been treated with direct or non-vitamin-K-dependent oral anticoagulants is challenging in the emergency scenario, because the availability of specific antidotes is limited. November 2015 saw the licensing of the monoclonal antibody fragment idarucizumab (FAB fragment), a specific antidote to dabigatran, for

FIGURE 1

Spectrum of results of the laboratory procedures available for determining the anticoagulatory effects (global coagulation tests) and plasma concentrations (specific tests) of direct or non-vitamin-K-dependent oral anticoagulants (modified from [6, 16]). The gray bars correspond to the assumed spectrum of detection (sensitivity) and the green bars to the assumed spectrum of the quantifiable plasma concentrations (linearity) for each procedure. The spectra may vary depending on the reagents used. aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; PT, prothrombin time; TT, thrombin time

intravenous administration in adults (20, e24). Factor Xa inhibitor antidotes (PRT4445 [andexanet alpha]; PER977 [aripazine]) are in the process of clinical testing (phases II und III) and could be approved for use in the near future (21–23, e25, e26).

In the absence of accumulation, interruption of the anticoagulant treatment together with supportive measures, e.g., support/maintenance of diuresis, suffices in most patients. There are no precise data on the risk of stroke and embolism during the treatment break. If at all possible, surgical interventions should be postponed until at least 12 h, ideally 24 h, after the last dose (5). The summaries of product characteristics for all direct or non-vitamin-K-dependent oral anticoagulants recommend that the substances should be discontinued at least 24 h before a planned operation. This also holds true for conditions with minimal bleeding that is easily controlled. The EHRA recommendations are as follows: for minor surgical interventions/procedures involving no danger of bleeding (e.g., hand surgery, dental extraction, “anterior” eye surgery), interruption of treatment with direct or non-vitamin-

K-dependent oral anticoagulants for 12–24 h before a planned operation depending on whether the drug is taken once daily (24 h) or twice daily (12 h); for intermediate interventions with low bleeding risk, interruption for at least 24 h; and for major operations with high risk of hemorrhage, interruption for 48 h (5) (Table 2). This last category includes orthopedic interventions, spinal column surgery, and neurosurgical operations on the brain and spinal cord. The French Working Group on Perioperative Hemostasis and the French Study Group on Thrombosis and Hemostasis suggest extended interruption of treatment before interventions with a high risk of bleeding (24, 25) (Table 2). Spinal and epidural anesthesia and lumbar puncture necessitate complete hemostasis (5). Although no confirmation has been provided by prospective data, plasma concentrations of direct or non-vitamin-K-dependent oral anticoagulants can be taken into account in the planning of interventions. Plasma concentrations <30 ng/mL can be viewed as the threshold level, and in the presence of concentrations between 30 and 400 ng/mL interventions/procedures

TABLE 2

Recommendations on the interval between last dose of direct or non-vitamin-K-dependent oral anticoagulant and intervention/procedure depending on bleeding risk and renal function*

	Apixaban/edoxaban/rivaroxaban		Dabigatran	
Renal function (CrCl, mL/min)	BR ↓	BR ↑	BR ↓	BR ↑
≥ 80	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 (–72*) h
50–79	≥ 24 h	≥ 48 (–72*) h	≥ 36 h	≥ 72 (–96*) h
30–49	≥ 24 h	≥ 48 (≥ 72–96*) h	≥ 48 h	≥ 96 h
15–29	≥ 36 h	≥ 48 (≥ 96*) h	No indication for DOACs!	
<15	No indication for DOACs!			

*Modified from [5, 25]). In the case of comedication with aspirin, platelet aggregation inhibitors, amiodarone, or phenothiazine, add 12 h (25). The recommendations here may diverge slightly from those in the summaries of product characteristics.

CrCl, creatinine clearance; DOAC, direct or non-vitamin-K-dependent oral anticoagulant; BR, risk of bleeding in the course of the intervention/procedure

should be postponed and the levels checked at 12- to 24-h intervals (25).

Antagonism of dabigatran

The anticoagulatory effect of dabigatran can be almost completely counteracted within a few minutes by idarucizumab (2×2.5 g/50 mL as successive infusion or boluses) (20). In a subgroup of patients plasma concentrations of dabigatran could again be demonstrated after 24 h, so renewed administration of idarucizumab should be considered in the event of repeated emergency interventions or new bleeding. The highest single dose yet investigated in healthy probands is 8 g. On the basis of experimental data, activated charcoal can be given to inhibit absorption of dabigatran if the last dose of the anticoagulant was taken less than 2 h beforehand (22, 23, 26, 27). There are only a small number of studies on the interaction of dabigatran and dialysis, so the risk of bleeding at the sites of access must be borne in mind (5, 15, 26, 27, e18). In the absence of severe hemorrhage associated with direct or non-vitamin-K-dependent oral anticoagulants, there is no need for prophylactic administration of hemostatically active substances such as prothrombin complex concentrate or fresh plasma.

If emergency surgery cannot be delayed in a patient in whom anticoagulatory medication is still partially or fully effective, the increased risk of hemorrhage has to be anticipated. The appropriate course of action depends on the scale of the bleeding and is outlined below.

Management of minor/non-life-threatening hemorrhage

All recommendations are based not so much on clinical data as on expert opinion, summaries of product characteristics, and clinical chemistry endpoints (5). In the case of minor/non-life-threatening hemorrhage with controlled blood loss and no relevance for the circulation, discontinuation combined with general/supportive measures, e.g., mechanical/surgical hemostasis and fluid treatment to maintain organ perfusion/diuresis, suffices (5). In the absence of accumulation, clinical

hemostasis can be expected 12–24 h after the last dose of anticoagulant (e27); with intake of dabigatran and CrCl of 50–80 mL/min, after 24–48 h; with CrCl of 30–50 mL/min, after 36–48 h; and with CrCl < 30 mL/min, after ≥ 48 h (5). Packed red blood cells should be substituted if necessary, and thrombocyte concentrates should be considered in the case of thrombocytopenia $\leq 60 \times 10^9/L$ or thrombocytopathy (5).

Management of major/life-threatening hemorrhage

The procedure in the event of heavy bleeding is shown in the algorithm in *Figure 2*. Administration of direct or non-vitamin-K-dependent oral anticoagulants must be stopped immediately. In the presence of circulatory instability the usual vasopressors are used, while patients receiving massive transfusions may require plasma/platelet products and fibrinogen concentrates (5, 6). Should conventional measures prove inadequate, off-label administration of prothrombin complex concentrates or activated prothrombin complex concentrate and/or recombinant factor VIIa (rFVIIa) in the recommended dosages can be considered (5, 6, 22, 23, 27–30) (*Figure 2*). In experimental studies (dabigatran) and tests on healthy volunteers (apixaban, edoxaban, and rivaroxaban), the best effect has been documented for prothrombin complex concentrate (29–32, e27–e33); no prospective randomized trials have been conducted. Experiments showed a dubious effect for rFVIIa (e34, e35); there is no clinical evidence for the efficacy of this substance and further evaluation is required (5). According to investigations in vitro, activated prothrombin complex concentrate was more effective than prothrombin complex concentrate in normalizing the coagulation parameters (e33, e36). The risk of thromboembolic events during treatment with prothrombin complex concentrate must be borne in mind (5). The use of further procoagulants, e.g., tranexamic acid or desmopressin (in coagulation disorder or thrombopathy) can be considered, although here too data are lacking. Successful dialysis in association with emergency surgery resulting in severe hemorrhage has been described (e37). Due to its high

FIGURE 2

Algorithm for treatment of patients with hemorrhage while being treated with DOAC (modified from [5, 6, 25, 38–40]). For definition of bleeding see (6).

¹ Consider use as adjuvant

² Consider use in individual cases, e.g., in the presence of coagulation disorder or thrombopathy

³ Preliminary evidence: 65% elimination after 4 h

⁴ Only experimental data

⁵ Possible for all oral anticoagulants. No clinical data (dabigatran) and data only from healthy volunteers (apixaban, edoxaban, rivaroxaban); no data on superiority of activated PPSB over PPSB

⁶ No indication of clinical benefit to date, only experimental data; further evaluation necessary

ASS, acetylsalicylic acid; CYP, cytochrome P450; DDAVP, desmopressin acetate; DOAC, direct or non-vitamin-K-dependent oral anticoagulants; FFP, fresh frozen plasma; GI, gastrointestinal; Hb, hemoglobin; kg, kilogram; NSARs, nonsteroidal antiinflammatory drugs; P-gp, P-glycoprotein; PPSB, prothrombin concentrate (vitamin-K-dependent coagulation factors: factor II (prothrombin), factor VII (proconvertin), factor X (Stuart-Prower factor), factor IX (antihemophilic factor B) + protein S and protein C as well as antithrombin and heparin); RBC, red blood cells; rFVIIa, recombinant factor VIIa; TCC, thrombocyte concentrate; TXA, tranexamic acid; U, unit

protein binding, apixaban and rivaroxaban may be eliminated by means of plasmapheresis. These procedures are practicable only to a limited degree in the acute situation and depend on local availability and infrastructure.

Traumatic intracranial hemorrhage

Every second victim of (severe) trauma suffers head injury, with any of various forms of intracranial bleeding, in addition to their extracranial injuries (e12). In those taking direct or non-vitamin-K-dependent oral anticoagulants, intracranial hemorrhage is associated with high mortality (33, e38). It is known that patients who

are being treated with vitamin K antagonists and suffer traumatic intracranial hemorrhage may experience ongoing bleeding or even additional new bleeding with overall increased hematoma volumes (34). Vitamin K and vitamin-K-dependent coagulation factors are administered with the aim of normalizing the INR (35, 36). Attainment of INR <1.3 and reduction of blood pressure to <160 mm Hg within 4 h was associated with a lower increase in the volume of intracranial hematomas (e39). Whether late posttraumatic hemorrhage also occurs in patients on direct or non-vitamin-K-dependent oral anticoagulants and what steps should then be taken remains unclear. Owing to the limited availability

of specific antidotes to direct or non-vitamin-K-dependent oral anticoagulants and the restriction of guidelines to the counteracting of vitamin K antagonists, these recommendations are also valid for the treatment of intracranial hemorrhage in patients on direct or non-vitamin-K-dependent oral anticoagulants (35, 36). Here too, the primary goal is swift correction of coagulation (*Figure 2*). After this has been achieved, surgical treatment of intracranial hemorrhages and other acute decompensating intracranial space-occupying lesions can be considered depending on the clinical circumstances (e40). Prospective studies and data on the reliability of clinical chemistry are needed to evaluate these measures.

Resumption of treatment after surgery and intervention

Patients being treated with direct or non-vitamin-K-dependent oral anticoagulants do not need to be switched to other anticoagulants before operation (5, 37, e8); indeed, early prospective studies have shown that switching is associated with a higher risk of bleeding than discontinuation, with no difference in the risk of thromboembolism (e32). The treatment with direct or non-vitamin-K-dependent oral anticoagulants can be resumed in therapeutic dosage 24 h after surgery with minimal risk of hemorrhage (37). Some authors have proposed shorter periods of 6–8 h (25). After interventions bearing a high risk of bleeding without postoperative immobilization, the interval before resumption should be 48–72 h, and only then in the presence of stable hemostasis and a dry wound. Patients who are immobilized after surgery must be temporarily switched to low-molecular heparin in prophylactic dosage (24, 37). Hemostasis having been achieved, this treatment should begin 6–8 h after operation; after 48–72 h the patient can go back to the direct or non-vitamin-K-dependent oral anticoagulant given previously (24, 37). In patients with traumatic epidural or subdural hematomas the recommendation is for

resumption of anticoagulation starting four weeks after injury or intervention, except in the presence of chronic alcoholism with liver failure, although data are lacking (5).

Conclusion

Due to the limited availability of validated (rapid) test systems and antidotes, direct or non-vitamin-K-dependent oral anticoagulants and the associated bleeding represent a challenge in the treatment of trauma victims in the emergency department.

Conflict of interest statement

Prof. Maegele has received consultancy fees from TEM International, CSL Behring, Bayer, and LFB France and reimbursement of costs for congress attendance, travel, and accommodation from TEM International, CSL Behring, Bayer, and LFB France. He has received payment for giving a presentation at scientific meetings and funding for a research project of his own initiation from LFB France and CSL Behring.

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Dr. Schöchl has received payments for giving presentations at scientific meetings from Bayer and CSL Behring.

Prof. Sakowitz has received reimbursement of costs for congress attendance, travel, and accommodation as well as payments for giving presentations at scientific meetings from CSL Behring.

Prof. Spannagl has received consultancy fees from Bayer, Böhrringer Ingelheim, and Pfizer and payments for giving presentations from Bayer, Böhrringer Ingelheim, Daiichi Sankyo, and Pfizer.

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KEY MESSAGES

- Direct or non-vitamin-K-dependent oral anticoagulants are being increasingly used and are associated with lower risks of intracranial and other life-threatening hemorrhages than vitamin K antagonists.
- Only for dabigatran is an antidote available in emergencies.
- The available coagulation tests react differently for the different direct or non-vitamin-K-dependent oral anticoagulants and often do not detect the full therapeutic range of these substances.
- Coagulation disorders, caused for instance by intake of anticoagulants, are associated with much higher mortality after trauma with and without head injury.
- Impairments of kidney and liver function increase the risk of accumulation and prolong the duration of effect of direct or non-vitamin-K-dependent oral anticoagulants.

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Supplementary material
For eReferences please refer to:
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eTable:
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Supplementary material to:

Direct Oral Anticoagulants in Emergency Trauma Admissions

Perioperative Management, and Handling Hemorrhage

Marc Maegele, Oliver Grottko, Herbert Schöchl, Oliver Sakowitz, Michael Spannagl, Jürgen Koscielny

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eTABLE

Pharmacokinetics and pharmacodynamics of the direct or non-vitamin-K-dependent oral anticoagulants currently on the market (data from [5] and summaries of product characteristics)

	Apixaban	Rivaroxaban	Edoxaban	Dabigatran
Point of action	Factor Xa	Factor Xa	Factor Xa	Factor IIa (thrombin)
Prodrug	No	No	No	Yes
Time to C _{max} (h)	1–3 (4)	2–4	1–2	2–3
CYP metabolism	15%	32%	<4%	0%
Bioavailability	(50% ?) 66%	80%	62%	3–7%
Transport	P-gp	P-gp/BCRP	P-gp	P-gp
Protein binding	87%	> 90%	55%	35%
Half-life (h)	8–15	(5–7 ?) 9–13	10–14	(8 ?)12–14(15 ?)
Renal elimination	27%	33% (65%)*	50%	80%

* Approximately half eliminated unchanged in the urine
BCRP, breast cancer resistant protein; C_{max}, maximal concentration (peak level); CYP, cytochrome P450; P-gp, P-glycoprotein.
The question marks indicate uncertainty.