Perioperative management of patients taking direct oral anticoagulants: challenges in high-bleed-risk surgery and neuraxial anesthesia

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ABSTRACT

Perioperative direct oral anticoagulants (DOACs) management has been supported by guidelines, however there is still limited high quality data to inform best practices regarding the perioperative management of DOAC-treated patients who need a high-bleed-risk surgery, including those receiving any neuraxial anesthesia. Currently there are two potential competing strategies known as the "PAUSE management" and "ASRA management". PAUSE management, based on the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study of patients with atrial fibrillation who underwent an elective surgery/procedure, provides a standardized 2 full-day DOAC interruption for high-bleed-risk surgery/procedure, without the need for pre-operative heparin bridging or DOAC level testing. ASRA management, based on recommendations from the American Society of Regional Anesthesia (ASRA) guidelines, is somewhat more complex to ensure no residual DOAC level at the time of a high-bleed-risk procedure, using longer DOAC interruption intervals. Despite convincing rationales of both approaches there is uncertainty as to whether to follow PAUSE- or ASRA-based perioperative DOAC management. The rationale of the PAUSE-2 trial is discussed. Optimal perioperative DOAC management should address the following questions, and will be discussed in this review: i) should DOAC be interrupted; ii) for how long should DOAC be interrupted; iii) is bridging with heparin necessary; iv) is DOAC level measurement necessary; and v) how to manage DOAC resumption? This approach will be illustrated with the following case: an 85-year-old female with colon cancer, atrial fibrillation, chronic heart failure, hypertension, diabetes mellitus, transient ischemic attack ($CHADS_2$=6) and chronic kidney disease, treated with apixaban 5 mg twice-daily is scheduled to undergo open colectomy with neuraxial anesthesia.

Key words: direct oral anticoagulant, perioperative, high bleeding risk, neuraxial anesthesia.

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Contributions: all authors contributed to the conception, design and writing of this work and approved its final version.

Conflict of interest: JDD has no relevant financial disclosures over the past 30 months. EA and MPNt have nothing to declare.

Ethical approval and consent for publication: not applicable.

Availability of data and material: not applicable.

Funding: no funding was provided for this work.

Editor's note: this manuscript belongs to the issue BTVB 2026;5(3), dedicated to the memory of Armando D'Angelo.

Received: 12 March 2026.
Accepted: 22 April 2026.

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Licensee PAGEPress, Italy
Bleeding, Thrombosis and Vascular Biology 2026; 5:471
doi:10.4081/btvb.2026.471

Introduction

In the last decade, the widespread use of direct oral anticoagulants (DOACs), comprising dabigatran, apixaban, rivaroxaban and edoxaban, in patients with atrial fibrillation and venous thromboembolism has reshaped the medical landscape.[1] In North America and the European Union alone it is estimated that 6-8 million patients are treated with DOACs and about 20% of such patients will require an elective surgery or invasive procedure each year.[2,3] Standardized perioperative DOAC management is supported by guidelines in patients undergoing low-to-moderate bleeding risk procedures (*e.g.,* hernia repair, cholecystectomy, colonoscopy).[4-8] However, there is still uncertainty and limited data to inform best practices regarding the perioperative management of DOAC-treated patients who need a high-bleed-risk surgery (*e.g.,* cardiac, spinal, intracranial), which includes any patient receiving neuraxial (spinal, epidural) anesthesia and deep nerve blocks.[9-12]

This narrative review aims to discuss perioperative DOAC management, focusing on high-bleed-risk patients, using a practical, case-based format. A discussion will follow as to the rationale for the PAUSE-2 trial.

Perioperative direct oral anticoagulants management strategies

Currently, there are two potential strategies that clinicians can follow, referred to as "PAUSE management" and "ASRA management". PAUSE management is based on the Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study, which

assessed a standardized perioperative management approach in DOAC-treated patients with atrial fibrillation who required an elective surgery/procedure.[13,14] This management, which aims to be simple and easy to apply in clinical practice. Patients who need a high-bleed-risk surgery or any neuraxial anesthesia/procedure interrupt DOACs for 2 days before and 2-3 days after the surgery/procedure (*i.e.*, 4-5 full days off DOACs), and foregoes heparin bridging and perioperative DOAC level testing. The PAUSE study included 3007 patients and although it was associated with overall low rates of major bleeding (1.4%) and stroke (0.3%).[13] ASRA management is based on recommendations from the American Society of Regional Anesthesia (ASRA) guidelines and is somewhat more complex than PAUSE-based management.[9-11] Thus, ASRA management requiring 72-120 hours DOAC interruption and, in selected patients, pre-operative heparin bridging and DOAC level testing. The ASRA approach is primarily based on DOAC related pharmacokinetic data and may be considered more cautious to ensure no residual DOAC level at the time of a high-bleed-risk surgery or any neuraxial procedure, using longer DOAC interruption intervals.

Despite compelling rationales of both approaches, there is uncertainty as to whether to follow PAUSE- or ASRA-based DOAC management in patients having a high-bleed-risk surgery and, especially, if they are receiving any neuraxial anesthesia/procedure.[15] On the one hand, ASRA management seems to be safer by allowing longer preoperative DOAC interruption and the option of DOAC level testing. On the other hand, PAUSE management seems to be simpler as the preoperative DOAC interruption is based on "days off" and not "hours off", and does not involve DOAC level testing which is not widely available.[2,3]

Illustrative case

An 85-year-old female with atrial fibrillation, chronic heart failure, hypertension, diabetes mellitus, transient ischemic attack 2 years ago ($CHADS_2$=6) and chronic kidney disease, with a creatinine clearance (CrCl) of 45 mL/min, is receiving apixaban 5 mg twice-daily (8AM, 6PM). She recently was diagnosed with colon cancer and requires a colectomy via laparotomy (scheduled for next Friday at 8AM), which is considered a major and high-bleeding risk procedure. The patient will receive neuraxial (epidural) anesthesia, and concerns have been raised in the perioperative team about the optimal timing of discontinuation and resumption of DOAC. Additional questions were raised about the need of bridging given the patient's high $CHADS_2$ score (Table 1).

Stepwise management approach

An overall approach to perioperative DOAC management should address the following questions: i) Should apixaban therapy be interrupted; ii) if apixaban is interrupted, for how long; iii) if apixaban is interrupted, is bridging necessary with a low-molecular-weight heparin (LMWH); iv) is DOAC level testing needed preoperatively, the day before the surgery; and v) after surgery, how to manage the timing of DOAC resumption?

Should apixaban therapy be interrupted?

An essential component of perioperative DOAC management is determining the bleeding risk associated with the surgery/procedure, whether low-, low/moderate-, or high-bleed-risk. Both colectomy and epidural anesthesia are classified as high-bleed-risk interventions necessitating apixaban interruption in this patient.[16] There are selected procedures that are also considered minimal-bleed-risk in which anticoagulant therapy can be safely continued without interruption. Such procedures include minor dental and skin procedures (*e.g.*, tooth extractions, skin cancer removal), selected cardiac procedures (*e.g.*, cardiac pacemaker insertion, cardiac catheterization with a radial approach), and cataract surgery, which is essentially an avascular procedure.[4,17]

Additional factors that may affect the bleeding risk determination such as a prior history of bleeding, need for concomitant perioperative antiplatelet therapy (*e.g.*, in patients with a coronary stent), and procedure-specific factors. For the later consideration, for example, a colonoscopy done for cancer screening would be considered low/moderate-bleed-risk whereas patients requiring polypectomy would be considered high-bleed-risk.

For how long should apixaban be interrupted?

With PAUSE-based management, patients treated with DOACs, such as apixaban, who need a high-bleed-risk procedure (colectomy via laparotomy) should discontinue apixaban for two full days before the surgery.[2,3] This patient, in whom surgery is scheduled for Friday at 8AM, should receive the last dose of apixaban on Tuesday at ~6PM and Wednesday and Thursday should be considered as the "days-off" DOAC therapy. This approach corresponds to 62 hours interval between the last apixaban dose and the procedure, which is approximately 5 half-lives based on a reported half-life of 10-13 hours,[18,19] also listed in drug product monographs.

On the other hand and according to ASRA-based management, patients treated with DOACs, such as apixaban, who need a high-bleed-risk surgery such as colectomy, should discontinue apixaban longer as compared with PAUSE-based management. In this patient, taking into account the 15.2±8.5 hours half-life of apixaban as mentioned in the ASRA guideline, apixaban should be interrupted for at least 76 hours to allow a 5 half-life interval of interruption.[9,10] This patient, for whom surgery is scheduled for Friday at 8AM, would receive the last dose of apixaban on Monday at 6PM and Tuesday, Wednesday and Thursday should be considered as "hours-off" DOAC therapy. Thus, according to the ASRA-based discontinuation interval the patient will be off apixaban for a total of 86 hours.

As neuraxial anesthesia is also a high-bleed-risk procedure perioperative apixaban management should follow the above-mentioned approach. Both PAUSE- and ASRA-based management harmonize with the updated joint European Society of Anaesthesiology and Intensive Care (ESAIC) and European Society of Regional Anesthesia (ESRA) guidelines on regional anesthesia in patients on antithrombotic drugs where at least 72-hours of DOAC interruption prior to a surgical procedure is recommended, in order to minimize the risk for epidural hematoma, a rare but devastating complication which could lead to permanent lower-limb paralysis.[12] These guidelines also recommend an individual risk-benefit analysis for perioperative antithrombotic management in patients receiving regional, including neuraxial, anesthesia. In patients considered at high thromboembolic risk, where it may be preferable to continue the antithrombotic agents peri-operatively without interruption, other anesthetic management alternatives, such as general anesthesia should be considered.

The 2025 ASRA guidelines also distinguish management according to DOAC dosing whereby, for example in our patient, apixaban 5 mg twice-daily is considered a "high-dose" regimen, whereas apixaban 2.5 mg twice-daily is considered a "low-dose" regimen.[10] Accordingly, the ASRA guideline recommends at least a 72-hour interruption interval in patients receiving a high-dose DOAC regimen and a 36-hour interval in patients receiving a low-dose regimen. This distinction might be difficult to reconcile in practice because whereas a regimen of apixaban 2.5 mg twice-daily is indeed a lower-dose regimen it is administered to have a full therapeutic effect for stroke prevention in patients with atrial fibrillation who have 2 of 3 of the following criteria:

Table 1. Stepwise perioperative direct oral anticoagulants management using an illustrative case.

Clinical questions	Proposed strategy
Should apixaban therapy be interrupted	Yes, *apixaban should be interrupted*, as both colectomy via laparotomy and neuraxial anesthesia with catheter placement are *high bleeding risk* procedures. *Keep in mind the increased risk of *epidural hematoma*, which could lead to permanent lower-limb paralysis.
For how long	PAUSE management: *This patient*, in whom surgery is scheduled for Friday at 8AM, should receive their last dose of apixaban on Tuesday at ~6PM and Wednesday and Thursday should be considered as the "days-off" DOAC therapy. ASRA management: *This patient*, in whom surgery is scheduled for Friday at 8AM, they should receive the last dose of apixaban on Monday at 6PM and Tuesday, Wednesday and Thursday should be considered as the "hours-off". *Neuraxial anesthesia with catheter placement: Both "PAUSE" and "ASRA management" harmonize with the joint ESAIC and ESRA guidelines, where an *at least 72-hour DOAC interruption* prior to a surgical procedure is recommended. Chronic Kidney Disease: If this patient had a *CrCl< 30 mL/min*, they should have received their last apixaban dose on Monday at 6PM and Tuesday, Wednesday and Thursday should be considered as the "hours-off".
Is bridging necessary with a LMWH	The ACCP guidelines suggest against heparin bridging during perioperative DOAC interruption, as this could increase the risk of bleeding. *For patients* in need of a high bleeding risk procedure and a concomitant high thromboembolic risk low-dose LMWH (*e.g.*, enoxaparin 40 mg daily or dalteparin 5000 IU daily) could be started postoperatively within 24 hours and continued for 2 to 3 days before resumption of DOAC therapy. "ASRA management" suggests that "if the risk of VTE is high, LMWH bridge therapy can be instituted during stoppage of the anticoagulant and the LMWH can be discontinued 24 hours before the procedure". For *this patient*, according to "PAUSE management" they should not receive LMWH, while she could receive postoperative low-dose LMWH (enoxaparin 40 mg daily) or a low-dose unfractionated heparin (heparin, 5000 IU twice-daily), according to "ASRA management" arm as she could be considered as facing a high VTE risk (5 points, according to Caprini score).
Is DOAC level measurement necessary preoperatively	A preoperative DOAC level considered safe to allow surgery, especially high bleeding risk surgery, is yet to be established and there are limited data available on the effect of measuring preoperative DOAC levels on perioperative bleeding risk. For *this patient*, who is treated with high apixaban dose, has a CrCl of 45 mL/min, and who will undergo an elective high bleeding risk surgery/procedure (colectomy +/- epidural anesthesia with catheter placement) DOAC level testing can be obviated if PAUSE-based management is followed, with 2 full days of interruption, or if ASRA-based management is followed, with at least 72 hours DOAC interruption.
How to manage apixaban resumption - Colectomy without neuraxial anesthesia	PAUSE management: apixaban could be resumed since Sunday night or since Monday night, if hemostasis is secured. ASRA management: apixaban could be resumed since Monday night, if hemostasis is secured *High VTE risk (5 points, according to Caprini score): perioperative implementation (before the induction to general anesthesia and until discharge) of IPC should take place.
How to manage apixaban resumption - Colectomy with epidural anesthesia with catheter placement	High dosing of DOACs following epidural anesthesia with catheter placement: that DOACs cannot be resumed with an indwelling epidural catheter in situ and postoperative resumption of high dosing of DOACs should be administered only after the catheter withdrawal. For *this patient*, low dose of LMWH, such as enoxaparin ≤40 mg/day could be administered on Friday night, and at least 12 hours after needle and catheter placement and only if hemostasis is secured, followed by a second dose on Saturday night and no sooner than 24 hours after the first dose. The catheter could be removed on Sunday morning, 12 hours after the last dose of LMWH, low enoxaparin dose could be administered at least 4-6 hours after catheter removal. Apixaban could be resumed on Monday morning and no sooner that 24 hours after catheter removal. *High VTE risk (5 points, according to Caprini score): perioperative implementation (before the induction to general anesthesia and until discharge) of IPC should take place. *Epidural hematoma: The patient should be properly informed for any signs or symptoms related to any new or progressive neurological deficiency postoperatively and she should be assessed by a trained perioperative physician every 6-8 hours for at least 24 hours postoperatively. The multidisciplinary healthcare team should have high vigilance for any signs or symptoms of neurological deficiency and if any concerns about an epidural hematoma occur this patient should be assessed by a neurologist, and if needed immediate magnetic resonance imaging and surgical decompression should take place within 6 hours for neurological recovery.

PAUSE, perioperative anticoagulant use for surgery evaluation; DOAC, direct oral anticoagulant; ASRA, American Society of Regional Anesthesia; EISAC, European Society of Anaesthesiology and Intensive Care; ESRA, European Society of Regional Anesthesia; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

age >80 years; body weight <60 kg; serum creatinine >133 mmol/L. In the PAUSE study patients undergoing a high-bleed-risk surgery had 2 full days of apixaban interruption irrespective of whether they were receiving a 5 mg or 2.5 mg twice-daily regimen as both were considered *full-dose* for stroke prevention in atrial fibrillation depending on the above criteria.

Concomitant use of other drugs that affect hemostasis, such as ASA, clopidogrel, ticagrelor and NSAIDs, should be considered in terms of perioperative bleeding risk.[20] In this patient the apixaban, 5 mg twice-daily, dosing should be considered as a "high apixaban" dose, while patient age (>80 years) may further increase the bleeding risk.[21]

Lastly, in patients with impaired kidney function the aforementioned therapeutic plan still applies as this apixaban-treated patient with CrCl of 45 mL/min is above the 30 mL/min that would require an adjustment of the apixaban interruption interval.[6] The same approach also applies for patients with CrCl ≥30 mL/min who are treated with rivaroxaban and edoxaban. However, there are still limited data about the optimal perioperative management of DOACs in patients presented with CrCl <30 mL/min with severe renal insufficiency or those with end-stage renal disease who are dialysis-dependent.[22,23] For those patients the latest clinical practice guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) suggest an extending DOAC interruption by 1-2 additional days, beyond the standard 2 full days interruption.[6] If this patient had a CrCl <30 mL/min, she should have received her last apixaban dose on Monday at 6PM and Tuesday, Wednesday and Thursday should be considered as the "hours-off".

Need to bridge with low-molecular-weight heparin?

In general, the rapid offset and onset of action of DOACs obviates the need to interpose another short-acting anticoagulant such as LMWH for perioperative bridging. The American College of Chest Physicians (ACCP) guidelines suggest against heparin bridging during perioperative DOAC interruption, as this could increase the risk of bleeding; moreover, the occurrence of bleeding would delay the resumption of anticoagulants with the potential to increase the risk of arterial thromboembolism.[4] ASRA-based management suggests that *if the risk of VTE is high, LMWH bridge therapy can be instituted during stoppage of the anticoagulant and the LMWH can be discontinued 24 hours before the procedure*.[9]

Although not considered "bridging", which typically refers to the perioperative use of a therapeutic-dose LMWH regimen (*e.g.*, enoxaparin 1 mg/kg twice-daily or dalteparin 100 IU/kg twice-daily),[17] patients at high risk for postoperative venous thromboembolism (VTE), as in this case, can receive low-dose LMWH (*e.g.,* enoxaparin 40 mg daily or dalteparin 5,000 IU daily) starting within 24 hours after surgery and continued for 2-3 days before resumption of DOAC therapy.

Need to measure direct oral anticoagulants levels preoperatively on the day before surgery?

If available for clinical use, DOAC level testing has a similarly rapid turn-around time (around 30 minutes) as with other tests of coagulation function such as the prothrombin time and partial thromboplastin time.[20,24] Laboratories that have DOAC testing capacity typically have DOAC-calibrated anti-factor Xa level assays for apixaban, edoxaban, and rivaroxaban, and dilute thrombin time or ecarin clotting time assays for dabigatran.[25] Some laboratories might use anti-factor Xa assays that have been calibrated against LMWHs to measure DOAC levels, specifically for oral factor Xa inhibitors.[25] However, most hospital-based and other clinical laboratories do not have this capacity and DOAC level testing may require testing in an outside facility with a turnaround time that can be up to several days. Another problematic issue with DOAC level testing is uncertainty as to what constitutes a safe threshold for high-bleed-risk surgery or any neuraxial anesthesia.[26] Although a putative therapeutic range for DOACs is 200-300 ng/mL, a level that is considered safe for surgery is uncertain. In general, a DOAC level of <30 ng/mL is considered safe for a high-bleed-risk surgery or any neuraxial procedure, whereas a level of <50 ng/mL has been proposed as a potentially safe target for such procedures and, albeit in a different clinical setting, is considered an acceptable threshold to allow thrombolytic therapy in DOAC-treated patients who present with an acute ischemic stroke.[27,28]

Based on these considerations, practice guidelines do not advocate for routine DOAC coagulation function testing to guide perioperative DOAC management during DOAC interruption in patients undergoing an elective surgery/procedure; however, DOAC level testing is suggested in selected clinical situations, for example in patients who require urgent surgery in whom DOAC-level testing may inform the need for active DOAC reversal with administration of blood products or DOAC specific reversal agents.[4] The ASRA guideline suggests that in patients receiving a high-dose apixaban regimen (5 mg twice-daily) if apixaban has been discontinued for less than 72 hours prior to neuraxial block or deep plexus/peripheral block, apixaban-specific levels or LMWH-calibrated anti-factor Xa level could be checked.[10] A residual apixaban level <30 ng/mL or a residual anti-factor Xa level ≤0.1 IU/mL is acceptable prior to neuraxial block or deep plexus/peripheral block.[10,12] As far as the anti-Xa assay is concerned, it can be used when the last dose of DOACs is uncertain and the calibrated drug-specific plasma levels are not available.[10,12] An anti-factor Xa level ≤0.1 IU/mL or less is considered a non-detectable anticoagulant effect. Moreover, anti-Xa activity is very sensitive to the presence of DOACs and it could increase even when concentrations are <30 ng/mL.[10,12]

For this patient, who is receiving apixaban, has a CrCl of 45 mL/min, and who will undergo an elective high bleeding risk surgery DOAC level testing can be obviated if PAUSE-based management is followed, with 2 full days of interruption, or if ASRA-based management is followed, with at least 72 hours DOAC interruption.

When to resume apixaban after surgery?

Post-operative DOAC resumption should be considered carefully given the rapid peak anticoagulant effect, occurring 1-3 hours after DOAC intake.[18] Accordingly, DOAC resumption is contingent on surgical site hemostasis, which subjectively can be determined based on visual inspection of the wound and surgical site dressings, and blood loss measured in drains. The management also depends on the type of anesthesia a patient receives and whether there is continued post-operative epidural analgesia.

General anesthesia or intra-operative neuraxial anesthesia

In patients undergoing a high-bleed-risk surgery, PAUSE-based management suggests apixaban can be resumed 2-3 days postoperatively, which is aligned with ASRA-based management that suggests resumption within 3 days or 72 hours. With both approaches, apixaban resumption is contingent on surgical-site hemostasis. If there are concerns about hemostasis or ongoing bleeding an additional 1-3 days postoperative DOAC interruption is advisable. Moreover, in patients with high thrombotic risk a combination of mechanical, such as intermittent pneumatic compression (IPC) devices, and pharmacological prophylaxis is suggested, with as early resumption of anticoagulation as possible (24-72 hours), provided that the risk of bleeding has been ruled out and hemostasis is secured.[29,30]

For this patient, with PAUSE- and ASRA-based management they would resume apixaban Sunday or Monday evening if hemostasis was secured. Moreover, due to the high VTE risk given the surgery type and associated cancer, the perioperative use (before the induction to general anesthesia and until discharge) of IPC should be considered.[29,30]

Neuraxial anesthesia and post-operative epidural analgesia

In patients who received neuraxial anesthesia with an epidural catheter remaining *in situ* to administer analgesia, DOAC can only be resumed after catheter removal. Continuous epidural analgesia may be used in selected thoracic and abdominopelvic surgery. In these situations, low-dose LMWH (*e.g.*, enoxaparin ≤40 mg/day or dalteparin 5000 IU daily) may be used whilst the neuraxial catheter remains in place.[31] The first postoperative LMWH dose is administered at least 12 hours after needle and catheter placement, with the second dose given no sooner than 24 hours after the first dose. The epidural catheter should be removed 12 hours after the last dose of LMWH (as similar time intervals should be respected for insertion of a needle and/or catheter and for removal of a neuraxial catheter) and subsequent LMWH low dosing should occur at least 4 hours after catheter removal if needed.[5,6] The catheter removal should occur at least 24 hours prior to the first postoperative high apixaban dose.

Several other issues relating to neuraxial anesthesia warrant consideration. First, the manifestation of vessel puncture with blood in the neuraxial needle or catheter does not necessitate postponement of surgery, however it may increase the time interval to the next hemostasis altering medications. The initiation of LMWH therapy in this setting should be delayed for 24 hours postoperatively. Second, co-administration of low-dose LMWH and continuous epidural analgesia via an indwelling epidural catheter alone does not appear to represent an increased bleeding risk.[31] However, medications that affect hemostasis, such as antiplatelet drugs or NSAIDs, may increase bleeding risk and should be avoided. Third, vigilance of such patients is advised for any signs or symptoms of new neurological deficits that are harbingers of spinal/epidural bleeding.

For this patient, low-dose LMWH can be started 12 hours after needle and catheter placement if surgical-site and catheter-site hemostasis is secured, and a second dose of LMWH could be given about 24 hours after the first dose. Thus, the first dose could be given on Friday night, followed by a second dose on Saturday night. The catheter could be removed on Sunday morning, with low-dose LMWH administered 4-6 hours after catheter removal and apixaban could be resumed on Monday morning.

PAUSE-2 trial and rationale

PAUSE-2 is a randomized trial (NCT 04192552) comparing PAUSE- and ASRA-based management strategies in DOAC-treated patients with atrial fibrillation or VTE who require anticoagulant interruption for an elective surgery/procedure associated with a high bleeding risk, which encompasses any neuraxial procedure.[15,32] The study hypothesis is non-inferiority between PAUSE- and ASRA-based management for the primary outcome, defined as the proportion of patients with a residual preoperative DOAC level <30 ng/mL. Secondary outcomes include clinically important bleeding and thromboembolism.

The rationale for this trial is anchored on the following considerations: first, there are disparate recommendations from practice guidelines regarding perioperative DOAC management, which can result in uncertainty for clinicians as to which approach to follow. Second, in the PAUSE study only 1/3 of patients had a high-bleed-risk surgery and fewer (8%) had neuraxial anesthesia, thereby necessitating further study to investigate perioperative DOAC management in such patients.[13] Third, a survey of perioperative clinician practices in DOAC-treated patients found disparity in management approaches between anesthesiologist and internists but agreement on the need for a clinical trial to compare PAUSE- and ASRA-based management.[33] Finally, the PAUSE-2 pilot trial demonstrated the feasibility of a randomized trial to compare PAUSE- and ASRA-based management; this small, 150-patient study found that ~95% of patients in both groups had residual DOAC levels <30 ng/mL and 98% had levels <50 ng/mL.[32] The findings from the PAUSE arm of the pilot trial were consistent with those observed in the initial PAUSE study, where ~94% of patients having high-bleed-risk surgery had residual DOAC levels <30 ng/mL.[34] Taken together, the conditions of clinical equipoise appear to be satisfied that justifies undertaking a randomized trial in this clinical setting.

Conclusions and future research

Perioperative management of DOAC-treated patients who need a high bleeding risk procedure, such as colectomy via laparotomy, including those receiving neuraxial anesthesia (spinal, epidural with or without catheter placement), is still challenging due to the lack of high quality data to inform best practices. Currently there are two potential competing strategies known as the "PAUSE management" and "ASRA management", respectively. The "PAUSE management" is based on the Perioperative Anticoagulant Use for Surgery Evaluation study and is simpler, while "ASRA management" is based on the recommendations form the American Society of Regional Anesthesia guidelines and is somewhat more complex to ensure no residual DOAC level at the time of the high-bleed-risk procedure, using longer DOAC interruption intervals. Despite convincing rationales of both approaches there is uncertainty as to whether to follow PAUSE- or ASRA-based perioperative DOAC management and with these considerations

in mind, a randomized controlled trial of PAUSE versus ASRA management seems reasonable and essential.

Additional studies assessing perioperative DOAC management are needed in specific high-risk patient groups, including those having cancer-related procedures, cardiac and urological surgery.[35,36] Another area requiring further study is the management of DOAC-treated patients who need an emergency/urgent surgery.[37,38] Novel methods of DOAC reversal also are being assessed, including factor Xa variants and hemadsorption.[39,40]

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