Update on Perioperative Antithrombotic Management

Daniel Boschitz[1] · Dominika M. Fastowiec[2] · Daniel Bolliger[2]

Abstract

Purpose of the Review In this review, we discuss the recent studies and recommendations on the perioperative management of oral anticoagulant and antiplatelet drugs.

Recent Findings In elective surgery, clear and simple recommendations exist for oral anticoagulants and antiplatelet drugs. The shorter stopping intervals with direct-acting oral anticoagulants have simplified the perioperative management compared with vitamin K antagonists. The specific use of laboratory testing is suggested for bleeding patients treated with antithrombotic drugs or for emergent surgery. The postoperative prevention of thromboembolism has gained more attention, and individualized strategies including extended treatment or use of aspirin has been suggested in specific patients. The use of risk scores might be helpful for decision making.

Summary The perioperative management of anticoagulants and antiplatelet drugs is still challenging, especially in urgent or emergent surgery. The use of individualized strategies to prevent perioperative bleeding and thromboembolic events rather than a "one-size-fits-all" approach is suggested.

Keywords Anticoagulants · Antithrombotic · Antiplatelet agents · Thromboembolism · Prophylaxis · Perioperative · Surgery

Introduction

Antithrombotic drugs are frequently used to prevent or treat various prothrombotic disorders like acute coronary syndrome (ACS), stroke, peripheral vascular disease, atrial fibrillation (AF), and venous thromboembolism (VTE). The perioperative management of patients on anticoagulants and antiplatelet therapy is a common challenge for physicians despite guidance by different recent guidelines [1, 2••].

From a pathophysiological view, a thrombus mainly consists of fibrin and platelets. Fibrin is a protein formed by cleavage of fibrinogen by thrombin. Fibrin form a mesh that traps different blood cells, mainly red blood cells and platelets. Platelets forms clumps that add to the mass of the thrombus. Fibrin and platelets interact via glycoprotein IIb/IIIa receptors expressed on the platelet surface after their activation thereby preventing the thrombus from falling apart. Differences in formation between venous and arterial clots have been suggested, with increased thrombin and fibrin generation in venous clot formation and exaggerated platelet activation in atherosclerosis [3]. The two main classes of antithrombotic drugs on the market are anticoagulants and antiplatelet drugs. Whereas anticoagulants slow down clot formation by controlling and reducing thrombin generation and formation of fibrin-stabilized clots, antiplatelet drugs prevent or temper inadvertent platelet activation and aggregation, thereby minimizing the formation and growth of stable clots [4, 5••].

Daniel Boschitz and Dominika M. Fastowiec contributed to this manuscript and should be listed as first authors.

✉ Daniel Bolliger
  daniel.bolliger@usb.ch

  Daniel Boschitz
  daniel.boschitz@usb.ch

  Dominika M. Fastowiec
  dominikamarta.fastowiec@usb.ch

[1] Clinic for Anaesthesiology, Intermediate Care, Prehospital Emergency Medicine, and Pain Therapy, University Basel Hospital, Basel, Switzerland

[2] Clinic for Anaesthesiology, Intermediate Care, Prehospital Emergency Medicine, and Pain Therapy, University Basel Hospital, University of Basel, Basel, Switzerland

In this review, we attempt to evaluate the recent findings in in the perioperative management of patients treated with oral anticoagulants or antiplatelet drugs.

Search Strategy

An extensive English literature search in PubMed was performed using the following terms: "antithrombotic(s)" AND "anticoagulant(s)" AND "perioperative". This search resulted in 456 publications. We focused on recent publications within the last 5 years resulting in 194 publications. Two authors reviewed titles and abstracts and identified 57 publications of potential importance, which were critically reviewed by all authors and eventually included in the present publication.

Human and Animal Rights

All reported studies and experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standers (including Helsinki declaration and its amendments, institutional and national research committee standards, and international, national, and institutional guidelines.

Estimating Perioperative Thromboembolic and Bleeding Risk

Exposure to antithrombotic drugs places patients at potential risk for bleeding in the perioperative period. This risk must be balanced against the increased endogenous risk of thromboembolism, especially after surgical procedures. Bleeding and thromboembolic complications might be related to the timing of preoperative stopping of anticoagulants and antiplatelets and on postoperative resumption. However, patient- and surgery-related factors including advanced age, comorbidities, surgical technique, and emergent surgery are potentially more important [6]. Patients treated with anticoagulants and antiplatelets are typically older and often have several comorbidities, including cancer. Preoperative identification and estimation of a patient's individual risk for thromboembolism or bleeding by using specific scores to estimate perioperative bleeding and thromboembolism risk seems appealing. Common risk scores for estimating thromboembolic risk include the CHA_2DS_2VASc (Table 1), the Caprini (Table 2), and the Rogers score [7–9]. For estimating the bleeding risk, the bleeding assessment tool (BAT) and the HAS-BLED score might be used [10–12].

The CHA_2DS_2VASc score is based on the $CHADS_2$ score (Table 1), which was developed to calculate the stroke risk in AF patients. Although the $CHADS_2$ and CHA_2DS_2VASc scores have been developed, evaluated, and primarily used

Table 1 $CHADS_2$ and CHA_2DS_2VASc scores

$CHADS_2$ parameters	Score	CHA_2DS_2VASc parameters	Score
CHF	1	CHF or LVEF $\leq 40\%$	1
Hypertension	1	Hypertension	1
Age $>$ 75 yrs	1	Age $\geq$ 75 yrs	2
Diabetes	1	Diabetes	1
Stroke or TIA	2	Stroke or TIA or thrombembolism	2
		Vascular disease	1
		Age 64–75 yrs	1
		Female	1

Modified after [54]

Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack

in non-surgical patients, they have also been used to estimate the perioperative stroke risk [13].

The Caprini risk assessment model (RAM) or score is more commonly used in the perioperative setting and has been validated in medical and surgical patients worldwide to identify patients at high risk for venous thromboembolism [8]. The Caprini RAM uses about 40 patient-related risk factors, weighted with 1 to 5 points (Table 2). The overall score can be used to guide postoperative management of pharmacological and/or mechanical prophylaxis [8]. A Caprini score < 2 is associated with a low risk, whereas a score > 5 suggests a high risk of developing VTE. Given that the Caprini RAM includes some modifiable risk factors, including the use of general anesthesia and neuromuscular relaxants, considering it would be valuable for the preoperative assessment. However, its use in clinical practice might be limited. For example, a surgery time > 45 min is associated with an increased thrombosis risk, but no further risk stratifications are made for duration of surgery. Further, the calculation of the score is time-consuming and might need the help of an electronic system. To overcome these limitations, the modified Caprini RAM has gained some attention [7]. The modified score includes only the 15 most important factors and can, therefore, be calculated more readily. However, neither the original nor the modified Caprini have gained major acceptance in daily anesthesia practice. Finally, the Rogers Score has also been specifically developed to evaluate the risk of perioperative thromboembolism [9]. This score considers several variables including sex, American Society of Anesthesiologists (ASA) score, work-relative value units for surgery (a surrogate for complexity), and multiple laboratory findings. Like the Caprini RAM, the Rogers score is not regularly used in perioperative clinical practice.

To evaluate the perioperative bleeding risk, mainly two scores were suggested: the HAS-BLED score and the BAT,

Table 2 Caprini Score

1 point for each:	2 points for each:
Age 41–60 yrs	Age 61–74 yrs
Minor surgery (< 45 min)	Major surgery (> 45 min)
Major surgery (> 45 min) in the last month	Current or past malignancies
Visible varicose veins	Confined to bed > 72 h
History of inflammatory bowel disease	Central venous access (including ports)
Swollen legs	Immobilizing plaster cast
BMI > 25 kg/m^2	**3 points for each:**
History of myocardial infarction	Age ≥ 75 yrs
Congestive heart failure	History of DVT or PE
Serious infection	Family history of DVT or PE
Lung disease	Family or personal history of positive blood tests indicating increased clotting risk
Restricted mobility	**5 points for each (now or within past month):**
Insulin-dependent diabetes mellitus	Knee or hip joint replacement
Chemotherapy	Broken pelvis, hip, or leg
Blood transfusion	Serious trauma (multiple bone fractures)
For women only:	Spinal cord injury resulting in paralysis
Oral contraceptive	Experienced a stroke
Pregnancy or postpartum	
History of unexplained or recurrent miscarriage	

Modified after [55]

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism

which is promoted by the International Society of Thrombosis and Haemostasis (ISTH) [11]. HAS-BLED is an acronym derived from the following risk factors: **h**ypertension, **a**bnormal renal or liver function, **s**troke, **b**leeding history, **l**abile international normalized ratio (INR), **e**lderly, and **d**rug or alcohol abuse. Presence of each item adds 1 point. BAT has been used as a research tool and has mainly been evaluated in its ability to identify non-surgical patients with von Willebrand disease (vWD). Its usefulness in the perioperative setting is questionable, and data are scarce. An exact cut-off for an abnormal score with increased bleeding perioperative bleeding risk has not been established for neither HAS-BLED nor BAT and appears to vary with patient characteristics, age, gender and clinical setting [10, 12]. In agreement, a secondary analysis of the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study found no reversible risk factors for perioperative bleeding in patients treated with direct-acting oral anticoagulants (DOACs) who underwent elective surgery after an adequate interruption interval [6].

The application of a structured patient questionnaire evaluating bleeding and thromboembolic risk, however, is recommended before any surgical or invasive procedure. It is also suggested over the use of conventional coagulation screening such as activated partial thromboplastin time (aPTT), prothrombin time (PT) and/or platelet count [14, 15••]. The optimal questionnaire has not yet been defined, and such questionnaires often have their limitations. For example, while they usually include the intake of anticoagulants and antiplatelet drugs, they do not specifically respect the length of stopping intervals.

Preoperative Management in Elective Surgery

Direct-Acting Oral Anticoagulants (DOAC)

DOACs, also known as novel or non-vitamin K antagonist oral anticoagulants (NOACs), are represented by two groups: the direct thrombin inhibitor dabigatran and direct inhibitors of activated factor X, among them rivaroxaban, apixaban and edoxaban. Other DOACs might be or will come on market in specific countries. Dabigatran was approved by the US Food and Drug Administration (FDA) in 2010 as the first DOAC, but today the market is dominated by the direct Xa inhibitors. DOACs have rapidly gained ground and will probably replace classic vitamin K therapy in most patients with or at risk for AF and VTE in the US and Europe [1], but they are contraindicated in several high-thrombotic risk conditions such as mechanical heart valve prosthesis or antiphospholipid syndrome. DOACs have many advantages compared to vitamin K antagonists (VKA), including more reliable pharmacokinetics and -dynamics, fewer interactions

with other drugs and food, and no need for regular laboratory testing [16].

The perioperative handling of DOACs in elective surgery is rather simple [2••]. It is recommended to interrupt administration of DOACs by an interval corresponding to four elimination half-lives based on the perioperative bleeding and thrombotic risk evaluation. Due to the short half-life, interruption intervals of 24 to 48 h are commonly sufficient to eliminate the anticoagulant effects of DOACs depending on the invasiveness and bleeding risk of the surgery [17•, 18•]. Bridging is not recommended, because necessary period of discontinuation before surgery is short and the restoration of clinical effect upon re-initiation is within a few hours with no relevant procoagulant effect [18•]. Reduction in bleeding risk seems to be the primary determinant of the DOAC discontinuation strategy for major surgery or interventions when faced with a potentially increased prothrombotic risk.

A recent study showed that DOAC-treated patients with active cancer were at increased risk for major surgical bleeding [19]. However, increased bleeding tendency might be mainly attributable to complex surgical procedures associated with higher bleeding risk [19]. Thus, adapted perioperative management of DOAC therapy does not seem to be necessary in cancer patients.

Vitamin K Antagonists

VKAs, also called coumarins, inhibit the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) by irreversibly binding to the liver enzyme epoxide reductase and reducing available vitamin K for enzymes depending on it. While warfarin is the VKA of choice in the US and UK, phenprocoumon and acenocoumarol are more commonly used alternatives in the rest of Europe. VKAs were the only reliable oral anticoagulant for years and were used for *I)* the prevention of stroke in patients with atrial fibrillation, *II)* the prevention and therapy of thromboembolism in patients with deep vein thrombosis and pulmonary embolism, and *III)* the prevention of thromboembolism in patients with valvular heart disease or prosthetic cardiac valves. The latter indication remains restricted to therapy with VKAs [20, 21], whereas in most other indications the use of DOACs has become standard.

The pharmacokinetics and -dynamics of VKAs are associated with several major concerns and drawbacks such as a low therapeutic index, delayed onset and offset of action due to the indirect mechanism, and many drug and food interactions necessitating constant monitoring and adjustment. Effect half-lives of different coumarins are drug-specific and span from about 36 h for warfarin and acenocoumarol to a least 72 h for phenprocoumon with relevant variability. These specific pharmacologic aspects complicate the

perioperative management of VKAs [1]. The recommended interruption of VKA therapy for procedures and surgical interventions with moderate or high bleeding risk and low thrombotic risk of the patient is 3–5 days before surgery for warfarin and acenocoumarol and 5–7 days for phenprocoumon. Usually, the intended target value of international normalized ratio (INR) is < 1.5 at the time of an invasive procedure or surgery, especially in those with increased bleeding risk. Given the widely variable half-lives and different therapeutic INR targets, it is suggested to determine INR values in most patients before surgery or interventions. VKA may be continued in patients undergoing minor procedures with a low or minimal bleeding risk [2••].

Perioperative bridging is not recommended in patients with low risk of thromboembolism (< 4%/y risk of arterial thromboembolism or < 2%/month risk of VTE) (Table 3). Typically, patients with bi-leaflet aortic valve replacement without major risk factors for stroke or patients with a CHA_2DS_2VASc score ≤ 4 or $CHADS_2$ score ≤ 2 belong to this category [2••]. According to present guidelines, perioperative bridging with low-molecular weight heparin or unfractionated heparins should be used in patients with moderate and especially with high risk undergoing major surgery [2••].

Antiplatelet Drugs

Antiplatelet therapy plays a critical role in the prevention and treatment of major cardiovascular diseases triggered by thrombosis. Despite antiplatelet therapy, recurrent thrombotic events may occur. In addition, the increased bleeding risk with perioperatively continued antiplatelet therapy remains a problem [22]. Aspirin is the oldest and most commonly used antiplatelet agent and irreversibly inhibits cyclooxygenase-1, thereby blocking the formation of thromboxane A_2 and platelet activation. More recently, inhibitors of adenosine diphosphate receptor $P2Y_{12}$ including clopidogrel, prasugrel, ticagrelor, and cangrelor have come on the market. These drugs more efficiently prevent the activation and aggregation of platelets than aspirin (Table 4). Other platelet inhibitors such as phosphodiesterase inhibitors or glycoprotein IIb/IIIa inhibitors are rarely used today.

Aspirin is usually continued in the perioperative period, especially in cardiac surgery [23] and in patients with secondary thrombosis prophylaxis in non-cardiac surgery. However, the latter approach might be associated with a slightly increased bleeding risk [24]. In contrast, $P2Y_{12}$ inhibitors are usually stopped before elective surgery to reduce the perioperative bleeding risk. The suggested stopping intervals for prasugrel, clopidogrel, and ticagrelor are 7, 5, and 3 days before surgery, respectively [1, 23]. Of note, the interruption interval should be individually adapted according to the patient's risk of arterial and/or coronary stent thrombosis,

Table 3 Risk Stratification for Patient-specific Periprocedural Thromboembolism

Risk Category	Mechanical heart valve	Atrial fibrillation	VTE
High (> 10%/yr risk for ATE or > 10%/mo risk of VTE)	-Mitral valve with major risk for stroke* -Caged ball or tilting-disc aortic valve	-$CHA_2DS_2VASc \geq 7$ -$CHADS_2$ 5–6 -Rheumatic valvular heart disease	-Recent VTE (< 3 mo) -Severe thrombophilia -Antiphospholipid antibodies
Moderate (4%-10%/year risk for ATE or 2%-10%/month risk for VTE)	-Mitral valve without major risk for stroke -Bi-leaflet aortic valve with major risk for stroke*	-CHA_2DS_2VASc 5–6 -$CHADS_2$ 3–4	-VTE within last 3–13 mo -Recurrent VTE -Non-severe thrombophilia
Low (< 4%/yr risk for ATE or < 2%/mo risk for VTE)	-Bi-leaflet aortic valve with major risk for stroke	-CHA_2DS_2VASc 1–4 -$CHADS_2$ 0–2	-VTE > 12 mo ago

Modified after [54]

* Includes: atrial fibrillation; prior stroke; prior valve thrombosis; rheumatic heart disease; hypertension; diabetes mellitus; congestive heart failure; age ≥ 75 years

For $CHADS_2$ and CHA_2DS_2VSACc scores please refer to Table 1

Abbreviations: ATE, arterial thromboembolism; VTE, venous thromboembolism

Table 4 Comparison of pharmacodynamic and pharmacokinetic properties of platelet inhibitors

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Administration	po, iv	po	po	po	iv
Frequency	od	od	od	bid	continuous
Platelet inhibition	low to moderate	moderate	strong	strong	strong
Bioavailability	po: 40–50%, iv: 100%	30–50%	80%	36%	100%
Pharmacological binding	irreversible	irreversible	irreversible	reversible	reversible
Onset of action	po: 2–4 h, iv: 10 min	1–3 h	1–2 h	1–2 h	10 min
Half-life (active metabolites)	20–30 min	30 min	7 h	8.5 h	3 min
Duration of effects	3–7 d	5–10 d	7–10 d	3–5 d	30 min

Modified after [25, 56, 57]

Abbreviations: bid, twice daily; iv, intravenous; od, once daily; po, peroral

the specific antiplatelet agent, and the invasiveness and bleeding risk of the planned procedures. The use of platelet function monitoring might be helpful in specific situations to optimize the timing of surgery and minimize the perioperative bleeding and ischemic risk [25, 26].

Preoperative Management in Emergent Surgery

Annually, about 10% of patients on anticoagulant therapy require invasive procedures or surgery [27, 28••]. In patients requiring urgent surgery or with severe organ- and life-threating bleeding, the rapid reversal of anticoagulants and antiplatelet agents remains a clinical challenge. In patients with recent intake of VKAs, it is recommended to administer vitamin K to accelerate the hepatic production of coagulation factors II, VII, IX, and X [29]. The latter requires several hours, and the administration of prothrombin complex concentrates (PCC) at a dose of 20–30 IU/kg is suggested

in emergent surgery [30]. However, the use of PCCs might be associated with increased risk of thromboembolic events, especially in patients at risk for them. The use of high doses of PCC (≥ 50 IU/kg) or activated concentrates is, therefore, discouraged.

In patients on DOAC therapy requiring emergent surgery, the optimal treatment strategy remains disputed, despite the recent availability of specific antidotes for DOAC (idarucizumab for reversal in patients treated with dabigatran and andexanet alfa for reversal in patients treated with direct factor Xa inhibitors) [28••]. So far, no results from prospective randomized trials comparing direct reversal agents with an unspecific agent to enhance the hemostatic function of the coagulation system, such as PCCs, activated PCCs, or recombinant activated factor VII (rFVIIa), has been published, and the majority of publications are uncontrolled and observational studies [28••]. Of note, the postponement of the surgical procedure or intervention to allow for elimination of the DOAC should be evaluated [28••]. The optimal management might depend on multiple factors including the

anticipated bleeding risk, localization of bleeding, urgency of surgical interventions, and cost-efficacy. Timing of the last DOAC intake, renal function, and determination of anti-coagulant activity must also be considered.

In patients with recent intake of antiplatelet agents, the administration of platelet concentrates is usually the therapy of choice. According to plasma half-time of active metabolites (Table 3), effective treatment should be successful in patients with last intake of clopidogrel or prasugrel > 12 h. However, platelet transfusion might not be effective in promoting clotting in patients with recent intake of the reversible $P2Y_{12}$ inhibitor ticagrelor when relevant plasma drug concentrations are present [31]. Other procoagulant hemostatic interventions including administration of antifibrinolytic agents, desmopressin or rFVIIa might be considered [32]. However, it is still unclear whether administration of platelet concentrates and procoagulant interventions should be given prophylactically during urgent surgery or only when relevant bleeding occurs.

In patients with recent intake of ticagrelor requiring urgent cardiac surgery with cardiopulmonary bypass, the use of CytoSorb® absorber has been suggested to reduce ticagrelor levels and associated bleeding risk [25]. A phase I study in healthy volunteers evaluated the safety and efficacy of ticagrelor neutralization by a monoclonal antibody fragment (bentracimab) [31]. Recently, the results of a prespecified interim analysis of a prospective single-arm study evaluating bentracimab in 129 patients treated with ticagrelor requiring urgent surgery or having major hemorrhage were published [33]. The authors reported an immediate reversal of the antiplatelet effect of ticagrelor within 5 to 10 min, which was sustained for more than 24 h. Effectiveness was evaluated by platelet function testing as well as clinically adjudicated hemostasis to be good in > 90% of patients [33]. Potentially, treatment with bentracimab will be prove beneficial in surgical patients on ticagrelor therapy requiring emergent coronary or vascular surgery.

Coagulation Testing

Routine coagulation tests have been used for many years in the perioperative setting to identify patients with bleeding disorders or to predict perioperative bleeding to allow for treatment to be given or to prevent it. However, routine preoperative testing in unselected patients is expensive and rarely identifies significant abnormalities. Accordingly, it is not recommended by experts [34, 35] or by guidelines [14, 36]. Selection of patients for preoperative coagulation testing should include family and bleeding history, concomitant use of antiplatelet and anticoagulant therapy, type of surgery, and ideally a physical examination.

In patients on VKA, the laboratory INR testing to determine restoration of hemostatic function by INR values < 1.5 is suggested before surgery associated with increased bleeding risks (Table 5) [2••]. In patients on DOAC, the use of standard coagulation testing including PT and aPTT is discouraged as they perform poorly in safely identifying patients with negligible DOAC levels [28••, 37]. In patients on DOAC therapy who require an urgent or emergent surgery and in those at high risk of elevated DOAC plasma levels, or at risk of severe complications from bleeding, determination of DOAC levels is suggested [28••]. Drug-specific, calibrated anti-Xa assays should be used as a gold standard to determine DOAC levels. If not available, the chromogenic anti-Xa test calibrated for unfractionated heparin can adequately estimate the activity of rivaroxaban, apixaban and edoxaban [28••]. For semi-quantitative assessment of dabigatran, the diluted thrombin time (dTT) is recommended as a gold standard. Alternatively, the ecarin-clotting time or the thrombin time can be used to exclude relevant activity of dabigatran [28••]. For optimal testing of DOAC plasma levels, last DOAC intake should not be within the last 12 h. Finally, it is not recommended to perform routine direct oral anticoagulant level measurements in patients with DOAC intake stopped 24 to 48 h before surgery based on bleeding risk [6]. These findings resulted in a secondary analysis of the PAUSE study [18•].

In patients receiving antiplatelet drug therapy undergoing an elective invasive procedure or surgery, the routine use of platelet function testing prior to the surgery is not suggested to guide perioperative antiplatelet management [1, 23, 25]. However, platelet function monitoring might be beneficial in specific situations to guide preoperative stopping time of antiplatelets and to balance the risk between intraoperative bleeding and ischemic events [25, 26, 38].

Table 5 Suggested laboratory testing of anticoagulants in urgent surgery

Drug	First choice	Second choice
Heparin	anti-Xa activity*	aPTT, TT
LMWH	anti-Xa activity*	-
Rivaroxaban	drug-specific anti-Xa activity	anti-Xa activity*
Apixaban	drug-specific anti-Xa activity	anti-Xa activity*
Edoxaban	drug-specific anti-Xa activity	anti-Xa activity*
Dabigatran	diluted thrombin time	ECT, thrombin time
Platelet inhibitors	-	-

* anti-Xa activity calibrated for heparins

Abbreviations: aPTT, activated partial thromboplastin time; TT; thrombin time; ECT, ecarin-clotting time; LMWH, low molecular weight heparins

Postoperative Management of Anticoagulants

Thromboembolic risk increases in the postoperative period due to acute phase reaction associated with increased thrombin generation, fibrin formation, and platelet reactivity. The need for an effective anticoagulation to reduce the risk of thromboembolism is obvious but is hampered by the significantly increased bleeding risk and complications from bleeding in the early postoperative period. An effective and balanced anticoagulation is crucial for optimal clinical outcomes. In orthopedic surgery, the incidence of VTE can reach up to 60% of patients without VTE prophylaxis, and this incidence has been lowered to about 1%-10% depending on the included patient population and risk factors [39]. Of note, evidence for optimal VTE prophylaxis is limited and primarily based on clinical consensus. Accordingly, there might be a wide variance in practices of VTE prophylaxis among institutions [40]. However, current clinical practice guidelines recommend both mechanical and pharmacological interventions for VTE prophylaxis [41, 42]. These guidelines do not recommend specific thromboprophylaxis agents. The optimal choice of drug, dosing, and duration of VTE prophylaxis is, therefore, still controversial. Available evidence suggests that the use of DOACs is as effective as but safer than low molecular weight heparins (LMWH). In patients with indications for therapy with VKA, these drugs offer a further alternative in the postoperative period.

Recent studies have raised the ambiguity about optimal postoperative anticoagulation. A matched case–control study in patients undergoing different surgical procedures found that the interruption of DOACs as compared to warfarin without bridging was associated with a higher incidence of 30-day postoperative bleeding (minor, major, and clinically relevant non-major). However, there was no difference in bleeding or thromboembolic events between patients with warfarin receiving bridging therapy and DOAC-treated patients [43]. A double-blinded randomized trial in patients with atrial fibrillation or mechanical heart valves who had warfarin interrupted for a surgical or invasive procedure found no significant benefit of postoperative bridging with LMWH to prevent major thromboembolism [44•]. Of note, the preoperative warfarin treatment was stopped 5 days before surgery and bridged with LMWH at therapeutic doses in all patients and was restarted on the first postoperative day at doses twice the usual daily dose [44•].

Considering the evolving landscape of VTE prophylaxis and the availability of multiple regimens, the intriguing question arises: How to tailor these interventions to individual patients, especially with respect to type of drug and duration [39]? Instead of standardized uniform VTE prophylaxis, the use of VTE risk scores such as the Caprini RAM might help to modify specific antithrombotic medication and its duration. Finally, the advancement in surgical and anesthetic techniques and the implementation of early recovery after surgery (ERAS) programs have led to reduced duration of surgery, earlier mobilization, and shorter hospital stays or even earlier hospital discharge. These factors might contribute to lower incidence of thromboembolic events.

Prolonged Antithrombotic Therapy

Patients with high to very high-risk categories in VTE risk scores (for example, Caprini score > 5) are candidates for combined mechanical and pharmacological VTE prophylaxis, intensified therapy, and prolonged prescription of anticoagulation in the postoperative period. The extended VTE prophylaxis has recently gained specific attention, especially in patients undergoing cancer-related surgery [40, 45]. The latter seems important as a major part of VTE events occur during the post-discharge follow-up period. In a large retrospective database analysis including > 14,000 patients undergoing lung cancer surgery, 44% of identified VTE occurred after hospital discharge [46]. Accordingly, an extended prophylaxis (28–35 days) was recommended in patients undergoing thoracic cancer surgery with moderate to high VTE risk, although only conditional and with low certainty of evidence. Similarly, an extended prophylaxis (at least 4 weeks) is recommended to prevent postoperative venous thromboembolism after major abdominopelvic and gynecological cancer surgery in patients not at high risk of bleeding [47, 48]. The use of LMWH is preferred over VKAs in patients without renal failure (creatinine clearance < 30 ml/min) due to improved efficacy. DOACs are increasingly accepted in the long-term anticoagulation of cancer patients with and without surgery [47, 49]. The use of inferior vena cava (IVC) filters is generally not recommended and should be restricted to specific patients [47]. Of note, evidence is mainly coming from non-surgical cancer patients, and studies in patients with cancer-related surgery is limited.

Aspirin for Postoperative Anticoagulation

Although that aspirin is commonly used for primary or secondary prophylaxis in atherosclerotic diseases, its use has been also suggested for the prevention of postoperative VTE after orthopedic surgery. Aspirin for VTE prophylaxis might be especially attractive in patients, in whom the administration of DOACs might be challenging (e.g., elderly patients, patients with impaired renal or liver function or with low compliance for drug intake). In addition, aspirin is an inexpensive, generic and widely available drug. Clinical trials have suggested its effectiveness in preventing VTE after surgery [50, 51]. Accordingly, the 2012 guidelines of the American College of Chest Physicians (ACCP) and the 2018 guidelines of the European Society of Anaesthesiology

and Intensive Care (ESAIC) have acknowledged aspirin as a potential option for preventing VTE after major orthopedic surgery for the 10 to 14 postoperative days [42, 52]. However, the ACCP guidelines advise the use of LMWH over the use of aspirin [42]. The ESA guidelines recommend the use of aspirin especially in patients with low VTE risk undergoing surgery with high bleeding risk [52].

A more recent multi-center, double-blinded randomized trial included 3424 patients undergoing total hip or knee arthroplasty. All patients received 10 mg rivaroxaban once daily until postoperative day 5 and were afterwards randomized either to continue rivaroxaban or switch to 81 mg of aspirin per day for 9 to 30 days after surgery. The rate of VTE was 12/1717 patients in the rivaroxaban group and 11/1707 patients in the aspirin group. Likewise, bleeding events were not different between the two groups [53]. This study further supports the ESAIC guidelines stating that aspirin might be considered as VTE prophylaxis after major orthopedic surgery in patients at low risk for VTE. However, aspirin should not be used with the intention to reduce the tendency of postoperative bleeding, as the latter has never been shown.

Conclusions

The perioperative management of anticoagulants and antiplatelet drugs might remain a challenge, especially in urgent or emergent surgery. DOACs are increasingly used, and their preoperative management might be easier and more predictable than VKAs in elective surgery. However, the optimal treatment of DOAC-associated bleeding remains to be defined. The specific use of laboratory testing might be helpful, especially in bleeding patients or before emergent surgery. Prevention of postoperative thromboembolism has gained attention in the recent years, especially in patients at elevated or high risk for VTE. The goal must be the transition from a "one-size-fits-all" approach to a more personalized strategy to prevent postoperative thromboembolic events. The use of risk scores to predict thromboembolism or bleeding risk might be helpful, but such scores are not commonly used by perioperative physicians. Adapted strategies including extended thromboprophylaxis might become more important in the future.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

Conflicts of Interest There are no conflicts of interest to declare.

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Papers of particular interest, published recently, have been highlighted as:
● Of importance
●● Of major importance

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