Journal of Thrombosis and Haemostasis, **14**: 875–885 DOI: 10.1111/jth.13305

REVIEW ARTICLE

Periprocedural management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery

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To cite this article: Spyropoulos AC, Al-Badri A, Sherwood MW, Douketis JD. Periprocedural management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. *J Thromb Haemost* 2016; **14**: 875–85.

Summary. The periprocedural management of patients receiving chronic therapy with oral anticoagulants (OACs), including vitamin K antagonists (VKAs) such as warfarin and direct OACs (DOACs), is a common clinical problem. The optimal perioperative management of patients receiving chronic OAC therapy is anchored on four key principles: (i) risk stratification of patient-related and procedure-related risks of thrombosis and bleeding; (ii) the clinical consequences of a thrombotic or bleeding event; (iii) discontinuation and reinitiation of OAC therapy on the basis of the pharmacokinetic properties of each agent; and (iv) whether aggressive management such as the use of periprocedural heparin bridging has advantages for the prevention of postoperative thromboembolism at the cost of a possible increase in bleeding risk. Recent data from randomized trials in patients receiving VKAs undergoing pacemaker/defibrillator implantation or using heparin bridging therapy for elective procedures or surgeries can now inform best practice. There are also emerging data on periprocedural outcomes in the DOAC trials for patients with non-valvular atrial fibrillation. This review summarizes the evidence for the periprocedural management of patients receiving chronic OAC therapy, focusing on recent randomized trials and large outcome studies, to address three key clinical scenarios: (i) can OAC therapy be safely continued for minor procedures or surgeries; (ii) if therapy with VKAs (especially warfarin) needs to be temporarily interrupted for an elective procedure/surgery, is heparin bridging necessary; and (iii) what is the optimal periprocedural management of the DOACs? In answering these questions, we aim to provide updated clinical guidance for the periprocedural management of patients receiving VKA or DOAC therapy, including the use of heparin bridging.

Keywords: direct oral anticoagulants; hemorrhage; perioperative care; thromboembolism; warfarin.

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Received 8 October 2015
Manuscript handled by: I. Pabinger
Final decision: F. R. Rosendaal, 10 February 2016

Introduction

The periprocedural management of patients receiving chronic oral anticoagulant (OAC) therapy concerns patients who are receiving vitamin K antagonist (VKAs) such as warfarin, or direct OACs (DOACs), the latter comprising the direct thrombin inhibitor dabigatran and the direct activated factor X inhibitors rivaroxaban, apixaban, and edoxaban. It is estimated that 250 000 patients per year in North America alone, or approximately one in six patients receiving a chronic OAC per year, are assessed for periprocedural management [1].

The optimal perioperative management of patients receiving chronic OAC therapy is anchored on four key principles: (i) risk stratification of patient-related and procedure-related risks of thrombosis and bleeding; (ii) the clinical consequences of a thrombotic or bleeding event; (iii) discontinuation and reinitiation of OAC therapy on the basis of appropriate pharmacokinetic parameters of the OAC (including patient renal status, when appropriate); and (iv) whether an aggressive management strategy such as perioperative heparin bridging therapy has advantages for the prevention of postoperative thrombotic complications at the cost of a possible increase in bleeding risk. The elucidation of these key principles, coupled with accumulating clinical trial data relating to perioperative anticoagulant therapy, has prompted the need for clinical

practice guidelines dedicated to perioperative antithrombotic management [1–3]. Related to such guidelines are recommendations from the ISTH for standardized reporting of outcomes in periprocedural antithrombotic and bridging therapy trials [4].

This review summarizes the evidence for the perioperative management of patients receiving chronic OAC therapy – focusing on recent randomized trials and large outcome studies – to address three key clinical scenarios: (i) can OAC therapy be safely continued for selected minor procedures or surgeries; (ii) if therapy with a VKA (especially warfarin) needs to be temporarily interrupted for an elective procedure/surgery, is heparin bridging necessary; and (iii) what is the optimal perioperative management of the DOACs? We provide updated clinical guidance for the periprocedural management of patients receiving VKA or DOAC therapy, including the use of heparin bridging. For VKAs, our review will primarily refer to warfarin as opposed to other VKAs such as phenprocoumon and acenocoumarol, as they have not been extensively studied in elective periprocedural situations.

Assessment of periprocedural thromboembolic (TE) and bleeding risks

Both patient-related and surgical risk factors for thrombosis and bleeding should be assessed and risk-stratified in order to determine an overall periprocedural anticoagulant management strategy for a particular patient. The American College of Chest Physicians (ACCP) has suggested a three-tiered perioperative TE risk stratification in patients with either venous thromboembolism (VTE), a mechanical heart valve or atrial fibrillation (AF) who are receiving OAC therapy, as shown in Table 1 [3]. Patients are divided into low-risk, intermediate-risk and high-risk groups for perioperative TE risk. Although this scheme has not been validated in the perioperative period, it remains clinically useful, in that it provides a framework whereby a patient's TE risk would drive the need for a conservative or aggressive perioperative management strategy (such as heparin bridging therapy). It has been suggested that the use of perioperative bridging anticoagulation with parenteral heparin, either unfractionated heparin (UFH) or low molecular weight heparin (LMWH), would mitigate the risk of perioperative thromboembolism by minimizing the period without therapeutic anticoagulation during temporary interruption of VKA therapy for an elective surgery/procedure [5]. With respect to procedure-related thrombotic risk, it is well established that the absence of postoperative anticoagulant thromboprophylaxis confers an over 100-fold increased risk of VTE, especially after major surgery; however, the suggestion that anticoagulant interruption also confers an up to 10-fold increased risk of postoperative arterial thromboembolism (ATE) has been made mostly on the basis of mathematical modeling assumptions [6,7] [8,9].

For patient-related bleeding risk factors, a patient's previous history of bleeding, especially with invasive procedures or trauma, is an important determinant in assessing surgical bleeding risk [10]. In addition, continuing the use of an OAC is associated with an increased risk of bleeding in the perioperative period, in addition to the use of concomitant antiplatelet and non-steroidal anti-inflammatory drugs [11,12]. Procedural bleeding risks have also been identified by various surgical and subspecialty societies [13,14]. For procedure-related bleeding risk, it is useful to stratify patients into a three-tiered scheme of high, low and minimal bleeding risk, as shown in Table 2. The surgical bleeding risk will determine whether anticoagulant therapy needs to be interrupted and the timing of preoperative and postoperative resumption of an OAC, especially after high bleeding risk

Table 1 Suggested patient-related risk stratification for perioperative thromboembolism from American College of Chest Physicians antithrombotic guidelines [3]

Risk category	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High (> 10% per year risk of ATE or > 10% per month risk of VTE)	Any mechanical mitral valve Caged ball or tilting disk valve in mitral/aortic position Recent (< 6 months) stroke or TIA	$CHADS_2$ score of 5 or 6 Recent (< 3 months) stroke or TIA Rheumatic valvular heart disease	Recent (< 3 months) VTE Severe thrombophilia Deficiency of protein C, protein S, or antithrombin Antiphospholipid antibodies Multiple thrombophilias
Intermediate (4–10% per year risk of ATE or 4–10% per month risk of VTE)	Bileaflet mechanical aortic valve with major risk factors for stroke	$CHADS_2$ score of 3 or 4	VTE within the past 3–12 months Recurrent VTE Non-severe thrombophilia Active cancer
Low (< 4% per year risk of ATE or < 2% per month risk of VTE)	Bileaflet mechanical aortic valve without major risk factors for stroke	$CHADS_2$ score of 0–2 (and no prior stroke or TIA)	VTE more than 12 months ago

ATE, arterial thromboembolism; TIA, transient ischemic attack; VTE, venous thromboembolism.

Table 2 Suggested risk stratification for procedural bleeding risk

High bleeding risk procedures (2-day risk of major bleed of ≥ 2%)	Low bleeding risk procedures (2-day risk of major bleed of < 2%)	Minimal bleeding risk procedures
Major surgery with extensive tissue injury	Arthroscopy	Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi)
Cancer surgery	Cutaneous/lymph node biopsies	Cataract procedures
Major orthopedic surgery	Shoulder/foot/hand surgery	Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings
Reconstructive plastic surgery	Coronary angiography	Pacemaker or cardioverter-defibrillator device implantation*
Urologic or gastrointestinal surgery	Gastrointestinal endoscopy ± biopsy	–
Transurethral prostate resection, bladder resection, or tumor ablation	Colonoscopy ± biopsy	–
Nephrectomy, kidney biopsy	Abdominal hysterectomy	–
Colonic polyp resection	Laparoscopic cholecystectomy	–
Bowel resection	Abdominal hernia repair	–
Percutaneous endoscopic gastrotomy placement, endoscopic retrograde cholangiopancreatography	Hemorrhoidal surgery	–
Surgery in highly vascular organs (kidneys, liver, spleen)	Bronchoscopy ± biopsy	–
Cardiac, intracranial or spinal surgery	Epidural injections with INR of < 1.2	–
Any major operation (procedure duration of > 45 min)	–	–

INR, International Normalized Ratio.
*Associated with pocket hematoma, but randomized controlled trial (Level 1) evidence reveals that procedures can be performed without oral anticoagulant interruption.

procedures. Moreover, it will determine the timing of the postprocedural resumption of heparin bridging.

Overall periprocedural antithrombotic strategy

Patient-related and procedure-related risk factors and the clinical consequences for both thrombosis and bleeding should be considered when an overall periprocedural management strategy in patients receiving chronic OAC therapy is developed. As an example, mechanical heart valve thrombosis is fatal in 15% of patients, embolic stroke results in death or major disability in 70% of patients, VTE has a case-fatality rate of approximately 5–9%, and major bleeding has a case-fatality rate of approximately 8–10% [15–19]. Thus, because of the more severe clinical consequences of ATE than of major bleeding, a strategy that incurs 3–10 more major bleeds to prevent one stroke would be, in theory, clinically acceptable based on the trade-off between the clinical consequences of a stroke and those of a bleed.

Can OAC therapy be safely continued for selected procedures or surgeries?

Once the TE and bleeding risks have been estimated, a decision can be made about whether OAC therapy should be interrupted or continued, based on emerging studies comparing the benefits of continuing versus interrupting OAC therapy. There are low-quality to moderate-quality data showing that therapy with VKAs, including warfarin, acenocoumarol, and phenprocoumon, does not require interruption for minor procedures, as shown in Table 2. These include dental procedures (tooth extraction; root canal), skin procedures (biopsy; skin cancer removal), and cataract surgery [20–27]. The 2012 ACCP Antithrombotic Therapy Guidelines give only weak Grade 2C recommendations for continuing VKA therapy in these specific situations involving minor procedures, as they have been associated with a low risk of bleeding [3]. More recent high-quality evidence from a randomized trial (BRUISE CONTROL) showed that patients receiving warfarin who underwent pacemaker or defibrillator implantation had a significantly lower incidence of bleeding (absolute risk reduction of 12.5%) than those in whom warfarin therapy was interrupted and heparin bridging therapy was administered [21]. The results of the BRUISE CONTROL trial were supported by those of the COMPARE trial, in which patients with paroxysmal or persistent AF undergoing atrioventricular nodal ablation were randomly assigned to bridging with therapeutic-dose LMWH or continuation of warfarin therapy. This study showed no difference in the incidence of TE events or major bleeding complications

between the two groups [23]. Two subsequent meta-analyses have shown findings consistent with those of the BRUISE CONTROL and COMPARE trials, including one that included 3744 patients from 14 studies, and found that, in patients undergoing cardiac device implantation, heparin bridging conferred a significantly higher risk of bleeding than continuation of OAC therapy (hazard ratio 3.1; 95% confidence interval [CI] 2.0–4.8), with no significant reduction in the frequency of TE events [20,22]. Together, and as summarized in Table 3, these findings indicate that there are an increasing number of minor procedure/surgery types that can be safely performed without interruption of VKA therapy. There are also emerging data that selected minor procedures can safely be performed either without interruption of DOAC therapy or with interruption on the day of the procedure to avoid peak effects, given that the peak anticoagulant effect of DOACs occurs 1–3 h after intake. Acceptable 30-day major bleeding rates of ~ 1.5% were reported irrespective of DOAC interruption strategy, but additional study is needed in this area before more definitive recommendations can be made [28].

If a therapy with a VKA such as warfarin needs to be temporarily interrupted for an elective procedure/surgery, is heparin bridging necessary?

Most data on the periprocedural management of moderate TE risk to high TE risk patients who required VKA interruption and heparin bridging were derived from observational studies of low quality, characterized by heterogeneity in patient characteristics, bridging regimens studied, and clinical outcomes assessed [29]. Concurrent with these studies, the use of LMWH has supplanted the use of intravenous UFH as the bridging therapy, even in patients with mechanical heart valves, owing to significant cost savings resulting from outpatient administration and a similar or improved safety profile [30]. For many high bleeding risk procedures, such as major vascular and cardiac procedures, deferring therapeutic-dose bridging therapy for 48–72 h, the use of a stepwise approach in increasing the dose of bridging therapy or a no postoperative bridging strategy has been used to mitigate the risk of postprocedural bleeding [3,31–36]. The 2012 ACCP Antithrombotic Therapy Guidelines suggested the use of heparin bridging – defined as therapeutic doses of UFH or LMWH – in perceived high TE risk patients with a weak Grade 2C recommendation, and did not make any recommendations on the use of heparin bridging therapy in perceived moderate TE risk patients depending upon patient-specific risk factors for bleeding and thrombosis [3]. Over the past decade, the question of how to bridge effectively and efficiently in periprocedural situations has been addressed, with the publication of several standardized heparin bridging regimens [31,34,36,37]. The overall ATE risk of patients receiving such bridging regimens was 1.0% (95% CI 0–2.8%), with a risk of major bleeding of 4.2% (95% CI 0–11.3%) [38].

However, the fundamental question of whether we need to bridge patients who require periprocedural interruption of chronic VKA therapy has remained unanswered. Recently, emerging evidence from large meta-analyses and observational studies has revealed that heparin bridging

Table 3 Suggested overall periprocedural anticoagulant and bridging management for patients receiving chronic oral anticoagulants (including vitamin K antagonists and direct oral anticoagulants [DOACs]) based on thromboembolic and procedural bleeding risk

	High bleeding risk procedures	Low bleeding risk procedures	Minimal bleeding risk procedures
High thromboembolic risk	DOAC users: interrupt DOAC therapy; bridging with LMWH not suggested for DOACs Warfarin users: interrupt warfarin therapy with LMWH bridging suggested on the basis of clinician judgement and the most current evidence*†	DOAC users: interrupt DOAC therapy; bridging with LMWH not suggested for DOACs Warfarin users: interrupt warfarin therapy with LMWH bridging suggested on the basis of based on clinician judgement and the most current evidence*	Do not interrupt anticoagulant therapy‡
Intermediate thromboembolic risk	DOAC users: interrupt DOAC therapy; bridging with LMWH not suggested for DOACs Warfarin users: consider interrupting warfarin therapy without LMWH bridging on the basis of clinician judgement and the most current evidence*†	DOAC users: interrupt DOAC therapy; bridging with LMWH not suggested for DOACs Warfarin users: consider interrupting warfarin therapy without LMWH bridging on the basis of clinician judgement and the most current evidence*	Do not interrupt anticoagulant therapy‡
Low thromboembolic risk	DOAC users: interrupt DOAC therapy; bridging with LMWH not suggested for DOACs Warfarin users: interrupt warfarin therapy; bridging with LMWH not necessary†	DOAC users: interrupt DOAC therapy; bridging with LMWH not suggested for DOACS Warfarin users: interrupt warfarin therapy; bridging with LMWH not necessary	Do not interrupt anticoagulant therapy‡

LMWH, low molecular weight heparin. *Atrial fibrillation: bridging not recommended on the basis of Level 1 evidence, but evidence in a few high-risk $CHADS_2$ patients (scores of 5 and 6). Mechanical heart valve and venous thromboembolism (VTE): retrospective studies suggest that bridging increases bleeding risk without reducing thrombosis. †May administer prophylactic-dose LMWH for VTE prevention in patients undergoing high bleeding risk procedures or major surgeries that confer a high risk of VTE. ‡May consider interrupting DOAC therapy on the day of the procedure.

may not provide therapeutic benefit to mitigate the TE risk, and increases periprocedural major bleeding. A meta-analysis of 34 studies on periprocedural OAC management totaling 12 278 patients showed that there was no significant difference in the rate of periprocedural thromboembolism between patients (mostly with AF) who received bridging and patients who did not, whereas bridging conferred a more than three-fold increased risk of major bleeding as compared with no bridging (odds ratio [OR] 3.60, 95% CI 1.52–8.50).[38]. There were also no differences in the rates of TE according to whether therapeutic-dose or intermediate-dose bridging regimens were used. Study limitations included heterogeneity in the types of heparin dose used for bridging, procedure types, and bleeding definitions. Data from the community-based registry of outpatients with atrial fibrillation taking oral anticoagulation (ORBIT-AF) also showed that the number of bleeding events was almost four-fold higher in the bridged than in the non-bridged patients (OR 3.84, 95% CI 2.07–7.14). Moreover, the rates of myocardial infarction, stroke, systemic embolism, hospitalization and death within 30 days were higher in those who received bridging therapy [39]. A substudy from the RE-LY trial confirmed these findings, with an over four-fold increased risk of major bleeding (OR 4.62, 95% CI 2.45–8.72, $P < 0.001$), and no differences in stroke or systemic embolism between patients receiving warfarin who received bridging therapy and those who did not [40]. In addition, a recent retrospective cohort study of 1777 high TE risk patients receiving early heparin bridging after mechanical heart valve replacement found similarly increased harm with postprocedural heparin bridging [41]. Thus, in these patients who had mechanical heart valve surgery, there was a more than three-fold increased risk of major bleeding (OR 3.23, 95% CI 1.58–6.62, $P = 0.001$), and there was no difference in the rates of thromboembolism between patients who received therapeutic-dose heparin bridging and those who received prophylactic-dose bridging. Finally, a retrospective cohort study of 1178 patients receiving VKA therapy for VTE who required an elective surgery or procedure also found that heparin bridging increased the risk of bleeding as compared with a no-bridging strategy, with no significant effect on the rate of postprocedural recurrent VTE between the two groups [42].

Recently, the findings from the first randomized, double-blind, placebo-controlled trial of heparin bridging, the Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) trial, were published [43]. The BRIDGE trial was designed to address a simple question: is periprocedural heparin bridging needed in patients receiving chronic warfarin therapy with at least one stroke risk factor who require treatment interruption for an elective surgery/procedure? The trial used a validated bridging approach that was designed to maximize the putative therapeutic benefit of bridging while minimizing the risk of periprocedural bleeding. Patients were randomly allocated to receive bridging with subcutaneous dalteparin, 100 IU kg^{-1} twice daily, or matching placebo injections, starting 3 days before a surgery or procedure; also, warfarin therapy was stopped 5 days preprocedure in all patients. Warfarin therapy was resumed within 24 h of the procedure, whereas a full 24 h elapsed before dalteparin/placebo therapy was resumed in patients undergoing low bleeding risk procedures, and 48–72 h elapsed before dalteparin/placebo therapy was resumed in patients undergoing high bleeding risk procedures. There was adherence to the warfarin interruption and bridging protocol in 86.5% preprocedure and in 96.5% postprocedure. The mean $CHADS_2$ score of the study population was 2.3, which was representative of patients assessed for bridging in everyday practice and consistent with mean $CHADS_2$ scores of patients enrolled in recent large phase 3 stroke prevention in atrial fibrillation (SPAF) trials. The BRIDGE trial showed that, in patients with AF receiving chronic warfarin therapy who needed treatment interruption for an elective procedure/surgery, foregoing a strategy of bridging with therapeutic-dose LMWH resulted in no significant difference in the rate of ATE (0.3% versus 0.4%; $P = 0.01$ for non-inferiority) between bridging and no bridging. Furthermore, a no-bridging strategy was associated with a significantly lower risk of major bleeding (1.3% versus 3.2%, $P = 0.005$) [43]. Limitations included only 3% of patients with a high $CHADS_2$ score of 5 or 6, and only 11% of patients having a major surgery/procedure, although 31% of all patients were considered to be at high bleeding risk and were managed accordingly with postprocedure delayed (48–72 h) resumption of dalteparin/placebo therapy. Overall, the BRIDGE trial provides high-quality (Level 1) evidence and proof-of-concept that, for the majority of patients with AF undergoing an elective surgery/procedure, a strategy of simply interrupting and resuming warfarin therapy without heparin bridging is both non-inferior to a strategy of warfarin interruption with bridging for the prevention of ATE, and superior for the prevention of major bleeding. An ongoing randomized placebo-controlled trial, The Double-Blind Randomized Control Trial of Post-Operative Low Molecular Weight Heparin Bridging Therapy vs. Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism (PERIOP-2), will provide further evidence regarding the safety and efficacy of therapeutic-dose LMWH bridging in patients receiving chronic warfarin therapy who need temporary interruption for an elective surgery/procedure, and will include patients with AF or a mechanical heart valve (NCT00432796). The PERIOP-2 trial uses a different design from the BRIDGE trial, wherein all patients receive preprocedural bridging, with dalteparin 200 IU kg^{-1} once daily, and are randomized postprocedure to receive this bridging regimen or matching placebo, starting within 24 h postprocedure.

Patients at high bleeding risk receive a prophylactic dose of bridging with dalteparin 5000 IU daily, or matching placebo.

Taken together, the BRIDGE trial and analyses of > 33 000 patients have provided high-quality data regarding periprocedural heparin bridging, with no-bridging control groups. The studies have included patients receiving chronic VKA therapy for AF, mechanical heart valve and VTE indications with moderate-to-high TE risk who needed temporary VKA interruption for an elective procedure/surgery. These studies gave remarkably consistent results: there was a three-fold to four-fold increased risk of major bleeding with the use of therapeutic-dose heparin bridging, and either no advantages in reduction in the rate of TE events or a trend towards an increase in these events in the postprocedural period. The reasons for these findings may include the following: (i) the risk of rebound hypercoagulability and a postoperative prothrombotic state has been overestimated, and a 10-fold perioperative increased risk of ATE is not supported by the BRIDGE trial and other related studies, which showed ATE rates of ~ 0.5%; (ii) the mechanisms of perioperative ATE may be more related to factors other than anticoagulant-related factors, such as anesthetic techniques (including the increasing use of neuraxial anesthesia), changes in surgical procedures (including the increasing use of laparoscopic techniques and earlier patient mobilization), and the perioperative vascular milieu, including blood pressure fluctuations; and, importantly, (iii) mounting evidence that any heparin-based bridging strategy does not prevent ATE events but incurs a significant bleeding risk.

A proposed strategy of periprocedural interruption of warfarin therapy based on TE and procedural bleeding risk is shown in Table 3. In patients at low TE risk and in those with moderate TE risk, warfarin should simply be interrupted ~ 5 days preprocedure, and warfarin should be reinitiated within 24 h postprocedure, provided that there is adequate hemostasis. It would be expected that a shorter interruption interval would be required for acenocoumarol (2 days; half-life, ~ 8–10 h) and a longer one for phenprocoumon (7–10 days; half-life, ~ 100 h) [44,45]. Therapeutic-dose heparin bridging therapy should be reserved for patients with a mechanical heart valve with high TE risk features and, possibly, a selected group of high-risk patients with AF, comprising those with a recent (within 3 months) stroke/transient ischemic attack or a $CHADS_2$ score of 5 or 6. An example of a validated periprocedural warfarin and LMWH bridging protocol is shown in Table 4.

What is the optimal perioperative management of the DOACs?

Managing patients who are receiving DOACs, which comprise dabigatran, rivaroxaban, apixaban, and edoxaban, in periprocedural situations is becoming increasingly common as the uptake of DOACs in clinical practice increases. The same principles used for the periprocedural management of patients receiving VKA therapy apply to patients receiving DOAC therapy. First, there is a need to estimate patient-related thrombotic and bleeding risks [46]. Preprocedural management is anchored on the bleeding risk associated with the surgery/procedure and patient renal function, which guide the interruption interval for DOACs to allow the surgery/procedure to proceed safely. In the following section, we will examine the current data available on perioperative management of DOACs, with an emphasis on comparisons of safety and efficacy with warfarin, questions of bridging therapy, and resumption of therapy postprocedure.

Can DOAC therapy be safely interrupted in the periprocedural setting?

Dabigatran

In the RE-LY trial, which compared dabigatran (150 mg or 110 mg twice daily) with warfarin (International Normalized Ratio of 2.0–3.0) for SPAF, 4591 (of 18 113 enrolled) patients who required therapy interruption for a surgery/procedure were assessed [47]. Management of dabigatran or warfarin was left largely to the discretion of the investigators, as these drugs were given in an open-label manner, but a preprocedural dabigatran interruption protocol was introduced during the trial, based on procedure bleeding risk and patient renal function, to guide the timing of dabigatran interruption. The rates of thromboembolism and bleeding were ~ 0.5% and ~ 3%, respectively, and were not significantly different between dabigatran-treated and warfarin-treated patients (Table 5).

Rivaroxaban

In the ROCKET AF trial, which compared rivaroxaban (20 mg once daily) with warfarin for SPAF, 4692 (of 14 264 enrolled) patients required temporary interruption of study drug, of whom 2997 (39.7%) required a surgery/procedure [48]. In most patients, rivaroxaban therapy was stopped at least 3 days preprocedure, and heparin bridging was used infrequently (6.4% of patients), probably because of the double-blind nature of study drug allocation. The rates of ATE and major bleeding were low, and did not differ between the rivaroxaban-treated and warfarin-treated groups (Table 5).

Apixaban

In the ARISTOTLE trial, which compared apixaban (5 mg twice daily) with warfarin for SPAF, 4692 (of 18 201 enrolled) patients required a procedure, and study

Table 4 Validated periprocedural warfarin and low molecular weight heparin (LMWH) bridging protocol

Day	Warfarin dose	Bridging with LMWH	INR monitoring
− 7 to − 10	Maintenance dose	Assess for perioperative bridging anticoagulation; classify patients as undergoing high or low bleeding risk procedures	Check baseline laboratory findings (hemoglobin, platelet count, serum creatinine, INR)
− 6 to − 5	Begin to hold warfarin on day − 5 or day − 6	No LMWH	None
− 4	No warfarin	No LMWH	None
− 3	No warfarin	Start LMWH at a therapeutic or intermediate dose*	None
− 2	No warfarin	LMWH at a therapeutic or intermediate dose*	None
− 1	No warfarin	Last preprocedural dose of LMWH administered no less than 24 h before the start of surgery at half the total daily dose	Assess INR before the procedure; proceed with surgery if the INR is < 1.5. If the INR is > 1.5 and < 1.8, consider low-dose oral vitamin K reversal (1–2.5 mg)
0 or + 1	Resume the maintenance dose of warfarin on the evening of or morning after the procedure	None	None
+ 1	Maintenance dose	Low bleeding risk: restart LMWH at the previous dose High bleeding risk: no LMWH administration	According cto linician judgement
+ 2 or + 3	Maintenance dose	Low bleeding risk: LMWH administration continued High bleeding risk: restart LMWH at the previous dose	According to clinician judgement
+ 4	Maintenance dose	Low bleeding risk: INR testing (discontinue LMWH if the INR is > 1.9) High bleeding risk: INR testing (discontinue LMWH if the INR is > 1.9)	INR
+ 7 to + 10	Maintenance dose	–	INR

INR, International Normalized Ratio. Both twice-daily LMWH regimens (i.e. enoxaparin 1 mg kg−1 subcutaneous, daltepearin 100 IU kg−1) and once-daily LMWH regimens (i.e. enoxaparin 1.5 mg kg−1 subcutaneous, dalteparin 200 IU kg−1 subcutaneous) have been used. Intermediate-dose LMWH has been less studied in this setting.

drug was interrupted in 62.5% of these [28]. Overall, the rates of ATE were low and similar in apixaban-treated and warfarin-treated patients (Table 5). However, patients in whom therapy was interrupted had significantly lower rates of ATE (OR 0.49, 95% CI 0.27–0.90), death (OR 0.46, 95% CI 0.31–0.68) and major bleeding (OR 0.62, 95% CI 0.46–0.85) than patients who continued to receive the study drug. There was an interaction between study drug allocation and its interruption for major bleeding ($P = 0.0086$), indicating that patients receiving apixaban may have similar rates of major bleeding whether or not they have treatment interruption (1.65% versus 1.58%).

Is periprocedural heparin bridging necessary with DOACs?

In a registry of 2173 patients receiving a DOAC (the majority for AF), 595 patients underwent 863 procedures. DOAC therapy was continued in 21.7% of cases, and was temporarily stopped for the remainder [49], with heparin bridging being used in 30% of cases. Major cardiovascular and bleeding event rates were 1.0% and 1.2%, respectively, but the most significant factor predicting bleeding was a major invasive procedure, as compared with minor or minimal procedures (16.1% versus 2.2% and 4.5%, $P < 0.001$). For most procedures, heparin bridging increased the rate of major bleeding (2.7% versus 0.5%, $P = 0.01$); for major procedures, bridging increased the risk of major bleeding, although this was not statistically significant (OR 2.1, 95% CI 0.2–18.8, $P = 0.494$). A related study assessed the use of heparin bridging during dabigatran and warfarin therapy interruption in the RE-LY trial [40], and showed greater use of heparin bridging in warfarin-treated than in dabigatran-treated patients (27.5% versus 15.4%, $P < 0.001$). The rate of major bleeding was significantly higher in bridged than in non-bridged patients (6.5% versus 1.8%, $P < 0.001$), irrespective of treatment with dabigatran or warfarin, and there were comparable rates of thromboembolism in bridged and non-bridged patients (1.2% versus 0.6%, $P = 0.16$). In the ROCKET AF periprocedural substudy, patients receiving rivaroxaban who underwent heparin bridging had more bleeding events than those

Table 5 Clinical trial experience with periprocedural interruption of direct oral anticoagulants

	RE-LY*	ROCKET AF	ARISTOTLE
No. of patients studied	4591	4692	5439
$CHADS_2$ score	2.1	3.4	2.1
Thirty-day TE risk: HR/OR versus warfarin (95% CI)	1.01 (0.35–2.87); $P = 0.99$	0.74 (0.36–1.50); $P = 0.40$	0.60 (0.32–1.12); P = NS
Thirty-day major bleeding risk: HR/OR versus warfarin (95% CI)	1.09 (0.80–1.49); $P = 0.58$	1.26 (0.80–2.00); $P = 0.34$	0.85 (0.61–1.12); P = NS

CI, confidence interval; HR, hazard ratio; NS, not significant; OR, odds ratio; TE, thromboembolic. Adapted from Krishnamoorthy *et al.* [52].
*HR/OR for RE-LY shown only for dabigatran 150 mg versus warfarin.

who did not receive heparin bridging (4.83 events/30 days versus 3.02 events/30 days); the rates of ATE were low and comparable in both groups (0.17 events/30 days versus 0.37 events/30 days) [48].

The timing of interruption of DOAC therapy is based on renal function and drug pharmacokinetic properties

A recent, 541-patient prospective cohort study [50] evaluated the safety of a standardized periprocedural dabigatran protocol, whereby dabigatran therapy was interrupted at least 24 h preprocedure in patients having a low bleeding risk surgery/procedure, and dabigatran therapy was interrupted at least 48 h preprocedure in patients having a high bleeding risk surgery/procedure. The interruption interval was extended by 1–2 days in patients with a creatinine clearance (CrCl) of < 50 mL min^{-1}. There was no preprocedural heparin bridging, and postprocedural prophylactic-dose heparin was used in 1.7% of patients. The incidence rates of thromboembolism and major bleeding events within 30 days of the procedure were low, at 0.2% and 1.8%, respectively. This standardized perioperative protocol for dabigatran appeared to be safe, but the study was limited by a low number of patients (~ 150) having high bleeding risk procedures and underrepresentation of patients having neuraxial anesthesia.

The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study

The PAUSE study (NCT02228798) is a prospective cohort study that aims to assess the safety of standardized protocols for the periprocedural management of AF patients receiving dabigatran, rivaroxaban or apixaban who require therapy interruption for an elective surgery/procedure. This study plans to recruit 3300 patients taking one of three DOACs, including dabigatran, rivaroxaban, and apixaban, and will assess the safety of standardized perioperative DOAC management protocols based on the rates of periprocedural thromboembolism and bleeding. In addition, the levels of residual anticoagulant effects will be measured just prior to the surgery/procedure. For each DOAC, therapy interruption will follow a standardized DOAC-specific protocol aimed at achieving a minimal to no residual anticoagulant effect at the time of a high bleeding risk procedure, which includes any procedure requiring neuraxial anesthesia.

Overall, observational data from both secondary analyses of randomized clinical trials and registry-based studies provide the basis for the following clinical guidance: (i) DOAC therapy can be safely interrupted and resumed in a periprocedural setting, with similar rates of thrombosis and bleeding as with warfarin; (ii) the use of heparin bridging therapy is probably unnecessary in DOAC-treated patients, given the short half-life of these drugs and the questionable risk/benefit of heparin bridging therapy seen in both VKA-treated and DOAC-treated patients; and (iii) the need for and timing of DOAC therapy interruption in the preoperative setting and resumption postoperatively should be DOAC-specific and based on patients' renal function and procedural bleeding risk.

A suggested strategy for the interruption and resumption of DOAC therapy based on patient renal function and procedure-related bleeding risk is shown in Table 6. This is based on the principles of allowing an interval of two to three drug half-lives between the last DOAC dose and low bleeding risk procedures, and an interval of four to five drug half-lives between the last DOAC dose and high bleeding risk procedures, the latter to allow a minimal (3–6%) or no residual anticoagulant effect at the time of surgery. For most patients receiving DOACs with normal renal function to mild/moderate renal insufficiency, this means that the last DOAC dose will be taken 2 days before surgery in patients undergoing low bleeding risk procedures, and 3 days before surgery in patients undergoing high bleeding risk procedures. An additional 1–2 days of interruption is required in patients receiving dabigatran with a CrCl of < 50 mL min^{-1}, to reflect the primarily renal route of elimination (~ 80%) of dabigatran. For postprocedural DOAC therapy resumption, we suggest waiting for ~ 24 h after low bleeding risk procedures and for 48–72 h after high bleeding risk procedures, given the rapid peak action of DOACs 1–3 h after oral intake. In general, we recommend against the use of

Table 6 Suggested periprocedural direct oral anticoagulant therapy interruptions (adapted from [4])

Drug	Renal function	Low bleeding risk surgery	High bleeding risk surgery*	Resumption of therapy	
				Low bleeding risk surgery	High bleeding risk surgery
Dabigatran	CrCl > 50 mL min^{-1}	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Resume ~ 24 h after procedure	Resume 2–3 days after procedure (48–72 h postoperatively)†
	CrCl 30–50 mL min^{-1}	Last dose: 3 days before procedure	Last dose: 4–5 days before procedure		
Rivaroxaban	CrCl > 50 mL min^{-1}	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Resume ~ 24 h after procedure	Resume 2–3 days after procedure (48–72 h postoperatively)†
	CrCl 30–50 mL min^{-1}	Last dose: 2 days before procedure	Last dose: 3 days before procedure		
	CrCl 15–29.9 mL min^{-1}‡	Last dose: indivualized on the basis of patient and procedural factors for bleeding and thrombosis	Last dose: indivualized on the basis of patient and procedural factors for bleeding and thrombosis		
Apixaban	CrCl > 50 mL min^{-1}	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Resume ~ 24 h after procedure	Resume 2–3 days after procedure (48–72 h postoperatively)†
	CrCl 30–50 mL min^{-1}	Last dose: 2 days before procedure	Last dose: 3 days before procedure		
	CrCl 15–29.9 mL min^{-1}	Last dose: indivualized on the basis of patient and procedural factors for bleeding and thrombosis	Last dose: indivualized on the basis of patient and procedural factors for bleeding and thrombosis		
Edoxaban	CrCl > 50 mL min^{-1}	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Resume ~ 24 h after procedure	Resume 2–3 days after procedure (48–72 h postoperatively)†

CrCl, creatinine clearance. *Includes any procedure/surgery requiring neuraxial anesthesia. †For patients at high risk for thromboembolism and with a high bleeding risk after surgery, consider administering a reduced dose of dabigatran (75 mg twice daily), rivaroxaban (10 mg once daily) or apixaban (2.5 mg twice daily) on the evening after surgery and on the following day (first postoperative day) after surgery. ‡Value for patients receiving rivaroxaban 15 mg once daily.

heparin bridging, with the exception of postprocedural heparin for VTE prevention doses in patients who cannot tolerate oral medications (e.g. after gastrointestinal surgery). There is no evidence for or an established role of DOAC monitoring to improve clinical outcomes in periprocedural settings. Finally, special care regarding these timelines for DOACs should also be taken in patients undergoing neuraxial anesthesia [51].

Conclusion

This review has attempted to summarize over three decades of progress in the management of anticoagulated patients who require an elective surgery/procedure: the 1990s witnessed the transition from in-hospital periprocedural bridging with intravenous UFH to out-of-hospital use of subcutaneous LMWH; in the 2000s, the question of how to bridge was addressed; and the 2010s has witnessed major steps in addressing the questions of whether we should interrupt anticoagulation and, importantly, whether we should bridge. A summary of recommendations for both VKA-treated and DOAC-treated groups in periprocedural settings is available for clinicians at the following website: http://mappp.ipro.org.

The lessons learned from this collective work will, in future, help to inform best practices for the periprocedural management of patients receiving DOAC therapy. Additional questions that require attention include the need for bridging in patients with mechanical heart valves, especially in the majority with a presumably lower TE risk bileaflet aortic valve. In addition, further research is needed on the management of patients receiving VKA or DOAC therapy who require an urgent surgery/procedure, given the availability of rapidly available but costly reversal agents such as prothrombin complex concentrates, and the emergence of antidotes specific to individual DOACs.

Addendum

All authors had full access to all data and contributed to drafting of the paper.

Disclosure of Conflict of Interests

A. C. Spyropoulos has served as a consultant for Boehringer Ingelheim, Jansen, Bayer, and Daiichi Sankyo, and has served on advisory committees for Bristol-Myers Squibb and Pfizer. M. W. Sherwood has served as a

consultant for Boehringer Ingelheim. J. D. Douketis has served as a consultant for Actelion, Biotie, Boehringer Ingelheim, Janssen, and Portola, and has served on advisory committees for Bayer, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, The Medicines Co., Pfizer, and Sanofi. A. Al-Badri states that he has no conflict of interest.

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