

How I manage patients with anticoagulation-associated bleeding or urgent surgery

Sauter Thomas C.^a, Eberle Balthasar^b, Wuillemin Walter A.^c, Thiele Thomas^d, Angelillo-Scherrer Anne^e, Exadaktylos Aristomenis K.^a, Erdoes Gabor^b, Cuker Adam^f, Nagler Michael^e

^a Department of Emergency Medicine, Inselspital, University Hospital Bern, Switzerland

^b Department of Anaesthesiology and Pain Therapy, Inselspital, University Hospital Bern, Switzerland

^c Division of Haematology and Central Haematology Laboratory, Luzerner Kantonsspital, Lucerne, Switzerland

^d Institute for Immunology and Transfusion Medicine, Universitätsmedizin Greifswald, Germany

^e Department of Haematology and Central Haematology Laboratory, Inselspital University Hospital, and Department for BioMedical Research, University of Bern, Switzerland

^f Departments of Medicine and Pathology & Laboratory Medicine, University of Pennsylvania, Philadelphia, PA, USA

Summary

Antithrombotic treatment puts patients at risk of major bleeding. Fast and adequate response to anticoagulant-associated bleeding may not only stop the bleeding but prevent severe complications. However, practical treatment algorithms to guide physicians in emergency situations are lacking. Important principles that arise from management of bleeding in general are (a) implementation of an in-house algorithm, (b) rapid identification and treatment of the bleeding source, (c) adequate fluid resuscitation, (d) consideration of the application of tranexamic acid and (e) appropriate coagulation testing. We present an algorithm for anticoagulant-associated bleeding and urgent surgery, derived from available data and recommendations, and implemented at our institution. Decisions regarding reversal agents or postponing surgery are based on two questions: the occurrence of a life-threatening bleed or urgent indication for surgery, and the presence of a relevant drug level. Immediate application of reversal agents is suggested if the clinical situation is urgent and laboratory test results are delayed or unavailable. A relevant anticoagulant drug level is required in all other cases. We discuss appropriate laboratory assays for all commonly available anticoagulants, report respective target ranges or expected values, discuss time intervals before surgery, and present critical cut-off values to be used as decision criteria. Specific and unspecific reversal agents for all anticoagulants including the direct oral anticoagulants will be presented. We aim to provide practical guidance for physicians in emergency situations. In addition, we summarise and discuss available experimental and clinical data as well as recommendations provided by scientific societies, authorities and manufacturers.

Key words: anticoagulants, bleeding, urgent interventions, reversal, antidote, phenprocoumon, apixaban, dabigatran, edoxaban, heparin, idarucizumab, rivaroxaban

Introduction

Any anticoagulation treatment is associated with an increased risk of bleeding. Whereas the annual risk of any bleeding is estimated to be 2-4%, the risk of *major* bleeding increases in some patient populations to as much as 15%/year [1]. Intracranial haemorrhage is the most dangerous adverse event; it is associated with a high risk of death or permanent disability [2]. About 25% of intracranial haemorrhages are linked to oral anticoagulant treatment [3]. The anticoagulant-related bleeding risk is particularly relevant in the case of trauma. Uncontrolled bleeding is the leading cause of death in trauma patients, but it is regarded as potentially preventable [4, 5]. Physicians treating patients with anticoagulation-associated bleeding are confronted with a confusing number of drugs, laboratory tests and reversal agents. Often, clear treatment algorithms are lacking and issues arise in terms of availability of laboratory tests and reversal agents. Moreover, recommendations issued by scientific societies, pharmaceutical companies and regulatory authorities can be vague and sometimes contradictory [6-8].

Management of anticoagulation-associated bleeding has become more challenging as the number of available drugs increases. Several direct oral anticoagulants targeting either factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran etexilate) have entered the market and are increasingly being used [9]. Vitamin K antagonists, unfractionated heparin and low molecular heparin are still widely utilised.

With this review, we aim to provide a practical approach for emergency scenarios. We propose a pragmatic treatment algorithm implemented in our institution (Inselspital,

Correspondence:

Michael Nagler, MD, PhD,
MSc, Inselspital, Freiburg-
erstrasse, CH - 3010 Bern,
[michael.nagler\[at\]insel.ch](mailto:michael.nagler[at]insel.ch)

University Hospital, Bern, Switzerland). Our considerations have largely been based on current statements issued by scientific societies, regulatory authorities, companies and experts, which we recognise is a limitation. This is a reflection that high quality evidence in terms of randomised controlled trials or prospective observational research focused on clinical outcomes is scant [10]. Here we collate important concepts of bleeding management in general and regarding anticoagulant-associated bleeding in particular, and discuss all aspects of available reversal agents and laboratory aspects. We also summarise the management in case of urgent surgery. In addition, we provide clear decision criteria in terms of drug levels and time intervals focussing on all common anticoagulants (unfractionated heparin, low molecular weight heparins, vitamin K antagonists, direct oral anticoagulants), but omitting those drugs that are rarely used in Switzerland, such as fondaparinux.

General management of major bleeding

Implementation of algorithms

Several scientific guidelines provide recommendations for the management of major bleeding, such as the current European guideline on management of major bleeding and coagulopathy following trauma, and the European Society of Anaesthesiology guidelines for severe perioperative bleeding [4, 11]. Implementation of in-house algorithms and protocols is regarded as crucial for improving the care of affected patients [12]. Detailed protocols improve communication between multidisciplinary teams in a setting where several diagnostic and therapeutic measures must be taken simultaneously [13]. Indeed, implementation of management protocols have been associated with improved clinical outcomes [14–16].

Rapid identification and treatment of the bleeding source

Identification and treatment of the bleeding source is the critical first step in the management of patients with major bleeding [4, 12]. Care teams must identify bleeding sources as soon as possible by clinical examination and early imaging (ultrasonography, contrast enhanced computed tomography, angiography, or endoscopy). When the bleeding source has been identified, patients should undergo an immediate procedure to control the bleed, which often requires direct transfer to the operating theatre or the angiography or endoscopy suite. This approach is supported by the observation that 80% of trauma deaths occur within the first hour after injury [12]. Indeed, distance from a computed tomography (CT) scanner has been associated with mortality in observational studies [17]. Several additional observational studies also support early bleeding treatment [4, 18, 19].

Fluid resuscitation

In uncontrolled haemorrhage, fluids should be replaced in accordance with the concept of “permissive hypotension” [20, 21]. Although maintenance of an adequate blood pressure is crucial to restore tissue perfusion in haemorrhagic shock, which requires fluid replacement, excessive fluid administration can result in relevant adverse events [22]. A restrictive volume replacement strategy targeting a systolic

blood pressure of 80 to 90 mm Hg is therefore suggested, at least in the absence of traumatic brain injury [20, 21]. This approach is supported by clinical data obtained in a small randomised controlled trial [23], and several observational studies and meta-analyses [24–28]. Since colloid use in volume resuscitation has been associated with coagulopathy and kidney injury, a balanced isotonic crystalloid solution is generally recommended [4]. Early administration of red blood cells and fresh frozen plasma (at least in a ratio of 2:1) is another strategy employed to avoid crystalloid overinfusion and to mitigate dilutional coagulopathy, with the goal of achieving a target haemoglobin range of 70 to 90 g/l [4]. Implementation of structured transfusion protocols has been shown to improve survival, to prevent organ failure and to reduce use of blood products and costs [14]. In addition, prevention of hypothermia helps to avoid coagulopathy, acidosis and hypotension associated with a core body temperature less than 35°C.

Tranexamic acid

The anti-fibrinolytic agent tranexamic acid (Cyclokapron®) is a valuable adjunct in the setting of acute bleeding. It has few side effects, is inexpensive and is easily applied. In orthopaedic surgery, tranexamic acid reduced the need for blood transfusions by up to 40% [29]. In trauma patients, the efficacy of early administration of 1 g tranexamic acid was tested in a large scale randomised controlled trial including more than 20,000 patients (CRASH-2) [30]; the overall mortality was reduced by 10%. A small case-control study suggests efficacy also in the context of perioperative venous thromboembolism prophylaxis with a direct oral anticoagulant [31]. Equally important was that none of these studies reported an increase of thromboembolic events, suggesting a good safety profile. Only when tranexamic acid was given in higher dose regimens in the context of cardiac surgery was a small but significantly increased incidence of seizures observed [32]. Based on the available evidence, published reviews suggest that trauma-dose tranexamic acid should also be administered to patients with anticoagulant-associated bleeding [33, 34].

Coagulation testing

Early and repeated determination of coagulation function and platelet counts are recommended in all patients with bleeding events [4]. Conventional coagulation tests are not only useful to detect hereditary diseases (such as haemophilia and von Willebrand’s disease) but also most acquired disorders, namely fibrinogen deficiency, disseminated intravascular coagulation, vitamin K deficiency, liver failure, acute traumatic coagulopathy, and anticoagulant treatment [35]. The Inselspital screening panel for bleeding emergencies contains prothrombin time (INR; Quick %), activated partial thromboplastin time (aPTT), Clauss fibrinogen concentration, thrombin time, and the point-of-care thromboelastometry assay (ROTEM®). ROTEM® or thromboelastography (TEG®) are available in many institutions. These tests can rapidly detect fibrinogen deficiency, thrombocytopenia and (severe) hyperfibrinolysis, and are widely used to guide replacement therapy [11]. An anti-Xa assay for screening of all Xa inhibitors, even though data on its accuracy are lacking, could also be implemented

as a screening test. Specific laboratory tests for the monitoring of anticoagulants are discussed further below.

Management of anticoagulant-associated bleeding

General principles

Primary resuscitation of patients with suspected anticoagulant-associated bleeding should follow the same general management strategies outlined above. However, major haemorrhage is but one manifestation of anticoagulant-associated bleeding and is not always in conjunction with trauma. A substantial proportion of patients on anticoagulant treatment suffer a non-traumatic major haemorrhage, such as gastrointestinal bleeding or ruptured abdominal aortic aneurysm; life-threatening bleeding events, such as intracranial haemorrhage or (spontaneous or iatrogenic) spinal haematoma or pericardial tamponade, can occur without hypovolaemia. Moreover, many patients on anticoagulant treatment, though not bleeding actively, may need to be prepared for major emergency surgery.

Thus, there are numerous important differences from non-anticoagulant-associated bleeding, which must be addressed during management. First, specific and nonspecific agents exist that can reverse the anticoagulant effect within minutes and stop active bleeding rapidly [10] or reduce the risk of emergent surgery. Second, patients with anticoagulant-associated bleeding remain at high risk of thromboembolic complications due to their underlying disease (atrial fibrillation, venous thromboembolism, mechanical heart valve), because of the active bleeding event and the associated administration of reversal agents [33]. The risks of bleeding and thrombosis must be monitored and balanced carefully, and the period of reversal must be kept as brief as possible. Third, knowledge of plasma levels of the anticoagulant agent is important for management, with specific laboratory assays required for individual anticoagulant drugs [34]. These issues will be discussed in detail below.

Assessment of severity and urgency

Assessment of the severity of bleeding and urgency of intervention is an important first step in patient management to allocate subsequent treatment [4]. In patients with an anticoagulant-associated bleeding event the question arises whether and when a reversal agent should be applied. Application of reversal agents may stop the bleeding rapidly, but can also increase the risk of thromboembolic events [33]. If the plasma level of the anticoagulant drug is not known, reversal agents should not be used. Although a relevant drug level can be estimated from the time of last administration, this can be uncertain. Laboratory tests to measure anticoagulant drug levels can take time, but they have become increasingly available in the Swiss healthcare setting. Thus, we use – and propose – an algorithm considering both the severity of bleeding as well as assay results (fig. 1). Core aspects of this algorithm were utilised in the pivotal study of idarucizumab, a reversal agent for dabigatran etexilate [36]. This algorithm has been implemented as an in-house guideline for Inselspital University Hospital, Bern, Switzerland.

Proposed treatment algorithm

In patients with supposed or known anticoagulant treatment, assessment of urgency has a high priority (fig. 1). The physician in charge must decide if the bleeding is life threatening and requires immediate action. Identification and treatment of bleeding sources is pivotal. Typical examples include severe haemorrhagic shock or extensive intracranial haemorrhage. In these clinical situations, the risk of bleeding-associated complications is higher than the risk of thromboembolic complications related to reversal agents. In the context of intracranial haemorrhage, several studies have demonstrated markedly improved clinical outcomes if reversal agents are applied rapidly [6]. In our practice, we treat patients suffering from life-threatening bleeding with reversal agents without waiting for laboratory results (fig. 1; left column) [6, 37]. We proceed similarly in patients who require emergency surgery within 1 hour. In contrast, in severely bleeding patients whose haemodynamic and vital functions can be stabilised with treatment according to protocol, we postpone the application of reversal agents until the specific anticoagulant drug level has been determined with the appropriate laboratory test (discussed below) (fig. 1; central “severe bleeding” scenario). For severe bleeding events we use a time cut-off of 1 hour, because all anticoagulant drug levels can be determined and communicated within this timeframe at our institution, but this can be tailored to accommodate laboratory timings at other institutions. Any further patient intake of anticoagulant drugs is of course stopped in both these scenarios. The management of mildly bleeding, haemodynamically stable patients is shown in the right column of figure 1. Patients in this category may require surgery that can be scheduled 24 hours or more in the future. Generally, such patients will not receive reversal agents and anticoagulant intake will be stopped. Treatment decisions, however, for patients with a high thromboembolic risk are assessed on a case-by-case basis (see below).

It is important to note that a panel of screening laboratory tests (blood count, PT, aPTT, fibrinogen and thrombin time) as well as drug-specific assays (discussed below) are required before and after treatment to detect haemostatic disorders and to document treatment efficacy. The drug-level cut-offs for use of reversal agents are shown in figure 1 (left table) and are discussed below.

Anticoagulant drug levels and activity may be estimated by considering the time of last administration. This is, however, fraught with uncertainty as a result of incomplete medication records, the patient’s memory or mental health status and many other pitfalls.

Assessing the thrombotic risk

Patients with anticoagulant-associated bleeding or requiring urgent surgery are at increased risk of thromboembolic complications. This can arise as a result of the underlying disease, the acute event and, potentially, the application of reversal agents. Knowledge of the underlying thromboembolic risk is important for management [38]. Scientific societies have summarised epidemiological data and created risk categories with regard to peri-interventional procedures as reported by the American College of Chest Physicians (ACCP), but these data can also be considered in the case of bleeding as well [38]. Table 1 summarises the data and groups patients into three risk categories. In

patients with an intermediate or high thromboembolic risk, anticoagulant treatment should ideally be resumed within 24 hours, because the thromboembolic risk will increase further owing to procedural risks and the effect of reversal.

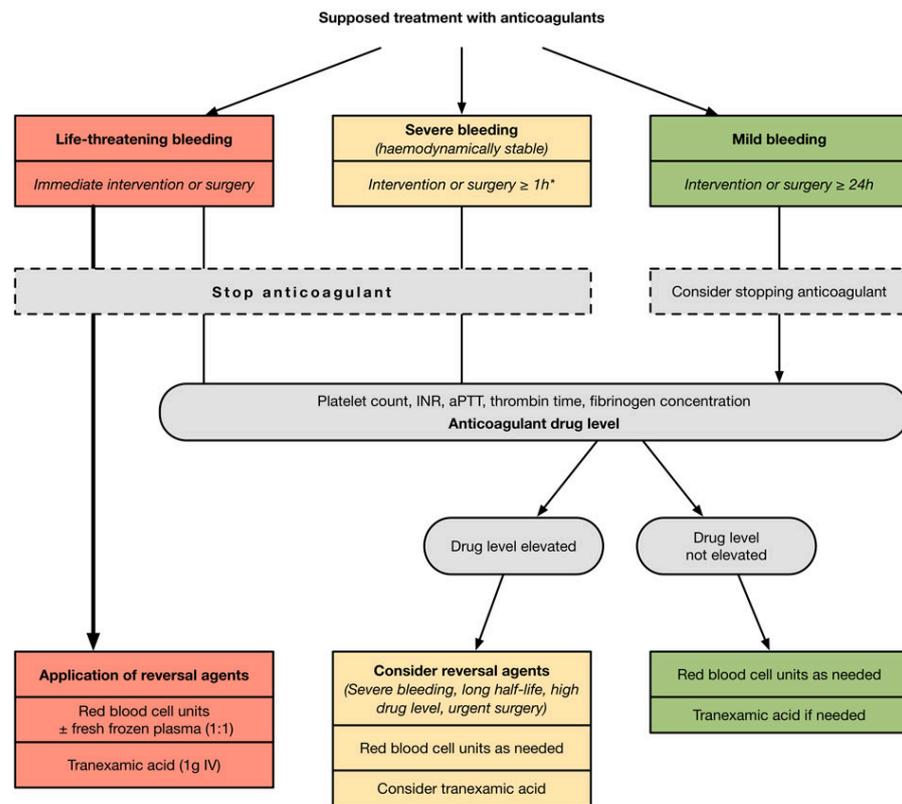
Anticoagulants and their reversal agents

Unfractionated heparin

Because of its short half-life, unfractionated heparin is still ubiquitously used in the perioperative setting and in the intensive care unit. Administered intravenously, its biologi-

cal half-life varies according to the dosage and is typically between 30 minutes and 2.5 hours [8]. The antithrombotic effect is usually gone 4 hours after discontinuation and surgery can be performed safely. Therefore, use of a reversal agent can be avoided in most cases. When reversal is required, protamine (as hydrochloride or sulphate) is employed. It is a small, basic cationic protein made from salmon sperm that binds to the anionic glycosaminoglycan heparin, acting as a stoichiometric reversal agent that can rapidly inactivate unfractionated heparin. One unit (0.01 mg) of protamine will neutralise approximately 1 unit of heparin. Protamine has been used worldwide every day in

Figure 1: Management of patients with anticoagulant-associated bleeding or urgent surgery. Proposal for a treatment algorithm detailing laboratory tests, cut-off values and administration of reversal agents. INR = international normalised ratio; aPTT = activated partial thromboplastin time; UFH = unfractionated heparin; LMWH = low molecular weight heparin; VKA = vitamin K antagonists. A larger version of this figure is downloadable from <https://smw.ch/en/article/doi/smw.2018.14598>.



Relevant anticoagulant drug-levels	
UFH:	aPTT > internal reference (e.g. 35 s) anti-Xa activity > 0.1 U/mL (thrombin time > internal reference, e.g. 30s)
LMWH:	anti-Xa activity > 0.15 U/mL
VKA:	INR > 1.3 (PT > internal reference; Quick-test < 70%)
Rivaroxaban:	anti-Xa activity > 30-50 ng/mL
Apixaban:	anti-Xa activity > 30-50 ng/mL
Dabigatran:	diluted thrombin time (or ecarin clotting time) > 30-50 ng/mL
Edoxaban:	anti-Xa activity > 30-50 ng/mL

* time interval until laboratory results are available

Reversal agents	
UFH:	<ul style="list-style-type: none"> • 1:1 units of protamin IV per unit UFH given in previous 3 hours (if stop within previous hour or anti-Xa activity > 0.35 U/mL), 5000 IU maximum • ½:1 units of protamin IV per unit UFH given in previous 3 hours (if UFH stop within previous 3 hours or anti-Xa activity > 0.1 U/mL), 2500 IU maximum
LMWH:	<ul style="list-style-type: none"> • 5000 IU protamine sulphate IV if therapeutic dose LMWH and last application < 8h or anti-Xa > 0.5 U/mL • 2500 IU protamine sulphate IV if therapeutic dose LMWH and last application < 12h or anti-Xa > 0.3 U/mL
VKA:	<ul style="list-style-type: none"> • Prothrombin complex concentrate: 2400 IU IV (or 30 U/kg body weight in patients below 30 kg) • Vitamin K 10 mg IV (daily until recovery)
Rivaroxaban/ Apixaban/ Edoxaban:	<ul style="list-style-type: none"> • Prothrombin complex concentrate: 50 IU per kg body weight IV
Dabigatran:	<ul style="list-style-type: none"> • Idarucizumab (Praxbind®) 2 x 2.5 g IV

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cardiac surgery for decades, but has well-recognised adverse events such as hypotension, pulmonary vasoconstriction, anaphylactoid reactions and thromboembolic complications [6, 8, 40]. In accordance with guidelines, we recommend the slow application of 1 unit of protamine (diluted in normal saline) per unit unfractionated heparin administered within the previous 3 hours if the heparin was stopped within <1 hour previously or in the case of anti-Xa activity > 0.35 U/ml (with a maximum dose of 5000 units). We propose the application of 0.5 units of protamine per unit unfractionated heparin, if the heparin was stopped within the previous 3 hours or anti-Xa activity is >0.1 U/ml [6, 8]. Protamine should not be given if the anti-Xa level is ≤0.1 U/ml. Protamine dosage can also be monitored using the point-of-care activated clotting time (ACT) test.

Low molecular weight heparin

Low molecular weight heparin consists of short chains of polysaccharides, which have a longer half-life (3–5 hours) than unfractionated heparin, and this permits a once or twice daily subcutaneous application for treatment and prophylaxis of thromboembolism [8]. However, owing to the molecular structure, only about 50% of the anticoagulant effect of low molecular weight heparin can be reversed by protamine, with no other reversal agent currently available. To counteract low molecular weight heparin anticoagulation with protamine, we suggest giving an intravenous dose of 5000 units of protamine slowly (preferably diluted) if a therapeutic dose of low molecular weight heparin was given within the last 8 hours, or if the anti-Xa activity is >0.5 U/ml (fig. 1, right table). A dose of 2500 units is given if a therapeutic dose of low molecular weight heparin were administered more than 8 but ≤12 hours previously or if anti-Xa activity is between 0.3 and 0.5 U/ml. We suggest withholding protamine in all other cases.

Vitamin K antagonists

Vitamin K antagonists block vitamin K epoxide reductase, among other effects, thus inhibiting synthesis of clotting factors II, VII, IX and X [7, 41]. This effect lasts for several days and administration of exogenous agents are required to stop effects of vitamin K antagonists in patients with active bleeding or prior to urgent surgery. Three agents are available to reverse vitamin K antagonist anticoagulant effects.

1. Vitamin K itself which provides the substrate for synthesis of the aforementioned clotting factors. Even though repeated doses of vitamin K should be given (in emergencies by slow intravenous injection; fig. 1, right table) [6], the earliest physiological

effect is 3 hours after administration, rendering this an inadequate treatment for immediate vitamin K antagonist reversal.

2. Fresh frozen plasma, which contains all coagulation factors at approximately physiological levels, has been used for vitamin K antagonist reversal for decades as it is inexpensive and widely available. However, treatment with fresh frozen plasma is associated with disadvantages [6], such as a considerable time delay until a correction of anticoagulant effects is observed, a large fluid load, which increases the risk of transfusion-associated circulatory overload, and also, albeit a very small, residual risk of transfusion-related acute lung injury. Thus, recent guidelines recommend vitamin K antagonist reversal with fresh frozen plasma only if the more specific reversal option, prothrombin complex concentrate (see below) is not available [6].
3. “Four-factor” prothrombin complex concentrate, which contains vitamin K-dependent coagulation factors (factors II, VII, IX, X; proteins S, C, Z) in variable amounts. Prothrombin complex concentrate is regarded as the vitamin K antagonist reversal agent of choice because of its rapid action, small volume load and low risk of transfusion reactions [6, 7, 42]. Its efficacy has been demonstrated in two randomised controlled trials focusing on patients with major bleeding [43] and urgent surgery [44]. In the setting of intracranial haemorrhage, several observational studies suggest superiority of prothrombin complex concentrate over fresh frozen plasma with regard to time until reversal, haematoma expansion, mortality and functional outcomes [6]. However, prothrombin complex concentrate may increase the risk of thromboembolic complications and not more than 2400 units should be given initially [45] (fig. 1, right table).

Dabigatran etexilate (Pradaxa®)

The main advantage of direct oral anticoagulants is their relatively short half-life, which in the case of dabigatran is 12 to 14 hours [46]. Thus, stopping the drug is sufficient in many cases of bleeding and urgent surgery. Nevertheless, development of a reversal agent was considered an important objective to improve patient care. Idarucizumab, a humanised monoclonal antibody fragment which binds to and inactivates dabigatran, has been developed and tested in a single-arm interventional study (n = 503) [36, 47]. Consecutive infusion of two vials, each containing 2.5 g of idarucizumab, reverses the anticoagulant effect of dabigatran rapidly and completely, both in laboratory testing and clinically. Thus, idarucizumab (Praxbind®) has been licenced

Table 1: Patient-related risk for thromboembolism according to anticoagulation indication; adapted from [38, 39].

Indication	Low risk*	Intermediate risk†	High risk‡
Mechanical heart valve	Bileaflet mechanical aortic valve without risk factors for stroke	Bileaflet mechanical aortic valve with risk factors for stroke	Any mechanical mitral valve Any caged-ball or tilting-disc valve Recent stroke/TIA (< 6 months)
Atrial fibrillation	CHA ₂ DS ₂ -VASc score 0 to 3	CHA ₂ DS ₂ -VASc score 4 to 7	CHA ₂ DS ₂ -VASc score 8 to 9 Recent stroke/TIA (<3 months) Rheumatic valvular disease
Venous thromboembolism	VTE >1 year	VTE within <1 year Recurrent VTE Active cancer	Recent VTE (<3 month) Severe thrombophilia¶

TIA = transient ischaemic attack; VTE = venous thromboembolism * risk of arterial thromboembolism < 4% per year; VTE < 2% per month † risk of arterial thromboembolism 4-10% per year; VTE 4-10% per month ‡ risk of arterial thromboembolism > 10% per year; VTE > 10% per month ¶ Deficiency of protein C, protein S, or antithrombin; antiphospholipid antibody syndrome

in the US (Food and Drug Administration, FDA), in Europe (European Medical Agency, EMA) and Switzerland (Swiss Agency for Therapeutic Products, Swissmedic). In our practice so far, application of idarucizumab has been simple, effective and safe, even in special situations [48]. We suggest administration of idarucizumab as the sole reversal agent in dabigatran-treated patients with severe bleeding or need for urgent surgery (fig. 1). Dialysis might be considered in patients with renal failure if idarucizumab is not available, but this only removes approximately two thirds of dabigatran and typically requires several hours [49].

Oral factor Xa inhibitors: rivaroxaban (Xarelto®), apixaban (Eliquis®) and edoxaban (Lixiana®)

The oral factor Xa inhibitors rivaroxaban, apixaban and edoxaban share important characteristics with dabigatran, in particular the short half-life (5–15 hours) [46]. Thus, stopping these drugs is adequate in many patients. Four-factor prothrombin complex concentrate has been suggested for nonspecific reversal of oral factor Xa inhibitors [10]. The effects have been variable in a number of animal and *ex-vivo* studies [50–53]. Prothrombin complex concentrate corrected the prothrombin time in healthy volunteers taking rivaroxaban, suggesting potential efficacy [54, 55]. In addition, a number of case reports exist [56–58]. Consistent with existing guidelines [6, 59], we apply prothrombin complex concentrate at a dosage of 50 U per kg body weight in patients with (a) life-threatening bleeding, (b) severe bleeding and relevant drug levels, or (c) need for urgent surgery and relevant drug levels (fig. 1). We generally do not use recombinant factor VIIa because of potential adverse events and a paucity of data.

Future perspectives

Two agents are currently under development for the reversal of factor Xa inhibitors. Andexanet alfa is a recombinant protein mimicking factor Xa but lacks any coagulant activity [60]. Andexanet alfa was effective and well tolerated in animal studies and healthy volunteers [60, 61]. Efficacy and safety have been tested in an open-label single-arm interventional study in elderly patients with acute major bleeding (interim report n = 67) [62]. A partial reversal of rivaroxaban, apixaban or enoxaparin was observed with regard to anti-Xa activity. Clinical efficacy was rated to be good in the majority of patients. However, a high rate of thromboembolic events, as well as deaths, have been ob-

served; this has been suggested to have resulted from the baseline thrombotic risk of the study patients (but it might indeed reflect a certain prothrombotic risk). Andexanet alfa was only moderately effective in reversing low molecular weight heparin in animal experiments [42, 63].

Ciraparantag is another agent developed to reverse the effect of factor Xa inhibitors [64]. It is a positively charged molecule that binds directly to these molecules. It has been tested in a phase I/II study in healthy volunteers [65]. Another study is ongoing in healthy volunteers taking rivaroxaban (NCT03172910). Clinical data obtained in patients are still lacking.

Measurement of anticoagulants

Monitoring of drugs requires established target ranges. The definition of a target range is based on comprehensive data on efficacy and safety outcomes at defined anticoagulant concentrations or activity levels. These criteria are met for vitamin K antagonists only. It is, however, common practice to monitor treatment with unfractionated heparin as well [8]. One of the main benefits of direct oral anticoagulants is that routine laboratory monitoring of anticoagulant activity is not necessary. All direct oral anticoagulants have been studied at fixed doses and no target ranges of drug levels are established. Knowledge of the anticoagulant drug level is, however, important in certain clinical situations [34] and the bleeding patient on anticoagulants is a good example where administration of reversal agents may be lifesaving. Drug concentrations were measured in some of the clinical studies, and an “expected range” for peak and trough levels have been published. For interpretation of test results, it is important to know whether they were measured at peak level (corresponding to the time point t_{max} after ingestion; table 2) or at the trough level (before the next application). Knowledge of the appropriate laboratory test and expected values is necessary to put results into context. In addition, treating physicians must be aware that large interindividual variabilities exist [66]. Table 3 illustrates appropriate laboratory tests for commonly available anticoagulants and reports target ranges or expected values.

Vitamin K antagonists

Prothrombin time (in Switzerland usually expressed in relation to standardised human plasma as a prothrombin ratio [PR] or Quick %) has been used for monitoring of vitamin

Table 2: Characteristics of commonly used anticoagulants: mechanism of action, pharmacokinetics and elimination.

Agent	Mechanism of action	t_{max}	Half-life	Elimination	Prolonged half-life
Rivaroxaban (Xarelto®)	Inhibits factor Xa	2–4 h	5–9 h	66% renal, 28% faecal	Older patients, renal impairment
Apixaban (Eliquis®)		3–4 h	8–15 h	30% renal, 70% faecal	Older patients, renal impairment
Edoxaban (Lixiana®)		1–2 h	9–10 h	50% renal	Older patients, renal impairment
Dabigatran (Pradaxa®)	Inhibits thrombin	0.5–2 h	12–14 h	Renal	Older patients, renal impairment
VKA (Marcoumar®, Sintrom®)	Inhibits vitamin K metabolism and reduces Factor II'	48–72 h+	ca. 160 h+	Hepatic metabolism, renal elimination	Multiple interactions with medications as well as nutritional interactions, impaired hepatic function
UFH	Activates antithrombin	30–120 min	30–150 min	Liver	Hepatic impairment, high doses
LMWH	Inhibits factor Xa	2–4 h	3–5 h	Mostly renal	Renal impairment

LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist * And other coagulation factors

K antagonists ever since the discovery of “sweet clover disease” [69]. Standardisation of thromboplastins using the international sensitivity index (ISI; based on a WHO standard) has enabled the implementation of the international normalised ratio (INR). Using the INR, the intensity of anticoagulation in individual patients is comparable between individual laboratories using different reagents worldwide. Results of large epidemiological studies have led to a precise definition of the optimal target range, which is 2.0 to 3.0 for most patients and indications [70]. INR values <1.3 or PR >70% Quick are regarded as sufficient for most surgical procedures and in the case of major bleeding.

Unfractionated heparin

It is common practice to monitor treatment with unfractionated heparin though there are major methodological concerns and very few clinical studies support this approach [8, 71]. The aPTT is recommended most often, but it is associated with important shortcomings: a large variability among different reagents and a high sensitivity to other factors that are prevalent in critically ill patients [72–74]. In contrast, chromogenic anti-Xa assays have been developed to determine heparin concentration accurately (though inconsistencies among reagents exist) [75]. Indeed, monitoring with anti-Xa assays was associated with fewer complications than monitoring with aPTT in a small randomised controlled trial [76]. The aPTT target range must be determined by every laboratory in relation to either anti-Xa levels or a protamine/heparin titration curve [8]. In our institution, the aPTT target range is 46–70 sec; the cut-off for surgery and major bleedings is the upper limit of the reference range (35 sec; fig. 1). In terms of anti-Xa activity, the target range is 0.35–0.7 U/ml and a relevant cut-off is 0.1 U/ml (fig. 1) [8]. The thrombin time is also a very sensitive laboratory test to monitor effects of unfractionated heparin, although its response curve is not

linear. However, a normal thrombin time essentially excludes the presence of unfractionated heparin.

Low molecular weight heparin

The dosage of low molecular weight heparin is based on body weight, and laboratory monitoring is usually not required [8]. However, knowledge of the plasma concentration is important in the case of major bleeding or urgent surgery. Drug-level adapted treatment is recommended in special situations such as pregnancy, extreme body weight or renal failure [77]. Anti-Xa activity is the most accurate test and is recommended for the measurement of low molecular weight heparin [8]. Target ranges are 0.6–1.0 U/ml (twice daily dosing) and 0.9–1.6 U/ml (once daily dosing) (fig. 1, left table). An appropriate cut-off for most operations is 0.15 U/ml.

Dabigatran etexilate

Thrombin time is a widely available assay and is extremely sensitive to the thrombin inhibitor, dabigatran. Even moderate dabigatran drug levels prolong thrombin time beyond its range of measurement [67]. Thus, a normal thrombin time rules out the presence of dabigatran. Adapted assays have been developed to measure dabigatran drug concentration across the normal therapeutic range [68]. This “diluted thrombin time” provides adequate accuracy, both as an in-house assay and as commercially available test kit (HEMOCLOT[®], HYPHEN BioMed, Neuville-sur-Oise, France) [78]. The ecarin clotting time is another assay developed to measure dabigatran activity, but important reproducibility issues remain [68]. Expected dabigatran concentrations at peak and trough are reported in table 3. Cut-off values, which are relevant for considering reversal agents or postponement of surgery, are 50 ng/ml in the case of major bleeding or surgery associated with a low bleeding risk, and 30 ng/ml in the case of life-threatening bleed-

Table 3: Laboratory tests, expected drug levels, critical drug levels and required time interval before intervention.

Drug	Laboratory assay	Expected drug levels* (dosage)	Proposed cut-off for surgery	Time interval before operations, interventions and spinal anaesthesia
Rivaroxaban (Xarelto [®])	Anti-Xa activity (PT/INR)	Peak: 270 ng/ml (189–419) [†] Trough: 26 ng/ml (6–87) [†] (20 mg daily)	<50 ng/ml for urgent surgery and low bleeding risk <30 ng/ml for high-risk surgery	≥24 h if bleeding risk of surgery is low/intermediate ≥48 h in case of high bleeding risk with surgery, elderly patients, renal failure [¶]
Apixaban (Eliquis [®])	Anti-Xa activity (PT/INR)	Peak: 171 ng/ml (91–321) [†] Trough: 103 ng/ml (41–230) [†] (5 mg twice daily)	<50 ng/ml for urgent surgery and low bleeding risk <30 ng/ml for high-risk surgery	≥24 h if bleeding risk of surgery is low/intermediate ≥48 h in case of high bleeding risk with surgery, elderly patients, renal failure [¶]
Edoxaban (Lixiana [®])	Anti-Xa activity (PT/INR)	Peak: 170 ng/ml (120–250) [‡] Trough: 22 ng/ml (10–40) [‡] (60 mg daily)	<50 ng/ml for urgent surgery and low bleeding risk <30 ng/ml for high-risk surgery	≥24 h if bleeding risk of surgery is low/intermediate ≥48 h in case of high bleeding risk with surgery, elderly patients, renal failure [¶]
Dabigatran (Pradaxa [®])	Diluted thrombin time Ecarin clotting time (thrombin time)	Peak: 184 ng/ml (64–443) [†] Trough: 90 ng/ml (31–225) [†] (150 mg twice daily)	<50 ng/ml for urgent surgery and low bleeding risk <30 ng/ml for high-risk surgery	≥36 h if bleeding risk of surgery is low ≥48 h in the event of high bleeding risk with surgery, elderly patients, renal failure [¶]
VKA (Marcoumar [®] , Sintrom [®])	INR	2.0–3.0 (target range)	INR <1.3	>5 to 7 days
UFH	aPTT Anti-Xa activity	0.35–0.7 U/ml (target range)	aPTT <35 s or anti-Xa ≤0.1 U/ml	≥4–6 h (longer in case of renal failure, elderly patients, subcutaneous application)
LMWH	Anti-Xa activity	0.6–1.0 U/ml (target range twice daily) 0.9–1.6 U/ml (target range once daily)	Anti-Xa ≤0.15 U/ml	≥12 h (50–100 U/kg body weight) ≥24 h (150–200 U/kg body weight) ≥48 h in the case of high bleeding risk with surgery, elderly patients, renal failure [¶]

aPTT = activated partial thromboplastin time; INR = international normalised ratio; LMWH = low molecular weight heparin; PT = prothrombin time; UFH = unfractionated heparin * adapted from [67, 68] † median; 5th to 95th percentile ‡ median; interquartile range ¶ in patients with renal failure, the interruption interval shall be extended by 1 to 2 days (depending on the severity and the bleeding risk of the intervention) or drug level determined using an appropriate laboratory test

ing or surgery associated with a high bleeding risk (table 3; fig. 1) [37].

Oral factor Xa inhibitors: rivaroxaban, apixaban, and edoxaban

Factor Xa inhibitors affect the PT and PT-based assays, and therefore these assays have been proposed to estimate drug levels [67]. However, most authors do not suggest use of PT-based assays because of limited sensitivity and specificity, and large variation among different reagents [68]. However, the point-of-care coagulometer CoaguChek[®] XS detects peak rivaroxaban levels with high sensitivity [79]. Anti-Xa assays have been developed for the measurement of oral factor Xa inhibitors [80, 81]. A high accuracy and consistency has been demonstrated, particularly for rivaroxaban plasma concentrations [66]. Expected drug levels at peak (3 hours after intake) and trough (24 hours after intake) with a 20 mg dose are shown in table 3. Scientific societies recommend considering reversal agents or postponement of surgery at an anti-Xa level of 50 ng/ml in the case of major bleeding or urgent surgery, and at 30 ng/ml in the case of life-threatening bleeding or surgery with a high risk of bleeding [37].

Management of anticoagulants in the case of urgent surgery or interventions

The periprocedural risk of patients treated with antithrombotic drugs is determined by four main issues, which must be considered: (1) the thromboembolic risk of the underlying disease which corresponds to the indication for anticoagulation (patient-related risk), (2) the thromboembolic risk associated with the planned surgery or the clinical situation (surgical risk factors), (3) the bleeding risk due to the anticoagulant drugs and the drug level at the time of surgery, and (4) the bleeding risk of the surgery and the potential consequences of a bleeding complication. All issues are discussed in detail elsewhere [38, 39, 82, 83].

Patient-related thromboembolic risk is discussed above and summarised in table 1 [38, 39]. Patients with a high risk should not be left without anticoagulation therapy for a long period of time [38, 39]. The same holds true for patients undergoing a surgical procedure with a high thromboembolic risk (cancer surgery, cardiovascular surgery, extensive abdominal, thoracic or pelvic surgeries, hip fracture, or major trauma) [38, 39]. Nevertheless, a prophylactic dose of anticoagulation treatment should be started about 6 hours postoperatively and a therapeutic dose should be started about 24 hours postoperatively.

The third important aspect is the bleeding risk of the intended surgery or intervention. No interruption of anticoagulation treatment is necessary in procedures with minimal bleeding risk, such as cataract surgery and most dermatology or dental procedures; for colonoscopy, gastrointestinal endoscopy, or arthroscopy decisions should be made on a case by case basis [39]. In contrast, anticoagulation must be interrupted adequately prior to surgeries with a high bleeding risk (intracranial or intraspinal surgery, other major surgery in general).

In the event of emergency surgery and a high bleeding risk (potentially also in cases with an intermediate bleeding risk), use of reversal agents is necessary in virtually all patients treated with a vitamin K antagonist. Specific drugs

have been discussed above. Reversal agents are rarely necessary in the case of single anticoagulation treatment with unfractionated heparin. Surgery can usually be conducted 4 hours after stopping unfractionated heparin. Determination of anti-Xa activity can help to adapt the time interval (in the case of high urgency or renal impairment; see table 3). When low molecular weight heparin has been used and paused, most operations can be done after 12 hours (prophylactic dose) or 24 hours (therapeutic dose; table 3). Again, determination of anti-Xa levels can help to adapt the time interval. Protamine can be considered in special situations (table 3) and andexanet or ciraparantag might be options in the future. Manufacturers of direct oral anticoagulants recommend relatively long intervals between administration of the last dose and interventions, up to 72 hours in the case of dabigatran. However, clinical data from large registries suggest that short-term interruption is a safe approach [82]. Considering these data together with manufacturers' recommendations, we suggest the time intervals mentioned in table 3. Again, determination of the drug level can help to adapt the waiting period in order to reduce or prolong the time to intervention (table 3).

Conclusions

Management of patients with anticoagulant-associated bleeding or urgent surgery is challenging. We present a simple treatment algorithm that is based on the assessment of severity and urgency as well as the measurement of drug levels. In addition, we provide information regarding appropriate drug levels and time intervals to follow in emergency situations. If implemented as a treatment protocol, this algorithm might help emergency and perioperative teams to provide high quality care and to minimise inherent risks of bleeding and thrombosis.

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