Received: 11 May 2020 | Revised: 5 July 2020 | Accepted: 7 August 2020

DOI: 10.1002/rth2.12430

ORIGINAL ARTICLE

rpth research & practice in thrombosis & haemostasis

A physician survey of perioperative neuraxial anesthesia management in patients on a direct oral anticoagulant

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Handling Editor: Dr Neil Zakai

Abstract

Background: The perioperative management of patients taking a direct oral anticoagulant (DOAC) who require a high-bleed-risk surgery and/or neuraxial anesthesia is uncertain. We surveyed clinician practices relating to DOAC interruption and related perioperative management in patients having high-bleed-risk surgery with neuraxial anesthesia, and assess the suitability of a randomized trial of different perioperative DOAC management strategies.

Methods: We surveyed members of the American Society of Regional Anesthesia and Pain Medicine, the Canadian Anesthesia Society and Thrombosis Canada. We developed four clinical scenarios involving DOAC-treated patients who required anticoagulant interruption for elective high-bleed-risk surgery. In three scenarios, patients were to receive neuraxial anesthesia, and in one scenario they were to receive general anesthesia. We also asked about the merit of a randomized trial to compare a 2-day versus longer (3- to 5-day) duration of DOAC interruption.

Results: There were 399 survey respondents of whom 356 (89%) were anesthetists and 43 (11%) were medical specialists. The responses indicate uncertainty about the DOAC interruption interval for high-bleed-risk surgery and/or neuraxial anesthesia; anesthetists favor 3- to 5-day interruption whereas medical specialists favor 2-day interruption. Anesthetists were unwilling to proceed with neuraxial anesthesia in patients with a 2-day DOAC interruption interval, preferring to cancel the surgery or switch to general anesthesia. There is general agreement on the need for a randomized trial in this field to compare a 2-day and a 3- to 5-day DOAC interruption management strategy.

Conclusions: There is variability in practices relating to the perioperative management of DOAC-treated patients who require a high-bleed-risk surgery with neuraxial anesthesia; this variability relates to the duration of DOAC interruption in such patients.

KEYWORDS

direct oral anticoagulant, perioperative, physician survey, surgery neuraxial anesthesia

Essentials

- There is uncertainty about when to interrupt DOACs before surgery with spinal anesthesia.
- Anesthetists favor longer interruption than other physicians: 3-5 days versus 2 days.
- Anesthetists appeared unwilling to do spinal anesthesia if DOACs were interrupted for 2 days.
- There is a need to compare 3-5 versus 2 days DOAC interruption for surgery with spinal anesthesia.

1 | INTRODUCTION

The perioperative management of patients who are receiving a direct oral anticoagulant (DOAC), comprising apixaban, dabigatran, edoxaban, and rivaroxaban, is a common clinical problem as DOACs are the preferred anticoagulant for patients with atrial fibrillation and venous thromboembolism.[1,2] About 4 million patients per year in North America and Europe alone are assessed for perioperative DOAC management,[3,4] and this number is likely to increase with an aging population and an increasing prevalence of clinical indications for DOAC therapy.[5,6]

There are few well-designed studies to inform best practices for perioperative DOAC management[7]; moreover, clinical guidelines from medical societies and guidance statements from experts provide inconsistent recommendations.[8-12] The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study was the first to assess a standardized perioperative DOAC management strategy in patients receiving apixaban, dabigatran, or rivaroxaban. This study found that a simple perioperative management approach, comprising a 2-day DOAC interruption before and after a high-bleed-risk surgery/procedure and a 1-day DOAC interruption before a low-bleed-risk surgery (longer interruption for dabigatran-treated patients with impaired renal function) and without heparin bridging or coagulation function testing, was associated with low rates of major bleeding (<2%) and arterial thromboembolism (<1%).[13]

However, there may be ongoing uncertainty as to the perioperative DOAC management of patients who require high-bleed-risk surgery, in particular any surgery/procedure with neuraxial (ie, spinal or epidural) anesthesia. Neuraxial anesthesia has purported advantages over general anesthesia to mitigate against postoperative cardiac, respiratory, and neurobehavioral complications but is associated with an increased risk for epidural/spinal bleeding, a rare but potentially catastrophic complication, whose risk may increase in patients who are receiving anticoagulants or antiplatelet drugs.[9] Consequently, considerable attention is accorded to patients who are receiving anticoagulants and require neuraxial anesthesia to ensure a minimal or, preferably, no residual anticoagulant effect at the time of placement of the neuraxial block after anticoagulant interruption.[8,9] In warfarin-treated patients, reassurance can be provided with the preoperative measurement of the international normalized ratio (INR) but for patients who are receiving a DOAC, rapid tests like the INR to measure the anticoagulant effect are not widely available or if easily available, in the case of the thrombin time, are applicable only to patients on dabigatran.[14,15] In DOAC-treated patients, reassurance of no residual anticoagulant effect before surgery and neuraxial anesthesia is dependent on the timing of DOAC interruption so that a sufficient time interval elapses, based on the DOAC drug half-lives and (for some DOACs) the patient's renal function to allow elimination of their anticoagulant effect. Identifying the optimal DOAC interruption interval is important because if it is too long, it may expose patients to an increased risk for stroke and other thromboembolism, whereas if is too short, it may expose patients having high-bleed-risk surgery and/or neuraxial anesthesia to an increased risk for perioperative bleeding, including epidural/spinal hematomas.[16-18]

Among perioperative practice guidelines, those of the American Society of Regional Anesthesia and Pain Medicine (ASRA) provide comprehensive recommendations for managing DOAC-treated patients who require neuraxial anesthesia.[8,9] ASRA recommends interruption of DOACs for 3-5 days before a neuraxial procedure, with heparin bridging considered for patients at high thrombosis risk. The recommended DOAC interruption interval was based on conservative assumptions of DOAC elimination half-lives; the recommended use of heparin bridging was based on consensus/expert opinion. By comparison, guidance statements from thrombosis experts recommend a shorter 2-day DOAC interruption interval before any high-bleed-risk surgery/procedure, which encompasses any neuraxial procedure, and avoidance of perioperative heparin bridging.[19] Prior physician surveys of perioperative anticoagulant management did not address management in patients having high-bleed-risk surgery and/or neuraxial anesthesia.[20-24]

Against this background, we surveyed clinicians involved in perioperative DOAC management with the primary aim of identifying practices relating to DOAC interruption in patients having high-bleed-risk surgery and/or neuraxial anesthesia. Secondarily, we assessed the perioperative use of heparin bridging in such patients and management if patients presented for surgery with DOAC interruption of 2 days, which may be considered insufficient. Finally, we gauged clinicians' viewpoints regarding the need for additional clinical trials in this area.

2 | METHODS

2.1 | Survey administration

The survey was sent between October 1 and November 30, 2019, to three medical societies, selected to include anesthetists/

TABLE 1 Clinical Scenarios and Questions Presented to Survey Participants

Scenario 1	*A 66-year-old man with hypertension and diabetes with chronic atrial fibrillation ($CHADS_2$ = 2) is scheduled for elective radical prostatectomy with general anesthesia this coming Monday at 8 AM. He takes dabigatran 150 mg twice daily and his CrCl = 66 mL/min.*
Questions	The DOAC interruption interval you recommend is: • 2 d (last dose Friday PM) • 3 d (last dose Thursday PM) • 4 d (last dose Wednesday PM) • 5 d (last dose Tuesday PM)
Scenario 2	*A 66-year-old man with hypertension and diabetes with chronic atrial fibrillation ($CHADS_2$ = 2) is scheduled for elective radical prostatectomy with spinal anesthesia this coming Monday at 8 AM. He takes dabigatran 150 mg twice daily and his CrCl = 66 mL/min.*
Questions	1) The DOAC interruption interval you recommend is: • 2 d • 3 d • 4 d • 5 d 2) This patient arrives at hospital on Monday at 6 AM, having been told by his doctor to continue dabigatran until Friday PM. You would recommend: cancel surgery proceed with surgery but change to general anesthesia proceed with surgery and spinal anesthesia proceed with surgery and spinal anesthesia but administer a DOAC reversal agent
Scenario 3	*A 75-year-old woman with hypertension and diabetes ($CHADS_2$ = 3) with chronic atrial fibrillation and severe COPD is scheduled for radical hysterectomy for endometrial cancer with spinal anesthesia this Monday at 8 AM. She takes apixaban 5 mg twice daily and her CrCl = 66 mL/min.*
Questions	1) The DOAC interruption interval you recommend is: • 2 d • 3 d • 4 d • 5 d 2) Should she receive heparin bridging? • yes • no
Scenario 4	*A 75-year-old woman with hypertension and diabetes with a TIA 2 years ago ($CHADS_2$ = 5) with chronic atrial fibrillation and severe COPD is scheduled for radical hysterectomy for endometrial cancer with spinal anesthesia this Monday at 8 AM. She takes apixaban 5 mg twice daily and her CrCl = 66 ml/min.*
Questions	1) The DOAC interruption interval you recommend is: • 2 d • 3 d • 4 d • 5 d 2) Should she receive heparin bridging? • yes • no 3) This patient arrives at hospital on Monday at 6 AM, having been told by her doctor to continue apixaban until Friday PM. You would recommend: • cancel surgery • proceed with surgery but change to general anesthesia • proceed with surgery and spinal anesthesia • proceed with surgery and spinal anesthesia but administer a DOAC reversal agent

Abbreviations: COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; TIA, transient ischemic attack.

anesthesiologists (hereafter referred to as anesthetists) and medical specialists, comprising hematologists and internists (hereafter referred to as medical specialists): the American Society of Regional Anesthesia and Pain Medicine (www.asra.com); the Canadian Anesthesia Society (www.cas.ca); and Thrombosis Canada (www.thrombosiscanada.ca). The survey was reviewed by the executive director or equivalent of each society and was distributed electronically to its membership. The survey timing was chosen so that it occurred after the dissemination of the PAUSE study, which was initially presented in December 2018, at the American Society of Hematology conference (https://doi.org/10.1182/blood-2018-120770) and published in full in August 2019.[13]

All survey participants and responses were anonymized. There were no financial or other material incentives provided for survey participants. Among anesthesia or thrombosis society members to whom the survey was sent, we asked that survey participation be

limited to clinicians with experience in perioperative DOAC management. We anticipated, given the relative size of the three medical societies, that we would obtain considerably more responses from anesthetists than from medical specialists.

2.2 | Clinical case and questionnaire development

A multidisciplinary group (internist, hematologist, anesthesiologist, research coordinator) developed and/or reviewed four hypothetical clinical scenarios, described in Table 1, all of which involved DOAC-treated patients with chronic atrial fibrillation who required anticoagulant interruption for an elective high-bleed-risk surgery; patients were to receive neuraxial anesthesia in three scenarios and general anesthesia in the fourth scenario. For each scenario, survey participants were asked to indicate the duration, in days, of preoperative DOAC interruption they would recommend; in two scenarios, participants were asked to indicate if they would administer perioperative heparin bridging; and in two other scenarios, participants were asked to provide management if the patient presented on the morning of the day of surgery having had 2 days of DOAC interruption. The management options provided to the survey participants are shown in Table 1.

Survey participants were also asked, as shown in Table 2, to comment on which practice guidelines they follow for perioperative DOAC management, their understanding of the existing knowledge relating to perioperative DOAC management, and the need for future research in this clinical domain. Specifically, as there is discordance between thrombosis societies (ie, Thrombosis Canada) and anesthesia societies (ie, ASRA) as to the recommended duration of DOAC interruption before a high-bleed-risk surgery/neuraxial anesthesia, we inquired as to the merit of a randomized trial to compare a short (2 days) versus longer (3-5 days) duration of interruption as advocated by these respective medical societies.

2.3 | Analysis

Given the exploratory, descriptive nature of this clinician survey, there were no planned hypotheses and associated statistical (ie, comparative) analyses. We planned to describe the proportion of all respondents and, separately, the proportion of anesthesiologists and nonanesthesiologists who selected each of the potential responses to the survey questions. We also planned to describe the characteristics of the survey respondents.

3 | RESULTS

3.1 | Survey administration and respondent characteristics

The survey was carried out in October and November 2019, with two reminders sent to medical society members 3 weeks apart after the initial request. As shown in Table 3, there were 399 survey respondents of whom 356 (89%) were anesthetists, and 43 (11%) were medical specialists. Of these respondents, 342 (86%) completed all of the survey questions. The proportion of members of the Canadian Society of Anesthesiology and Thrombosis Canada who were eligible to complete the survey (ie, dealt with perioperative DOAC management) and participated in the survey was 19%, and 41%, respectively. We could not reliably determine the proportion of members from the ASRA who were eligible to complete the survey, as this is a large (>5000 member) North American organization; however, we estimate that it was <5%.

3.2 | Responses to clinical scenarios

The responses to the clinical scenarios are shown in Figure 1.

TABLE 2 Questions related to practice guidelines, existing evidence, and future research

Question 1	*For perioperative DOAC management, I follow:* • guidance from expert opinion sources (eg, Up-to-Date) • guidance from thrombosis expert sources (eg, Thrombosis Canada) • guidelines from the American Society of Regional Anesthesia • guidelines from nonanesthesiology groups (eg, European Society of Cardiology)
Question 2	*For perioperative DOAC management in high-bleed-risk surgery (as described in the clinical scenarios), the existing evidence to inform clinical practice is*: • high quality (ie, additional research unlikely to affect practice) • moderate quality (ie, additional research may affect practice) • low quality (ie, additional research likely to affect practice) • very low quality (ie, additional research definitely needed)
Question 3	*For perioperative DOAC management in high-bleed-risk surgery, there is a need for a randomized trial to compare shorter preoperative DOAC interruption (advocated by thrombosis experts) with longer DOAC interruption (advocated by anesthesia societies)*: • definitely yes • possibly yes • possibly no • definitely no

TABLE 3 Characteristics of Survey Respondents

Survey Respondent Characteristic	Number (%)
Specialty	
Anesthetist	356 (89)
Medical specialist (internist, hematologist)	43 (11)
Practice setting	
Academic/teaching hospital	193 (48)
Community hospital	79 (20)
Mixed academic/community	111 (28)
Other	16 (4)
Years in practice	
<10	141 (35)
10-20	115 (29)
>20	143 (36)
Country of practice	
Canada	228 (57)
United States	139 (35)
Other	32 (8)

3.2.1 | Scenario 1

In this scenario involving a patient on dabigatran scheduled to have a high-bleed-risk surgery with general anesthesia, the most frequently recommended dabigatran interruption interval was 3 days (32%), with a higher proportion recommending either a 4- or 5-day interruption (45%), and a minority recommending a 2-day interruption (23%). There was an apparent preference of anesthetists to select a > 2-day dabigatran interruption (73%) as compared with medical specialists who selected a 2-day interruption (67%).

3.2.2 | Scenario 2

In this scenario involving the same patient as scenario 1 but with planned neuraxial anesthesia, there was a tendency to favor a longer dabigatran interruption interval than in scenario 1. The most frequently recommended dabigatran interruption interval was 5 days (28%), with a higher proportion recommending a 3- or 4-day interruption (43%), and a minority recommending a 2-day interruption interval (14%). As in scenario 1, anesthetists appear to favor a longer interruption interval than medical specialists. When presented with the situation that the patient presented for surgery having had 2 days of dabigatran interruption, a high proportion of respondents recommended proceeding with surgery but changing to general anesthesia (37%) or canceling the surgery (36%). A minority of respondents would proceed with the surgery and neuraxial anesthesia without (14%) and with (2%) administration of a DOAC reversal agent. As in the other scenarios, anesthetists (81%) preferred a >2-day interruption interval than medical specialists (63%) and, if presented with a 2-day dabigatran interruption, were more likely to cancel the surgery (38%) than medical specialists (21%).

3.2.3 | Scenario 3

In this scenario involving a patient on apixaban with a $CHADS_2$ score of 3 who was scheduled to have surgery with neuraxial anesthesia, the most frequently recommended apixaban interruption interval was 3 days (63%), with a lower proportion recommending a 2-day interruption (28%), and a minority recommending either a 4- or 5-day interruption (9%). Heparin bridging was recommended by a small minority of respondents (20%). As in scenarios 1 and 2, more anesthetists (77%) preferred a > 2-day apixaban interruption interval than medical specialists (24%), and, in this scenario, preferred heparin bridging (22%) than medical specialists (3%).

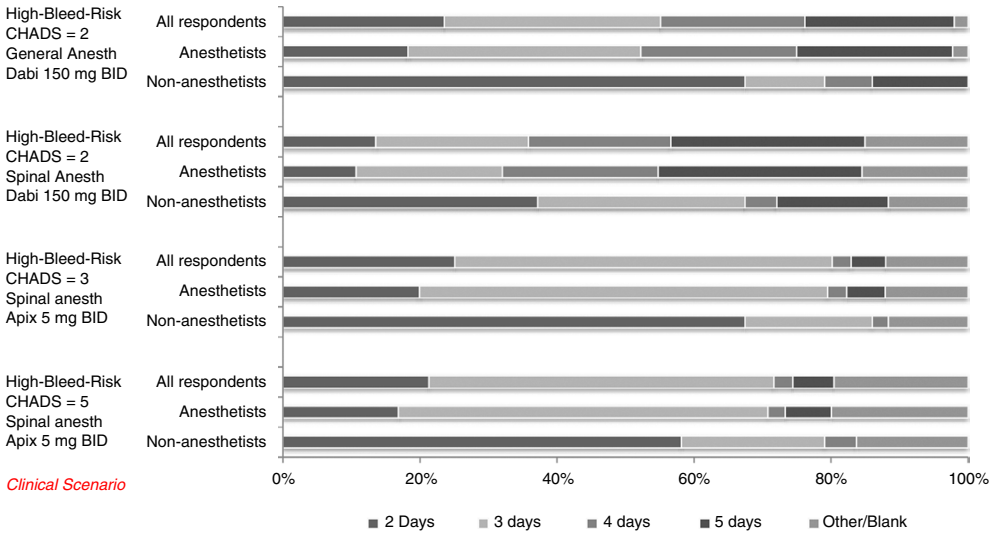
3.2.4 | Scenario 4

In this scenario involving a patient on apixaban with a $CHADS_2$ score of 5 who was scheduled to have surgery with neuraxial anesthesia, the most frequently recommended apixaban interruption interval was 3 days (64%), with a lower proportion recommending a 2-day interruption (35%), and a minority recommending either a 4- or 5-day interruption (11%). Heparin bridging was recommended by a considerable minority of all respondents (44%). As in scenarios 1, 2, and 3, anesthetists (73%) preferred a > 2-day interruption interval than medical specialists (31%) and, if confronted with 2 days of apixaban interruption, were more likely to cancel the surgery (37%) than medical specialists (3%). As in scenario 3, it appeared that anesthetists (48%) preferred heparin bridging more than medical specialists (9%).

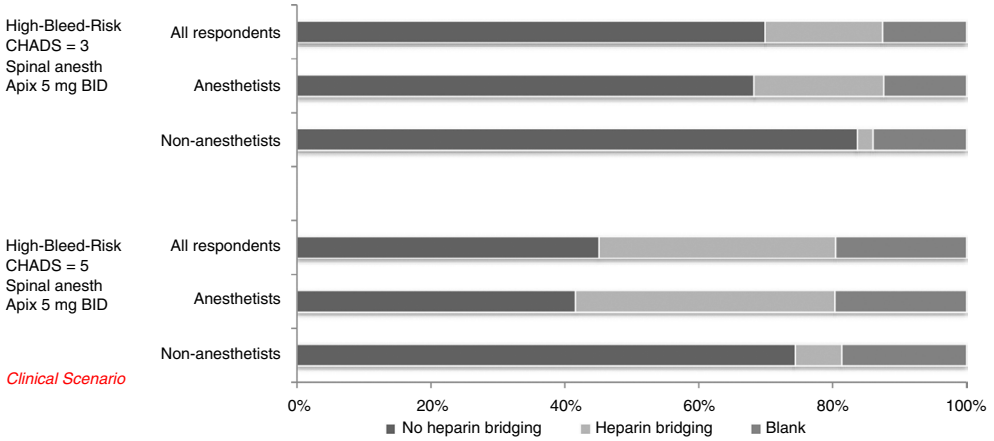
3.3 | Questions about practice guidelines, current evidence, and need for additional research

As shown in Figure 1, when asked which clinical practice guidelines are followed for perioperative DOAC management, most anesthetists (69%) followed the ASRA guidelines, whereas most medical specialists (85%) followed other society guidelines. As regards the quality of current evidence to inform perioperative DOAC management, the majority of respondents rated it as low quality (48%) or moderate quality (39%), with small minority of respondents rating the evidence as very low quality (8%) or high quality (5%). As regards the need for a randomized controlled trial to compare short (2 days) versus longer (>2 days) durations of DOAC interruption before a high-bleed-risk surgery/neuraxial anesthesia, the majority of respondents considered the need for such a trial as definitely yes (46%) or possibly yes (44%), whereas a small minority considered the need for such a trial as definitely no (9%) or possibly no (1%). There appeared to be concordance

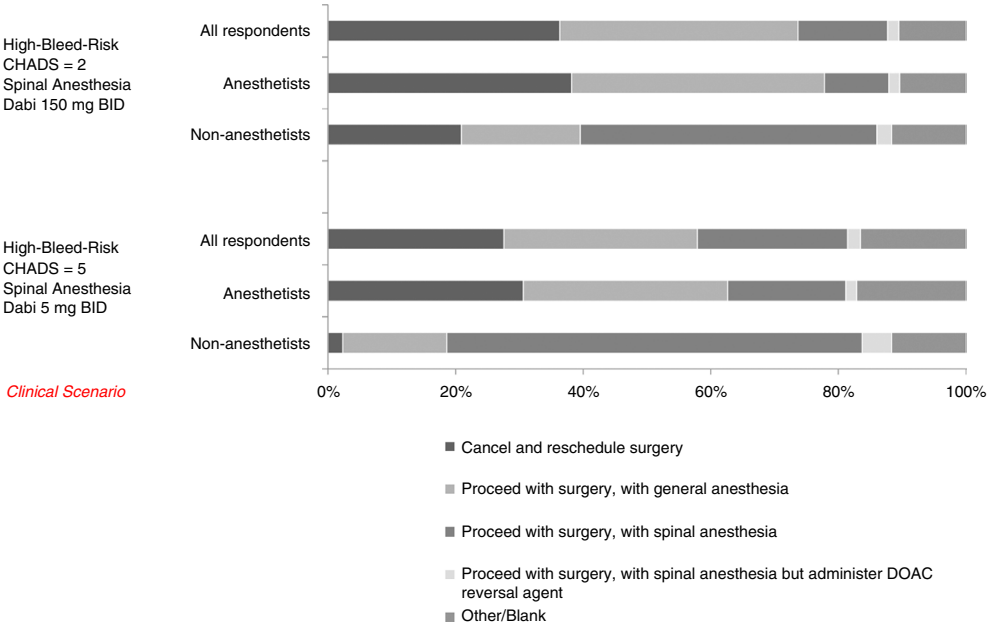
(A) *When would you interrupt a DOAC before surgery?*



(B) *Do you use pre-operative heparin bridging?*



(C) *What is your management if patient present for planned surgery with spinal anesthesia and as interrupted DOACs for 2 days?*



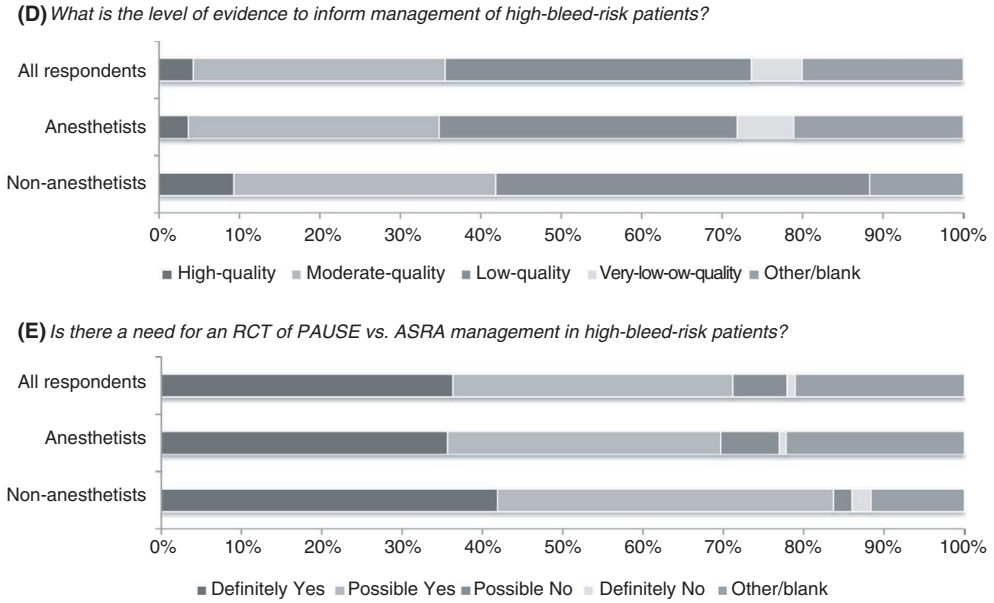


FIGURE 1 Replies to survey questions

on these nonclinical management questions between anesthetists and medical specialists.

4 | DISCUSSION

We surveyed clinicians involved in the perioperative management of DOAC-treated patients who required an elective high-bleed-risk surgery with, in most cases, neuraxial anesthesia with the aim of identifying practice patterns to different clinical scenarios and to gauge the need for future research in this field. There are two principal findings from this clinician survey. First, there is uncertainty as to the optimal DOAC interruption interval before high-bleed-risk surgery and/or neuraxial anesthesia, although it appears that anesthetists favor a longer, 3- to 5-day, interruption duration, whereas medical specialists favor a shorter 2-day interruption. Related to this finding, clinicians, particularly anesthetists, appear unwilling to proceed to surgery with neuraxial anesthesia in patients with a 2-day DOAC interruption interval, preferring to either cancel the surgery or switch from neuraxial to general anesthesia. Second, there is acknowledgment that the evidentiary basis for perioperative DOAC management is limited in patients having elective high-bleed-risk surgery and/or neuraxial anesthesia, and there is general agreement on the need for a randomized trial in this field to compare a shorter (2 days) versus a longer (3-5 days) DOAC interruption management strategy in such patients. An additional, secondary finding is that patient thrombosis risk appears to be of importance in perioperative management. Thus, a sizeable minority of clinicians would consider use of heparin bridging and were more likely to choose a shorter-duration DOAC interruption in patients perceived to be at high thrombosis risk (ie, $CHADS_2$ score > 3). These findings can be considered within the context of the PAUSE study, which reported low rates of major bleeding (<2%) and arterial thromboembolism (<1%) in high-bleed-risk patients who had a 2-day DOAC interruption interval.[13]

Our first main finding can be explained, in part, by anesthetists' perhaps justifiable tendency to follow the ASRA guidelines on perioperative DOAC management, which recommends a 3- to 5-day interruption before a neuraxial intervention. Thus, when comparing the DOAC interruption interval in the first and second scenarios, which involving patients undergoing general or spinal anesthesia, an interruption interval of 2 days was chosen by a lower proportion of patients having spinal than general anesthesia. The reluctance among anesthetists to proceed with neuraxial anesthesia after a 2-day DOAC interruption is further demonstrated when, if asked to manage patients who presented on the surgery day with a 2-day interruption, a higher proportion of anesthetists than medical specialists would cancel the surgery. The more conservative approach in this group of clinicians is likely due to the much more catastrophic risk of paralysis if a bleed occurs in the neuraxial space (however rare) versus a surgical bleed, which typically is easier to diagnose and more readily managed.

We also found that most respondents acknowledged the limitations of the existing evidence for perioperative DOAC management, despite the fact that the PAUSE study, which provided the first assessment of a standardized perioperative DOAC management strategy, was first presented 10 months before the study was presented and 2 months after formal publication. Moreover, there was agreement as to the need for a randomized trial to compare a short PAUSE-based DOAC interruption strategy to the longer ASRA-based interruption strategy.

Previous studies that assessed physician practices for perioperative anticoagulant management addressed general perioperative management in unselected patients,[21,22,24] focused on patients having cardiac device implantation[23] or dermatologic procedures,[20] addressed the type of clinician managing perioperative anticoagulation,[25] or only assessed management in patients who required

emergency surgery.[26] The present study is the first, to our knowledge, to address perioperative DOAC management in an important high-risk patient group undergoing a high-bleed-risk surgery/any neuraxial anesthesia.

We acknowledge limitations of this clinician survey, foremost of which is the low response rate among anesthetists and the overall modest number of respondents, especially medical specialists Although this may have impacted on the generalizability of results, this appears less likely, as there was apparent consistency in responses according to the physician group. Second, the study also only addresses a few fixed, although generalizable, scenarios with limited information. However, the intent of the study was exploratory, aimed to investigate perioperative DOAC management after the publication of the PAUSE study. Moreover, other contemporary, electronically administered clinician surveys have similar low response rates.[20,24] Third, we acknowledge that our survey addressed a narrow component of perioperative anticoagulant management, focusing on patients who are undergoing a high-bleed-risk surgery with neuraxial anesthesia, as this is the area that we consider to have the most uncertainty in terms of best practices. Other clinician surveys have addressed a broader scope of perioperative antithrombotic management involving DOAC- and warfarin-treated patients and those receiving antiplatelet therapy.[20-22,25] Finally, it is possible that the survey was administered in too close proximity to publication of the PAUSE study results, 10-11 months after its initial presentation in December 2018. However, the PAUSE study received considerable attention after publication and our intent was to capitalize on interest after its dissemination.

In summary, this clinical survey suggests there is variability in practices relating to the perioperative management of DOAC-treated patients who require an elective high-bleed-risk surgery with neuraxial anesthesia; in particular, there was variability as to the duration of DOAC interruption in such patients. The findings from this survey support the need for randomized trials, for example, comparing ASRA- and PAUSE-based management in high-bleed-risk patients (to include those having any neuraxial procedure), to inform best practices for perioperative DOAC management.

AUTHOR CONTRIBUTIONS

JD, NL, SS, SN, SS, JD, and ACP contributed to the conception of the paper; all authors contributed to data analysis; JD, NL, SS, and ACP developed the first draft (), and all authors critically reviewed the final draft of this paper.

RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

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How to cite this article: Douketis JD, Syed S, Li N, et al. A physician survey of perioperative neuraxial anesthesia management in patients on a direct oral anticoagulant. *Res Pract Thromb Haemost*. 2021;5:159–167. https://doi.org/10.1002/rth2.12430