

ORIGINAL ARTICLE

# Management of oral anticoagulants prior to emergency surgery or with major bleeding: A survey of perioperative practices in North America: Communication from the Scientific and Standardization Committees on Perioperative and Critical Care Haemostasis and Thrombosis of the International Society on Thrombosis and Haemostasis

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## Abstract

**Background:** There is limited information on real-world practice versus current clinical practice guidelines for oral anticoagulant reversal before emergency surgery.

**Objective:** To identify current practice/knowledge gaps for oral anticoagulant reversal emergency surgery among anesthesiologists.

**Methods:** A 22-question survey covering aspects of clinical practice relating to oral anticoagulant reversal was sent to American Society of Anesthesiology members with weekly reminders during data collection from October to December 2018.

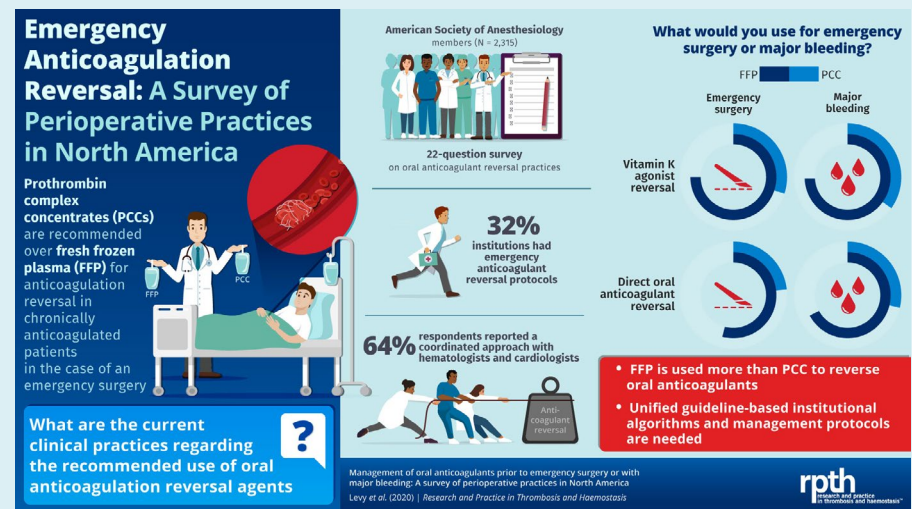
**Results:** Responses were received from 2315 anesthesiologists of which 86% of respondents were United States based. Emergency surgery was defined as occurring within 4 hours of the decision to operate by 60% of respondents. Fresh frozen plasma (FFP) was used by 75% of respondents for vitamin K antagonist (VKA) reversal and by 54% for direct oral anticoagulant (DOAC) reversal in emergency surgery and 67% in major operative bleeding. Only 32% of institutions had emergency anticoagulant reversal protocols, and 54% of respondents selected an international normalized ratio (INR) ratio goal for VKA reversal of  $\leq 1.5$ . Only 13% initially consulted or coordinated management with hematologists, and the final decision regarding coagulation management was made by the respondent in 26% of cases. A coordinated approach with hematologists and cardiologists was reported by 64%, and over half (51%) required approval for prothrombin complex concentrate administration for emergency procedures.

**Conclusions:** Despite recommendations to the contrary, FFP is extensively used for emergency VKA and DOAC reversal. There is a clear need for institutions to develop

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guideline-informed recommendations/management algorithms based on input from medical professionals routinely involved in management of these patients.



#### KEYWORDS

anticoagulants, antidotes, apixaban, bleeding, dabigatran, fresh frozen plasma, prothrombin complex concentrates, rivaroxaban, warfarin

#### Essentials

- Perioperative management of oral anticoagulants was surveyed among anesthesiologists.
- Plasma was preferred over commercial prothrombin complex concentrates to reverse oral anticoagulants in emergencies.
- Only 32% of institutions had protocols for emergency oral anticoagulant reversal for surgery.
- Oral anticoagulant guideline-based institutional algorithms and management protocols are needed in this setting.

## 1 | INTRODUCTION

Patients presenting for surgery are often chronically anticoagulated, typically for the treatment of venous thromboembolism, and the prevention of embolic stroke in patients with atrial fibrillation or a mechanical heart valve.<sup>1</sup> When these patients require an emergency surgery or invasive procedure, urgent anticoagulation reversal is required, but such management is often poorly understood by clinicians. Anticoagulant reversal is likely to become an increasingly common clinical scenario, given an aging population and associated potential for increased anticoagulant use.

In several guidelines and guidance documents (eg, American College of Cardiology, American College of Chest Physicians), prothrombin complex concentrates (PCCs) are the recommended agents for vitamin K antagonist (VKA) reversal in adults requiring an urgent surgery/procedure or with acute major bleeding.<sup>2-7</sup> They are also recommended for patients receiving direct oral anticoagulants (DOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban if a DOAC-specific reversal agent is not available.<sup>2,8,9</sup> In our experience, multiple factors may complicate emergency therapy of patients who are receiving anticoagulants, including a lack of product availability, insufficient knowledge about use, or an inefficient hospital-based

process that impedes timely access or release of anticoagulant reversal agents.

Against this background, we created a survey to distribute to anesthesiologists to determine current clinical practices and clinician understanding of the recommended use of these agents. The survey included questions relating to institutional protocols such as access to agents and need for approval from other clinical team members. We also reviewed the potential current uses for coagulation factor concentrates in alternative settings, such as in the management of VKA-associated life-threatening bleeding and DOAC reversal. We considered that the results of the survey would help to guide improved education and knowledge among clinicians who manage these perioperative emergency situations.

## 2 | METHODS

A 22-question survey relating to oral anticoagulant reversal was designed by the lead author of this publication, an anesthesiologist currently involved in clinical practice, and refined following discussions with colleagues in the field. The survey (Appendix S1) was circulated in its final form to approximately 50 000 members of the American

**TABLE 1** Characteristics of survey respondents

Characteristic	Proportion of respondents (%)
<b>Age</b>	
≤30 y	3
31-40 y	24
41-50 y	25
51-60 y	31
61-70 y	15
≥70 y	2
<b>Country</b>	
United States	86
Non-US	15
<b>Area of clinical focus</b>	
General anesthesia	36
No specific area of focus	24
Cardiothoracic	18
Other	11
<b>Practice setting</b>	
Community hospital	60
Academic teaching institution	40

Note: Participants could select ≥1 country or area of clinical focus. Areas including >5% of respondents are listed. N = 2310 for age, N = 2299 for country, N = 2251 for area of clinical focus, and N = 2304 for practice setting.

Society of Anesthesiology (ASA); the survey was not piloted prior to circulation. Anonymous responses were collected using the Survey Monkey platform; no incentivization was provided, and respondents were permitted to miss questions. For treatment strategy questions, respondents were asked to select their preferred treatment strategy and to indicate all applicable options; individual or combined use was not specified. Weekly reminders were sent during data collection from October 22 to December 4, 2018. Results are presented descriptively.

### 3 | RESULTS

We received responses from 2315 anesthesiologists (ie, 4.5% of ASA members). Of the 22 questions in the survey, 19 were answered by >97% of respondents; lower response rates were shown for conditional questions (ie, "If you answered 'Yes' to the previous question..." [Q19: 63%] or "If you use PCCs..." [Q20: 87%]) and questions requesting free text (Q22: 41%). Of the 2315 respondents, 86% were based in the United States, 60% were community practitioners, and 40% practiced in an academic clinical setting; key characteristics of respondents are shown in Table 1. All percentages were calculated based on the number of respondents who provided data response for that particular question rather than the overall number of participants.

General anesthesia was listed as the main clinical focus by 36% of respondents, with 24% reporting no specific area of focus.

Emergency surgery was defined as occurring within 4 hours of the decision to operate by 60% of respondents. Notably, only 32% of institutions had a protocol for emergency VKA reversal. In terms of routinely conducted coagulation tests for bleeding patients, 96% of respondents selected the International Normalized Ratio (INR) testing, 89% selected a platelet count, and 82% selected the activated partial thromboplastin time. Thromboelastometry, rotational thromboelastometry, and platelet function studies were less frequently selected, by 28%, 13%, and 13% of respondents, respectively.

#### 3.1 | Therapies for acute VKA reversal prior to emergency surgery

Fresh frozen plasma (FFP) was selected by 75% of respondents, with 30% selecting 4-factor (4F)-PCC (Figure 1A). Overall, 41% of respondents selected a single therapy; 25% selected FFP and 9% selected 4F-PCC as sole therapy. A total of 59% of respondents selected ≥2 therapies, including FFP and intravenous (IV) vitamin K (35%), FFP and 4F-PCC (15%), and 4F-PCC and IV vitamin K (13%). Overall, 54% of respondents selected ≤1.5 as the INR goal for VKA reversal; a further 16% selected an INR ≤ 1.4, while 13% selected an INR ≤ 1.3.

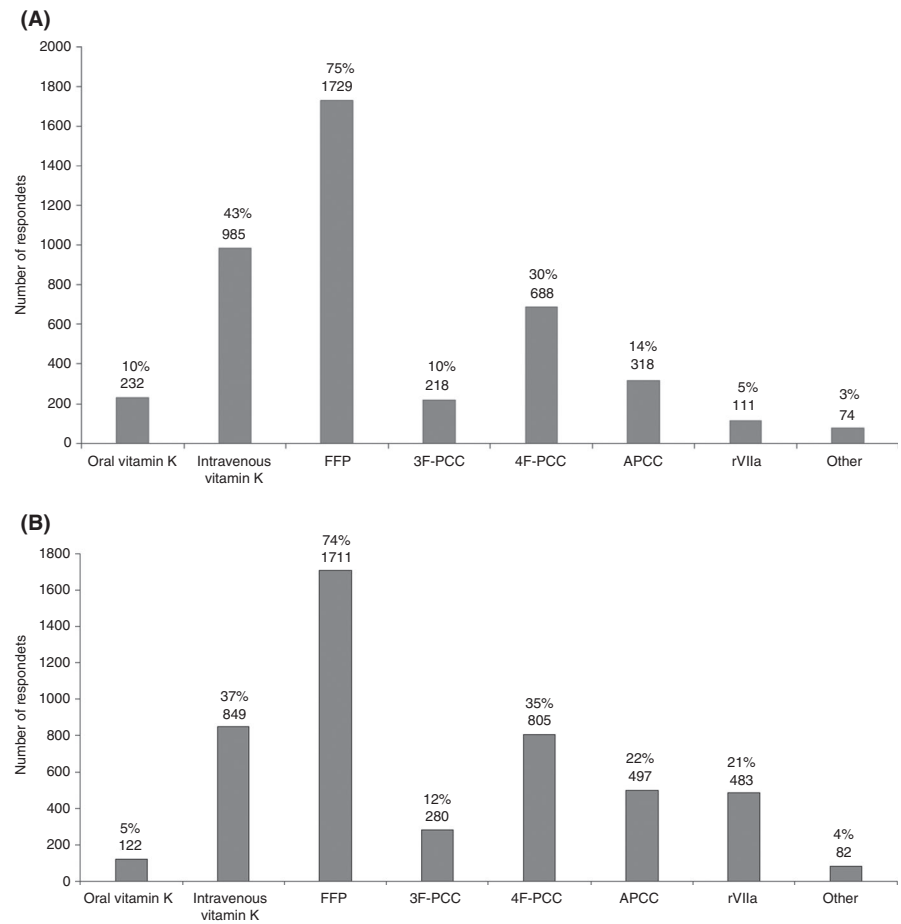
#### 3.2 | Therapies for VKA reversal in major bleeding

Results for emergency surgery and major bleeding (defined as overt, uncontrollable, or life-threatening bleeding) were similar, with 74% of respondents selecting FFP and 35% selecting 4F-PCC (Figure 1B). Approximately one-third (35%) of respondents selected a single therapy; of these, 18% selected FFP alone, and 8% selected 4F-PCC alone. Most respondents (66%) selected ≥2 therapies; 31% of respondents selected FFP and IV vitamin K, while 21% selected FFP and 4F-PCC and 14% selected 4F-PCC and IV vitamin K. Just under half of all respondents (47%) did not use any adjunctive therapies for VKA reversal, while 43% selected antifibrinolytic agents, and 24% selected desmopressin; the majority of respondents (64%) did not sequentially conduct routine preoperative bedside point-of-care INR monitoring for patients requiring VKA reversal.

#### 3.3 | Therapies for DOAC reversal prior to emergency surgery

FFP was the preferred management option prior to emergency surgery by 54% of respondents, with 23% selecting 4F-PCC (Figure 2A). Similar to VKA reversal, 45% of respondents opted for a single therapy, with 21% selecting FFP alone and 10% selecting DOAC withdrawal alone; fewer than 5% of respondents selected either the DOAC antidote (idarucizumab) or 4F-PCC as sole therapy. Most respondents opted for ≥2 therapies (55%), with 21% opting for combined DOAC withdrawal and DOAC antidote (idarucizumab). The type of DOAC used was not specified.

**FIGURE 1** A, Therapies selected for VKA reversal prior to emergency surgery. Respondents could choose more than 1 therapy. N = 2303. B, Therapies selected for VKA reversal in major bleeding. Respondents could choose more than 1 therapy. N = 2303. 3F-PCC, 3-factor prothrombin complex concentrate; 4F-PCC, four-factor prothrombin complex concentrate; APCC, activated prothrombin complex concentrate; FFP, fresh frozen plasma; rFVIIa, recombinant factor VIIa; VKA, vitamin K antagonist



### 3.4 | Therapies for DOAC reversal in major bleeding

Again, similar results were shown for both emergency surgery and major bleeding, with 68% of respondents selecting FFP and 29% selecting 4F-PCC (Figure 2B). Respondents were less likely to select a single therapy compared with VKA reversal (30% vs 35%), but those who did preferred FFP (16%); similar proportions of respondents selected stopping the DOAC only, DOAC antidote (idarucizumab), or 4F-PCC as sole therapy [2%-3%]. Overall, 71% of respondents selected treatment with  $\geq 2$  therapies for DOAC reversal in major bleeding, with combined DOAC withdrawal and DOAC-specific antidote therapy recommended by 23%.

### 3.5 | Factors affecting anticoagulant reversal strategy

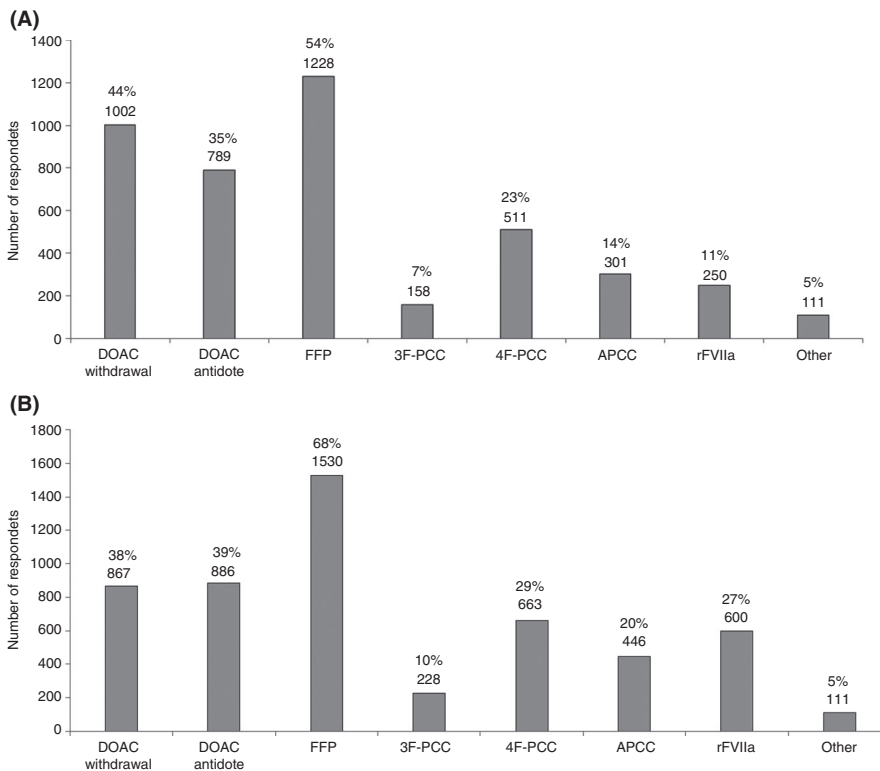
Surgery type (major or minor) was the dominant consideration when selecting the anticoagulation reversal strategy by 93% of respondents. Other factors considered important when selecting a therapy for emergency surgery or major bleeding included time to achieve hemostasis (85%) and risk of bleeding complications (61%), while risk of volume overload, time to infusion, and risk of thromboembolic complications were less frequently selected (41%, 37%, and 33%, respectively). Approximately half of the respondents (49%) selected  $\geq 3$  factors for consideration.

### 3.6 | Institutional protocols for anticoagulant reversal

Only 13% of respondents consulted/coordinated management with hematologists during their initial patient evaluation, and the final decision regarding coagulation management was made by the respondent in 26% of cases. Overall, 64% reported a coordinated approach in which potential approaches were discussed with hematologists and cardiologists, and over half of respondents (51%) required hematologist approval for PCC administration for emergency procedures. Respondents who were able to prescribe 4F-PCC without hematologist approval were generally permitted (85% of respondents) to prescribe for indications beyond intracranial hemorrhage. PCCs were obtained from the pharmacy at 61% of sites and the blood bank in 33%.

## 4 | DISCUSSION

The principal finding from this survey of anesthesiologist practices in clinical settings requiring rapid reversal of anticoagulation is that clinical management is suboptimal, heterogeneous, and not always in accordance with evidence-based practice recommendations.<sup>2-9</sup> Specifically, we found that FFP is used widely for emergency VKA reversal, with 75% of respondents selecting this treatment option prior to emergency surgery or in cases of major bleeding.<sup>10</sup> Although



**FIGURE 2** A, Therapies for direct oral anticoagulant (DOAC) reversal prior to emergency surgery. Respondents could choose more than 1 therapy. N = 2275. B, Therapies for direct oral anticoagulant (DOAC) reversal in major bleeding. Respondents could choose more than one therapy. N = 2264. 3F-PCC, three-factor prothrombin complex concentrate; 4F-PCC, four-factor prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate; FFP, fresh frozen plasma; DOAC, direct oral anticoagulant; rFVIIa, recombinant factor VIIa; VKA, vitamin K antagonist. DOAC antidote refers to idarucizumab – for use in patients treated with dabigatran only

4F-PCC has been available in the United States since 2013<sup>11</sup>, FFP continues to be the most consistently selected treatment for VKA reversal prior to emergency surgery. Multiple treatment options (including FFP, IV vitamin K, and 4F-PCC) were frequently selected, although the results of this survey do not specify whether agents were administered individually or in combination, or whether the agent selected for use might vary between patients. It should be noted that when administering 4F-PCC for VKA reversal, recommendations are to administer vitamin K concurrently to allow for hepatic synthesis of functional clotting factors, which is necessary, as the clotting factors in PCC have variable half-lives ranging from 6 to 72 hours.<sup>4,12</sup> Interestingly, the majority of respondents (68.3%) stated that their institution did not have a standardized protocol for managing emergency VKA reversal.

The frequent selection of FFP for emergency VKA reversal is in contrast with current guidelines, which recommend the use of 4F-PCC rather than FFP or plasma as the primary treatment for emergency VKA reversal.<sup>2,4</sup> Factor concentrates including PCCs, specifically, 4F-PCCs, offer advantages over FFP, as they can be stored at room temperature, require smaller volumes of administration (~20 mL per 500 U), and are more rapidly infused<sup>1,7,9,13,14</sup> The manufacturing process for PCCs includes steps to inactivate and/or remove viruses and other pathogens to minimize the risk of pathogen transmission.<sup>1,7,9</sup> They do not require ABO compatibility, obviating the need for crossmatching, and reduce the risk of acute volume overload, as they are usually administered in volumes not exceeding 500 mL, especially in patients needing preoperative reversal.<sup>7,14</sup> The United Kingdom National Health Service has reported that PCCs for emergency VKA reversal are more cost effective than plasma.<sup>15</sup> In randomized trials, 4F-PCC reduced the INR more rapidly than FFP, with 55% of patients treated with 4F-PCC achieving a target INR

of  $\leq 1.3$  versus 10% of patients in the plasma group at 30 minutes after the end of infusion.<sup>16</sup> Another trial showed similar results, with 62% of patients treated with 4F-PCC experiencing rapid INR reduction (ie,  $\leq 1.3$  30 minutes after infusion) compared with 10% of patients treated with FFP, although FFP achieved the same INR results at 24 hours.<sup>17</sup> The majority of respondents stated that surgery type was a key consideration for their choice of treatment strategy. Time to hemostasis was of high concern, while risk of volume overload was also noted; these considerations would be thought to support the use of PCCs, as they have a more rapid effect on INR and are associated with a lower risk of fluid overload compared with FFP.<sup>16,17</sup>

Notably, only a small number of anesthesiologists consulted/coordinated management with hematologists during their initial patient evaluation, and the final decision regarding coagulation management was made by anesthesiologists in approximately one-quarter of cases. Over half of respondents reported a coordinated approach with hematologists and cardiologists, and almost half required approval from a hematologist for PCC administration for emergency procedures. It is of interest that 4F-PCCs were obtained from the pharmacy at the majority of sites, as other transfused products (eg, factor concentrates, FFP, packed red blood cells, cryoprecipitate, platelets, and fibrinogen) are usually released from the blood bank. This institutional preference for pharmacy management of factor concentrates may be linked to superior tracking, purchasing, and inventory systems, as well as barcode labeling and the fact that storage requirements for factor concentrates are generally less stringent compared to blood products and so can be readily accommodated in a pharmacy environment.<sup>13,18,19</sup>

DOAC management continues to be an issue in the perioperative setting, as measuring the effects of the factor Xa (FXa) inhibitors is not always possible.<sup>20</sup> Although andexanet alfa has been approved



for FXa inhibitor reversal in the United States and European Union (for life-threatening or uncontrolled bleeding only),<sup>21</sup> the drug has not been studied in surgical or procedural patients and has a relatively short duration of effect of approximately 3 hours.<sup>22,23</sup> For emergency surgery, only idarucizumab is approved in most countries for dabigatran reversal.<sup>24</sup> However, dabigatran does not appear to be widely used in the United States, based on data from a cross-sectional analysis of medical and pharmacy claims made by patients with atrial fibrillation, with only 4% of those on DOAC therapy taking dabigatran.<sup>25</sup> Although off label, the use of PCCs for major bleeding in patients receiving DOACs is increasingly reported and provides a potential therapeutic approach for managing bleeding as a hemostatic measure.<sup>26,27</sup> Although PCCs are used by clinicians over DOAC-specific antidotes, their use can be considered counterintuitive, as coagulation factor levels in DOAC-treated patients are not diminished as with VKA-treated patients. Consequently, the premise that PCCs will reverse the effect of DOACs is predicated on the assumption that supraphysiologic levels of clotting factors will overwhelm the inhibitory effect of DOACs on thrombin generation. However, this assumption requires validation, with assays able to assess neutralization of DOAC activity not widely available. Approximately 20% of respondents in the current survey selected 4F-PCC as a treatment strategy for urgent DOAC reversal, indicating its relevance.

The relative popularity of activated PCC and recombinant factor VIIa (selected by 22% and 21% of respondents, respectively) for VKA reversal was unexpected, as these products are not recommended in this patient population<sup>2,5,7</sup> reasons for this include their relatively high thromboembolic risk and potential for lower efficacy (ie, vitamin K-dependent factors are not replenished as a result of their administration).<sup>5,7</sup> The frequent selection of FFP for patients requiring DOAC reversal is similarly perplexing, as administration of FFP has no obvious role in DOAC reversal. These findings are of concern, as they indicate a lack of understanding among anesthesiologists regarding oral anticoagulant pharmacology and optimal reversal methods for these agents.

There are some potential limitations to this study. Anesthesiologists routinely manage urgent preoperative anticoagulant reversal and procedural major bleeding, and this survey was designed to clarify their approaches to these tasks. However, it is conceivable that respondents may have misunderstood or misinterpreted questions, affecting the results. For example, it is possible that some respondents may have interpreted the question as asking how they would manage major bleeding in general (ie, outside the context of anticoagulation reversal). On a similar note, the question regarding coagulation tests routinely performed in bleeding patients did not specify whether the tests were being performed in patients whose anticoagulation status was known, and it is not clear whether respondents would wish to apply their selected treatment strategies for emergency surgery/major bleeding individually or in combination. In addition, no particular DOAC types were specified in the survey questions, so respondents may have selected several potential treatment strategies to encompass suitable approaches for direct thrombin inhibitor (ie, dabigatran) or FXa inhibitor (ie, rivaroxaban/apixaban/edoxaban) reversal. We acknowledge the possibility of misinterpretation and recognize that responses to hypothetical scenarios such as those posed by these questions do not always accurately reflect

actual clinical practice; however, this latter point is a known shortcoming of survey-based research. We note that scope for misinterpretation could have been partially reduced if the survey had been piloted prior to wider circulation; this will be taken into consideration for future surveys.

Over 2000 responses were received from anesthesiologists who frequently use oral anticoagulation reversal agents. The response rate is relatively low, considering the number of ASA members (52 000), and so may not be representative of the ASA membership as a whole; the distinction between respondents and nonrespondents (ie, factors leading to nonresponse) is also unclear. However, we believe the actual number of respondents is sufficiently high to render the results presented here both relevant and informative.

In summary, despite guidelines and guidance reports that recommend PCC as first-line therapy for reversal of VKA, FFP is still extensively used for emergency VKA and DOAC reversal. This result, in agreement with other results discussed here, may be symptomatic of a range of issues, including a need for ongoing training in the changing management of anticoagulated patients, misunderstanding of guideline recommendations, and a need to engage with hospitals and health care providers to ensure that protocols are in place to guide treatment of these patients. We believe improved knowledge translation of practice guidelines is needed to optimize the management of patients who need rapid reversal of anticoagulants for emergency surgery or life-threatening bleeding. Moreover, in an effort to optimize administration of anticoagulant reversal agents, we recommend a "top-down" approach whereby institutions develop guideline-informed recommendations and management algorithms with input from key stakeholders (eg, anesthesiologists, transfusion medicine, hematologists, laboratory services, surgeons, intensivists) involved in the management of such patients.

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## RELATIONSHIP DISCLOSURE

JHL serves on research steering committees or scientific advisory boards for CSL Behring, Instrumentation Laboratories, Janssen, Merck, and Octapharma. JMC: research funding to the institution: CSL Behring; consultancy, scientific advisory board participation, and data and safety monitoring board participation: Abbott, Bristol-Myer Squibb (BMS), Dova Pharmaceuticals, Portola, Unum Therapeutics. ACS serves on advisory role for Janssen, Boehringer Ingelheim, Bayer, ATLAS Group; research funds from Boehringer Ingelheim, Janssen. MS and JD declare nothing to report.

## AUTHOR CONTRIBUTIONS

JHL developed the survey, reviewed with JMC and MS, obtained approval to circulate from the American Society of Anesthesiologists, and wrote the initial manuscript draft. JHL, JMC, and MS analyzed

the data and wrote subsequent drafts. JD and ACS critically reviewed and edited the manuscript. JHL edited the revisions, with critical reviews from the other authors.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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