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IM - REVIEW

# Perioperative management of patients who are receiving a novel oral anticoagulant

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**Abstract** The use of novel oral anticoagulants (NOACs) is increasing since these drugs are at least as efficacious and safe as vitamin K antagonists (VKAs) for the management of patients with non-valvular atrial fibrillation and venous thromboembolism. Compared with VKAs, NOACs have a faster onset and offset of action, a predictable and consistent pharmacokinetic profile, fewer drug interactions, and ease of use since anticoagulant monitoring is not required. Current perioperative management will be affected by these characteristics, with the potential to obviate the need for heparin bridging. This review aims to summarize the current evidence of perioperative thromboembolic and bleeding risk during anticoagulant interruption, which is derived predominantly from patients receiving VKA therapy, and early studies involving NOACs which mainly focus on patients who are receiving dabigatran. The role of heparin bridging is discussed. We also provide a practical approach for the perioperative management of patients who are receiving NOAC therapy.

**Keywords** Bleeding · New oral anticoagulants · Perioperative · Thrombosis

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## Introduction

Vitamin K antagonists (VKAs) such as warfarin have been the mainstay of oral anticoagulant therapy for the past 60 years. However, VKA therapy has a narrow therapeutic index and requires periodic laboratory monitoring due to a variable inter-individual response and multiple drug interactions. The novel oral anticoagulants (NOACs), comprising the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban, are at least as efficacious and safe as VKAs for patients with non-valvular atrial fibrillation (AF) or venous thromboembolism (VTE) [1, 2]. The NOACs are appealing because of predictable pharmacokinetic and pharmacodynamic profiles, which allow fixed once- or twice-daily dosing and obviate the need for laboratory monitoring, and have few drug interactions [3, 4]. Another advantage of NOACs over VKAs is their rapid offset (half-life 9–15 h) and rapid onset (1–3 h) of action, which simplifies periprocedural anticoagulant management and, presumably, would obviate the need for heparin bridging. However, a sub-study of the RE-LY trial, which compared dabigatran (110 or 150 mg twice-daily) with warfarin for stroke prevention in AF, found that 17 % of patients on dabigatran who needed an elective surgery/procedure received some form of heparin bridging [5]. Moreover, in clinical practice, we have observed an increasing number of patients on NOACs referred for 'perioperative bridging'. Consequently, uncertainty remains about the perioperative anticoagulant management of patients receiving NOACs.

Against this background, the objectives of this review are (a) to summarize the evidence relating to the perioperative thromboembolic and bleeding risk in patients who receive heparin bridging, and (b) to provide a practical

approach to managing NOAC-treated patients who require an elective surgery/procedure [3]. The management approaches discussed for NOAC-treated patients who require a surgery/procedure will be prefaced by representative case vignettes followed by a brief overview of NOACs, focusing on how their properties affect perioperative management.

Case vignette 1

A 68-year-male with hypertension and type-2 diabetes is scheduled for elective AV node ablation because of recurrent paroxysmal AF. He has a $CHADS_2$ score of 2 and is receiving dabigatran 150 mg twice-daily, for stroke prevention.

Case vignette 2

A 75-year-female had total hip replacement surgery that was complicated by postoperative deep vein thrombosis 3 months ago. She is receiving rivaroxaban 20 mg once daily and requires a re-operation because of a loosened hip prosthesis.

## Overview of novel oral anticoagulants

Dabigatran

Dabigatran etexilate is a selective and reversible oral direct thrombin inhibitor [6]. It is a prodrug which is converted to dabigatran in the stomach and small intestine, and inhibits free and clot-bound thrombin and thrombin-induced platelet aggregation. It is rapidly absorbed and reaches peak plasma concentrations in 1–3 h after oral intake, and has a half-life of 14–17 h [4]. Dabigatran is dependent on the kidney for 80 % of its clearance and, consequently, its elimination half-life is prolonged to 18–24 h in patients with significantly impaired renal function [4].

Rivaroxaban and apixaban

Rivaroxaban and apixaban are selective and reversible oral factor Xa inhibitors that inhibit free factor Xa and prothrombinase activity and clot-bound factor Xa activity. Rivaroxaban reaches a peak level rapidly, 1–3 h after oral intake and has an elimination half-life of 8–9 h in patients without significant renal dysfunction. Rivaroxaban is dependent on the kidney for 33 % of elimination and, thus, clearance is mildly influenced by renal function [4]. Apixaban is also rapidly acting, with peak levels occurring at 1–3 h after oral intake. Its elimination half-life is 7–8 h in patients without significant renal dysfunction, having 25 % renal clearance and the remainder cleared through non-renal mechanisms [7].

## Risk for perioperative thromboembolism

Thromboembolism risk stratification

We adapted the current guidelines on perioperative management of VKA therapy from the American College of Chest Physicians (ACCP) Antithrombotic Practice Guidelines (9th Edition) since these guidelines may be relevant also for patients receiving a NOAC [3]. The suggested risk stratification for perioperative thromboembolism (Table 1) and bleeding risk (Table 2) can guide decisions regarding heparin bridging, although the need for bridging in NOAC-treated patients is questionable (Table 3).

Although the overall risk for perioperative thromboembolism during VKA interruption appears to be low, concerns remain because of the potential clinical impact of such events. Cardioembolic stroke is associated with death or a major neurological deficit in 70 % of cases and mechanical valve-associated thrombosis is associated with an overall mortality of 15–20 % [8–10]. Moreover, in patients with VTE who develop recurrent VTE within

**Table 1** Suggested risk stratification for perioperative thromboembolism (adapted from ACCP Evidence-based Guidelines on Perioperative Management of Antithrombotic Therapy, 9th edition [3])

| Risk stratum | Indication for NOAC therapy | |
|---|---|---|
| | Atrial fibrillation | Venous thromboembolism |
| High | • $CHADS_2$ score of 5 or 6<br>• Recent stroke/TIA (≤3 months) | • Recent VTE (≤3 months) |
| Moderate | • $CHADS_2$ score of 3 or 4 | • Previous VTE (3–12 months)<br>• Recurrent VTE |
| Low | • $CHADS_2$ score of 2 (assuming no prior stroke or TIA) | • Previous VTE (>12 months) and no other risk factors |

**Table 2** Suggested risk stratification for perioperative bleeding risk (adapted from Spyropoulos et al. [22])

| | Operative bleeding risk | |
|---|---|---|
| | Low (2-day risk of major bleed of <2 %) | High (2-day risk of major bleed 2–4 %)* |
| Cardio-respiratory procedure/ surgery | • Bronchoscopy ± biopsy<br>• Non-coronary angiography<br>• Atrial fibrillation ablation<br>• Pacemaker/cardiac defibrillator insertion | • Coronary artery bypass |
| Dental surgery | • Simple dental extractions | • Multiple tooth extractions |
| General surgery | • Abdominal hernia repair<br>• Abdominal hysterectomy<br>• Axillary node dissection<br>• Biopsies: cutaneous, bladder, thyroid, breast and lymph node<br>• Carpal tunnel repair<br>• Cholecystectomy<br>• Hemorrhoidal surgery<br>• Hydrocele repair<br>• Gastrointestinal endoscopy<br>• Skin cancer excision | • Endoscopically guided fine needle aspiration<br>• PEG placement<br>• Polypectomy, variceal treatment, biliary sphincterectomy, pneumatic dilatation<br>• Colon resection<br>• Major cancer surgery |
| Orthopedic surgery | • Arthroscopy | • Hip and knee arthroplasty<br>• Surgery of shoulder, foot and hand |
| Urological/ Gynecological surgery | • Dilatation and curettage | • Kidney biopsy<br>• Transurethral prostate resection |
| Others | • Central venous catheter removal<br>• Cataract surgery | • Abdominal aorta aneurysm repair<br>• Laminectomy |

* Neurosurgical/urological/head and neck/abdominal/breast cancer surgery, vascular surgery and any major operation (procedure duration >45 min)

**Table 3** Suggested perioperative bridging therapy (adapted from the ACCP Evidence-based Guidelines on Perioperative Management of Antithrombotic Therapy, 9th edition [3])

| Bleeding risk | Thromboembolic risk | Bridging therapy |
|---|---|---|
| High | High | Yes |
| | Moderate | No |
| | Low | No |
| Low | High | Yes |
| | Moderate | Consider |
| | Low | No |

3 months of diagnosis, the case-fatality rate is 11.3 % (95 % confidence interval [CI] 8.0–15.2 %) [11].

## Effect of patient and surgery-related factors

The risk for perioperative thromboembolism appears to depend on patient characteristics and the type of surgery/procedure. In a linked administrative database study assessing patients who had elective surgery, the 30-day postoperative rate of stroke in 69,202 patients with AF was 1.8 % (95 % CI 1.7–1.9 %) as compared with 0.6 % (95 % CI 0.58–0.62 %) in 2,470,649 patients without AF [12]. Neurologic or vascular surgery conferred the highest absolute stroke risk (~2 %), whereas abdominal-pelvic surgery (e.g., cholecystectomy, hysterectomy) had the lowest risk (<1 %) [12]. In a study involving patients undergoing coronary artery bypass surgery who required VKA interruption, the 3-month incidence of any thromboembolism was 5.1 % (95 % CI 1.4–12.6) [13]. Active cancer was an independent predictor of thrombotic recurrence (hazard ratio [HR] 4.86; 95 % CI 1.6–14.5; $P = 0.005$) and death (HR 32.7; 95 % CI 4.3–251.2) according to a cohort study of 775 patients with VTE referred for periprocedural anticoagulation management [14]. Patients with active cancer had more VTE (1.2 vs. 0.2 %; $P = 0.001$) and reduced survival (95 vs. 99 %; $P < 0.001$) compared with those without cancer [15].

### Perioperative thromboembolism risk in bridged and non-bridged patients

The effect of heparin bridging to mitigate the risk for perioperative thromboembolism remains uncertain as all available studies comparing bridging and non-bridging strategies are observational. The evidence in VKA-treated patients suggests that the absolute risk for thromboembolism is low in both bridged and non-bridged patients after VKA interruption [4, 5].

In a cohort study of 556 patients with a mechanical heart valve (372 aortic, 136 mitral, 48 multiple valves) who required VKA interruption, of whom those with bileaflet aortic valves and no other stroke risks were not bridged, the 3-month incidence of thromboembolism was 0.9 % (0.5 % cerebral ischemia, 0.4 % acute coronary syndromes) [16]. A registry of 268 patients (40 % AF, 19 % VTE, 17 % mechanical heart valves) who had heparin bridging for a surgery/procedure showed a 1.3 % (95 % CI 0.4–3.2 %) risk of thromboembolism and a major bleeding risk of 7.4 % (95 % CI 4.9–10.9) [17]. A prospective cohort study evaluating the efficacy and safety of heparin bridging in 328 patients found a thromboembolic risk of 1.8 % (95 % CI 0.4–3.2) and a major bleeding risk of 2.1 % (95 % CI 0.6–3.6) [18]. In another prospective cohort study of 260 patients (67 % AF, 33 % VTE) who had a surgery/procedure and received heparin bridging, the risk of thromboembolism was 1.9 % (95 % CI 0.6–4.4 %) and the risk of major bleeding was 3.5 % (95 % CI 1.6–6.5) [19]. Finally, in a prospective cohort study of 345 patients with AF who, in most cases, were not bridged, the 3-month risk of thromboembolism and bleeding was 1.1 % (95 % CI 0–2.1) and 2.7 % (95 % CI 1.0–4.4), respectively [20]. Taken together, these studies suggest low and comparable rates of thromboembolism in bridged and non-bridged patients who require VKA interruption.

A meta-analysis of these and other observational studies totaling 12,278 VKA-treated patients showed no statistical difference in the risk of arterial thromboembolism in bridged and non-bridged patients (0.9 vs. 0.6 %; odds ratio [OR] 0.80; 95 % CI 0.42–1.54), but bridging increased the risk for major bleeding (OR = 3.60; 95 % CI 1.52–8.50) [21]. Even though periprocedural VTE was higher in these patients with prior VTE (2.0 vs. 0.16 %; $P = 0.002$), the rate of postoperative VTE did not appear to be affected by bridging (0.7 vs. 1.4 %; $P = 0.50$) [15]. However, since the periprocedural bridging was not randomly allocated, caution is needed when interpreting these findings because of potential for bias due to unmeasured confounders in bridged and non-bridged patients.

## Risk for perioperative bleeding

### Bleeding risk stratification

A perioperative bleeding risk stratification (Table 2) has been proposed and is applicable to VKA- and NOAC-treated patients who require an elective surgery/procedure [22]. This approach divides bleeding risk into two categories: low risk (2-day bleeding risk <2 %) and high risk (2-day bleeding risk 2–4 %) [22]. The HAS-BLED bleeding risk score, typically used in the non-operative setting, may also facilitate prediction of perioperative bleeding. Thus, in a prospective cohort study in 1,000 VKA-treated patients having an elective procedure a HAS-BLED score ≥3 was predictive of bleeding [23]. In another study involving patients who had VKA interruption, independent predictors of periprocedural bleeding were prior bleeding (HR 2.6; 95 % CI 1.5–4.5), mechanical mitral valve (HR 2.2; 95 % CI 1.1–4.3), heparin bridging <24 h post-procedure (HR 1.9; 95 % CI 1.1–3.4), and active cancer (HR 1.8; 95 % CI 1.0–3.1) [24].

### Perioperative bleeding risk in bridged and non-bridged patients

Patients with cancer appear to have more major bleeding and reduced survival than patients without cancer, and heparin bridging appears to increase perioperative bleeding [14, 15]. Perioperative bleeding risk with heparin bridging therapy may be understated. A retrospective observational study of 69 patients on warfarin who underwent a procedure or surgery with low-molecular-weight heparin [LMWH] bridging therapy demonstrated that the risk of major and minor bleeding was 2.9 % (95 % CI 0.8–10.0 %) and 1.4 % (95 % CI 0.3–7.8 %), respectively. There were no cases of thromboembolism [25].

## Perioperative management of patients receiving a novel oral anticoagulant

### Current evidence

The evidence for perioperative management of NOAC-treated patients is emerging with most studies focusing on patients receiving dabigatran who required AV node ablation for AF. Thus, a retrospective study of 211 patients with AV ablation who received dabigatran 110 mg twice-daily or warfarin showed that the dabigatran group had less bleeding (4.5 vs. 12.9 %; $P < 0.05$). There were no thromboembolic complications in either group. Dabigatran was held on the morning of the procedure and resumed the

morning post-procedure whereas the warfarin group did not interrupt treatment. Both groups received intravenous unfractionated heparin (UFH) during the ablation and an additional 10,000 U 24 h post-procedure [26]. On the other hand, an observation study of 290 patients undergoing AV ablation (145 patients interrupted dabigatran, 145 patients continued warfarin) showed that major bleeding (6 vs. 1 %; $P = 0.019$), total bleeding (14 vs. 6 %; $P = 0.031$), and a composite of bleeding and thromboembolism (16 vs. 6 %; $P = 0.009$) were higher in the dabigatran group [27]. There was no difference in the thromboembolic risk (2.1 vs. 0 %; $P = 0.25$) but dabigatran use was an independent predictor of a composite of bleeding or thromboembolism (OR 2.76; 95 % CI 1.22–6.25). In this study, the dabigatran was held on the morning of the procedure and resumed within 3 h after hemostasis following ablation. The warfarin group had their warfarin treatment uninterrupted. Intravenous UFH (10,000 U bolus) was given to all patients before the transseptal puncture [27]. A case–control study of 763 patients who had ablation for AF showed that withholding dabigatran ($n = 191$) for at least 24 h pre-procedure (two doses) and resuming it 4 h post-procedure (when hemostasis was secured) appeared as safe and effective as uninterrupted warfarin ($n = 572$). A bolus of UFH followed by continuous infusion (target activated clotting time 300–350 s) was administered after transseptal puncture. There was no difference in major bleeding (2.1 vs. 2.1 %; $P = 1.0$), minor bleeding (2.6 vs. 3.3 %; $P = 0.8$) and non-fatal pericardial tamponade (1.0 vs. 1.2 %; $P = 1.0$), and no thromboembolic complications in both groups [28]. Finally, a randomized trial of 90 patients who received dabigatran, 110 mg twice-daily, or warfarin prior to AV ablation showed that there was less bleeding in the dabigatran-treated group (20 vs. 44 %; $P = 0.013$). In this study, both anticoagulants were stopped on the morning of the ablation procedure and were resumed 4 h post-ablation (when hemostasis was secured) without the use of heparin bridging. Intravenous UFH was given following transeptal puncture and was reversed with protamine at the end of the procedure [29].

A sub-analysis of the RELY trial involving 4,591 patients who underwent at least one invasive surgery/procedure including pacemaker/defibrillator insertion, dental procedures, diagnostic procedures, cataract removal, colonoscopy, and major surgery showed no significant difference in the rates of periprocedural major bleeding (dabigatran 110 mg vs. warfarin 3.8 vs. 4.6 %; relative risk [RR] 0.83; 95 % CI 0.59–1.17; dabigatran 150 mg vs. warfarin 5.1 vs. 4.6 %; RR 1.09; 95 % CI 0.80–1.49). Patients assigned to either dabigatran dose had their last dose of study drug given, on average, 49 h pre-procedure as compared with 114 h pre-procedure in patients receiving warfarin. The risk of major bleeding was similar for those requiring urgent surgery (dabigatran 110 mg vs. warfarin 17.8 vs. 21.6 %: RR 0.82; 95 % CI 0.48–1.41; and dabigatran 150 mg vs. warfarin 17.7 vs. 21.6 %: RR 0.82; 95 % CI 0.50–1.35). Overall, 17 % of dabigatran-treated and 27 % of warfarin-treated patients requiring an elective surgery/procedure received heparin bridging [5].

## Perioperative laboratory monitoring

In general, perioperative laboratory monitoring of NOACs for elective surgery is not required unless the surgery/procedure is urgent and reassurance is required as to whether there is any residual anticoagulant effect after NOAC interruption. Current knowledge of how NOACs affect coagulation tests is emerging; in the meantime, clinicians should be aware of the effects of NOACs on common tests of coagulation and how these tests might be used for perioperative management. Assessment of the anticoagulant effect of NOACs should be considered prior to surgery, especially if the NOAC has been administered within 24 h of surgery or if the creatinine clearance is less than 50 mL/min [30].

Dabigatran, at therapeutic levels, prolongs the activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin time (TT). For dabigatran-treated patients, we suggest using the aPTT as an initial qualitative test for screening purposes [4, 30, 31]. An elevated aPTT (>80 s), measured 4–8 h after the last dose, likely reflects a higher than expected anticoagulant effect (perhaps related to bioaccumulation) whereas an aPTT of 45–80 s is an expected effect. A normal aPTT provides reassurance that there is likely no clinically significant residual anticoagulant effect, although there will be some variability depending on the aPTT assay used [32]. A TT is the most sensitive (indeed, too sensitive) test to detect a dabigatran anticoagulant effect such that a normal TT (<30 s) confirms no detectable dabigatran anticoagulant effect. However, such a test may remain elevated even days after dabigatran is stopped and likely does not reflect a clinically important residual anticoagulant effect [4, 6, 33]. If available, we suggest using a diluted TT (Hemoclot Thrombin Inhibitory assay) as a quantitative measure of the anticoagulant effect of dabigtran. This test likely is the most accurate method to measure the dabigatran anticoagulant effect [4, 30].

In the approved dose, apixaban has limited effect on the PT level. However, for rivaroxaban, the PT level can be used as a qualitative test for screening purposes [4, 30]. An elevated PT suggests the presence of some rivaroxaban effect although such a finding is PT assay-dependent [32]. A normal PT provides reassurance that there is likely no clinically significant residual rivaroxaban effect. Alternatively, an anti-factor Xa assay (typically used to measure

**Table 4** Perioperative management of patients who are receiving a NOAC (adapted from Douketis and Van Ryn et al.) [4, 6])

| | Type of NOAC | Dabigatran | | Rivaroxaban/apixaban | |
|---|---|---|---|---|---|
| | Creatinine clearance | >50 mL/min | 30–50 mL/min | >50 mL/min | 30–50 mL/min |
| Preoperative interruption of NOAC | Aim for no or minimal residual anticoagulant effect at surgery (4–5 drug half-lives between last dose and surgery) | Last dose: day-3 preoperatively (skip 4 doses) | Last dose: day-4 to day-5 preoperatively (skip 6–8 doses) | Last dose: day-3 preoperatively (rivaroxaban: skip 2 doses; apixaban: skip 4 doses) | Last dose: day-4 to day-5 preoperatively (rivaroxaban: skip 3–4 doses; apixaban: skip 6–8 doses) |
| | Aim for mild-moderate residual anticoagulant effect at surgery (2–3 drug half-lives between last dose and surgery) | Last dose: day-2 preoperatively (skip 2 doses) | Last dose: day-3 preoperatively (skip 4 doses) | Last dose: day-2 preoperatively (rivaroxaban: skip 1 dose; apixaban: skip 2 doses) | Last dose: day-3 preoperatively (rivaroxaban: skip 2 doses; apixaban: skip 4 doses) |
| Postoperative resumption of NOAC | Low bleeding risk | Resume at 24 h postoperatively | | Resume at 24 h postoperatively | |
| | High bleeding risk | Resume at 48–72 h postoperatively | | Resume at 48–72 h postoperatively | |

the anticoagulant effect of LMWHs) can be re-calibrated to provide a quantitative measurement of the anticoagulant effect of rivaroxaban and apixaban [4, 30].

## Proposed perioperative management

The ACCP Antithrombotic Therapy Guidelines recommend the assessment of perioperative bleeding and thromboembolic risks to guide decisions regarding the peri-procedural interruption of VKA therapy and use of heparin bridging [3]. A therapeutic dose of subcutaneous LMWH is recommended for those who required VKA interruption. It is stopped 24 h pre-operatively and can be resumed after 24 and 48 h following surgery for those with low and high bleeding risks, respectively [3]. There is no universal strategy for perioperative anticoagulation on NOAC therapy. Therefore, we propose for patients receiving NOAC a perioperative management approach similar to the one of patients receiving warfarin by adapting the ACCP guidelines [3] (Table 4).

## Role for bridging

In general, perioperative heparin bridging is not needed in NOAC-treated patients who require an elective surgery/procedure because of the rapid offset and onset of NOACs. However, heparin bridging may have a role in patients with high thromboembolic risk especially, in situations where there is impaired intestinal absorption (due to intestinal surgery) or an inability to take oral medications, (e.g., with enoxaparin 40 mg one-daily). Once the issue with impaired intestinal absorption is resolved and if patients are able to ingest oral medication, NOAC can be recommenced within 12 h of the last LMWH dose.

## Case vignette management

### *Case vignette 1*

This patient has a low perioperative thromboembolic risk ($CHADS_2$ score of 2). Preoperatively, we recommend aiming for no or minimal residual anticoagulant effect at surgery by skipping at least four doses of dabigatran pre-procedure. Since the postoperative bleeding risk was low, we recommend that dabigatran to be continued at 24 h postoperatively. Heparin bridging will not be required unless the patient is unable to tolerate oral medication postoperatively.

### *Case vignette 2*

This patient is at high risk for both perioperative thromboembolism (recent VTE within 3 months) and bleeding

(major orthopedic surgery). Pre-operatively, we recommend aiming for mild-moderate residual anticoagulant effect at surgery by skipping one dose of rivaroxaban. Post-operatively, rivaroxaban can be resumed initially with a low-dose regimen (10 mg daily) for 1–3 days followed by a resumption of therapeutic-dose rivaroxaban (20 mg daily). Heparin bridging will not be required unless she is unable to tolerate oral medication postoperatively.

## Future studies

Ongoing studies in NOAC-treated patients

Sub-analyses of the ROCKET-AF and ARISTOTLE trials, which compared oral factor Xa inhibitors (rivaroxaban, apixaban) to warfarin in patients with non-valvular AF, will provide useful information regarding perioperative management of patients receiving these NOACs. However, such analyses will have limitations because of their retrospective, post hoc nature. Consequently, prospective studies are needed to assess the safety and efficacy of standardized perioperative management strategies involving patients who are receiving dabigatran, rivaroxaban or apixaban and require an elective or urgent surgery/procedure.

## Summary

The prevalence of NOAC use is increasing. Due to the relatively rapid onset and offset of action of these agents, heparin bridging therapy should not be required, in general, unless post-operative oral intake is impaired. The balance between efficacy and safety, improved convenience, and potential cost-effectiveness benefits of NOAC will impact on the perioperative management of these patients. Further validation is urgently required to establish standardized perioperative management protocols and to determine the role, if any, of heparin bridging in NOAC-treated patients.

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