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ORIGINAL RESEARCH

The Practice of Emergency Medicine

Definition of factor Xa inhibitor–related, life-threatening gastrointestinal bleeding and guidance on when to use reversal therapy: A Delphi panel

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Abstract

Objective: To define and contextualize life-threatening gastrointestinal (GI) bleeding in the setting of factor Xa (FXa) inhibitor therapy and to derive a consensus-based, clinically oriented approach to the administration of FXa inhibitor reversal therapy.

Methods: We convened an expert panel of clinicians representing specialties in emergency medicine, gastroenterology, vascular medicine, and trauma surgery. Consensus was reached among the clinician panelists using the Delphi technique, which consisted of 2 survey questionnaires followed by virtual, real-time consensus-building exercises.

Results: Hypovolemia and hemodynamic instability were considered the most important clinical signs of FXa inhibitor–related, life-threatening GI bleeds. Clinician panelists agreed that potentially life-threatening GI bleeding should be determined on the

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basis of hemodynamic instability, signs of shock, individual patient characteristics, and clinical judgment. Last, the panel agreed that all patients with life-threatening, FXa inhibitor–associated GI bleeding should be considered for FXa inhibitor reversal therapy; the decision to reverse FXa inhibition should be individualized, weighing the risks and benefits of reversal; and when reversal is elected, therapy should be administered within 1 h after initial emergency department evaluation, when possible.

Conclusions: Consensus-based definitions of life-threatening GI bleeding and approaches to FXa inhibitor reversal centered on hemodynamic instability, signs of shock, individual patient characteristics, and clinical judgment. The results from this Delphi panel may inform clinical decision-making for the treatment of patients experiencing GI bleeding associated with FXa inhibitor use in the emergency department setting.

KEYWORDS
anticoagulant reversal, factor Xa inhibitor, gastrointestinal hemorrhage

1 | INTRODUCTION

1.1 | Background

Bleeding is the most common complication of anticoagulant use, representing approximately 80% of anticoagulant-related emergency department visits.[1] The most frequent type of major bleeding associated with the use of oral anticoagulants is gastrointestinal (GI) bleeding,[2] which has significant implications for patient outcomes, including a high risk of all-cause mortality, thrombosis, and recurrent bleeding.[2–4] Mortality estimates ≥10% have been reported among adult patients hospitalized for acute upper GI bleeding without account for anticoagulation.[5,6] Additionally, real-world studies show that GI bleeding–related hospitalizations are associated with a prolonged length of stay of 5 days, on average,[4,7] and rates of hospital readmission >18% within 30 days of discharge.[4] Notably, a meta-analysis comparing the safety of direct oral anticoagulants (DOACs) with vitamin K antagonists found that DOACs were associated with an increased risk of GI bleeding.[8] As the use of DOACs increases,[9–11] a comprehensive understanding of DOAC-associated GI bleeding is critical for decision-making in emergency care environments, particularly in the setting of life-threatening GI bleeding and when considering the appropriateness and timing of anticoagulation reversal therapies.

1.2 | Importance

DOACs comprise the thrombin inhibitor dabigatran[12] and factor Xa (FXa) inhibitors, which include apixaban,[13] edoxaban,[14] and rivaroxaban.[15] Currently, 2 DOAC-specific reversal agents are available: idarucizumab, for the reversal of dabigatran,[16] and andexanet alfa (coagulation FXa [recombinant] inactivated-zhzo), which is approved for the reversal of apixaban and rivaroxaban in the United States (US) and the European Union and recently received approval for the reversal of apixaban, rivaroxaban, and edoxaban in Japan.[17–20] The use of reversal agents for the emergency treatment of patients with life-threatening, DOAC-associated GI bleeding is supported by US and European guidelines and agencies (eg, National Institute for Health and Care Excellence [NICE],[18] British Society of Gastroenterology,[21] American College of Gastroenterology [ACG],[22] and ACG-Canadian Association of Gastroenterology [ACG-CAG][23]). However, DOAC-related GI bleeding, specifically, is not well-defined. Furthermore, although previous research characterized the use of anticoagulant reversal therapies in the emergency department setting,[24] GI bleeding was not specifically addressed. A clear consensus has not yet been reached, and guidance is lacking for clinicians treating patients with DOAC-related GI bleeds in the emergency department setting.

Because DOAC reversal therapies are indicated in patients with life-threatening bleeding, it is crucial to support clinicians in understanding what defines life-threatening GI bleeding to ensure a standardized treatment approach, reduce delays to treatment, and improve patient outcomes. Recent ACG-CAG guidelines defined life-threatening GI bleeding as "major clinically overt or apparent bleeding resulting in hypovolemic shock or severe hypotension requiring pressors or surgery or associated with a decrease in hemoglobin of greater than 5 g/dL, requiring transfusion of greater than or equal to 5 units of packed red blood cells, or causing death."[23,25] However, this definition was derived from a 2011 consensus report aimed at developing a standardized definition of bleeding as an end point for cardiovascular clinical trials and registries[26] and is not specific to GI bleeding associated with FXa inhibitor use encountered in the emergency department setting. Accordingly, the present study aimed to refine the definition of life-threatening GI bleeding in the context of FXa inhibitor use.

1.3 | Goals of this investigation

We conducted a Delphi panel exercise to define and contextualize "life-threatening" GI bleeding among 8 selected expert practitioners based on their experience, knowledge, and consensus. Here, we focused on life-threatening GI bleeding in the context of FXa inhibitor use and decision-making considerations when administering FXa inhibitor reversal therapy.

The Bottom Line

In agreement with current guidelines, this industry-sponsored Delphi panel found that patients with a life-threatening gastrointestinal hemorrhage while being treated with a factor Xa inhibitor (FXaI) may benefit from FXaI reversal given within 1 hour of emergency department evaluation.

2 | METHODS

2.1 | Study design

Expert clinicians representing specialties in emergency medicine, gastroenterology, vascular medicine, and trauma surgery were identified for study participation. The Delphi technique, a widely employed iterative process for achieving convergence of opinion, was used to reach consensus among the clinician panelists. This technique captures real-world knowledge from experts within a given field and incorporates a controlled feedback process, which maintains focus and encourages participants to revisit their initial judgments.[27]

2.2 | Delphi technique

Our consensus-building approach consisted of 2 rounds of survey questionnaires, followed by virtual, real-time consensus-building exercises. Before administration of the first survey questionnaire, all panelists reviewed relevant literature regarding GI bleeding,[21,28,29] anticoagulant reversal,[24] and andexanet alfa.[17,18,30,31] The initial survey questionnaire, which was sent on February 4, 2022, was completed by panelists to collect feedback regarding the impact of individual patient characteristics on treatment decisions. To develop the initial survey, we reviewed relevant data sources, including published articles,[21,24] prescribing information for andexanet alfa,[17] NICE guidance on the potential use of andexanet alfa to reverse an FXa inhibitor in the presence of a potentially life-threatening GI bleed,[18] and measures of hemodynamic instability and shock.[28,29] Specifically, the initial survey included questions regarding patient characteristics such as age, comorbidities, bleed site (eg, esophageal, gastric, and duodenal) and severity, anticoagulation status, intervention setting, and resource availability. We analyzed data gathered from the initial survey to develop a second survey focused on disparate survey responses. Panelists then completed a second survey questionnaire with follow-up questions to elicit deeper feedback. Finally, we analyzed data from both surveys to develop discussion topics for real-time, virtual consensus-building exercises, which were structured around resolving outstanding areas of disagreement. The consensus-building exercises were held on June 23, 2022; November 29, 2022; and December 8, 2022.

3 | RESULTS

3.1 | Panelist characteristics

Eight practicing clinicians who are experts in treating GI bleeding and were principal investigators for clinical trials participated in the Delphi panel (Table 1). The panel contained multiple specialties, with

TABLE 1 Expert panelist characteristics.

Characteristic	No.
Specialty[a]	
Emergency medicine	3
Gastroenterology	3
Surgery	1
Vascular medicine	1
Country	
Germany	1
Switzerland	1
United Kingdom	2
United States	4
Years in practice	
11–15	2
16–20	2
More than 20 years	4
No. of patients treated for a GI bleed over the last 12 months	
Participant 1	200
Participant 2	85
Participant 3	50
Participant 4	80
Participant 5	50
Participant 6	50
Participant 7	6
Participant 8	60
Total no. of patients followed over the last 12 months	581

Abbreviation: GI, gastrointestinal.

[a]All panelists hold postgraduate degrees in medicine, including MD and MRCP degrees.

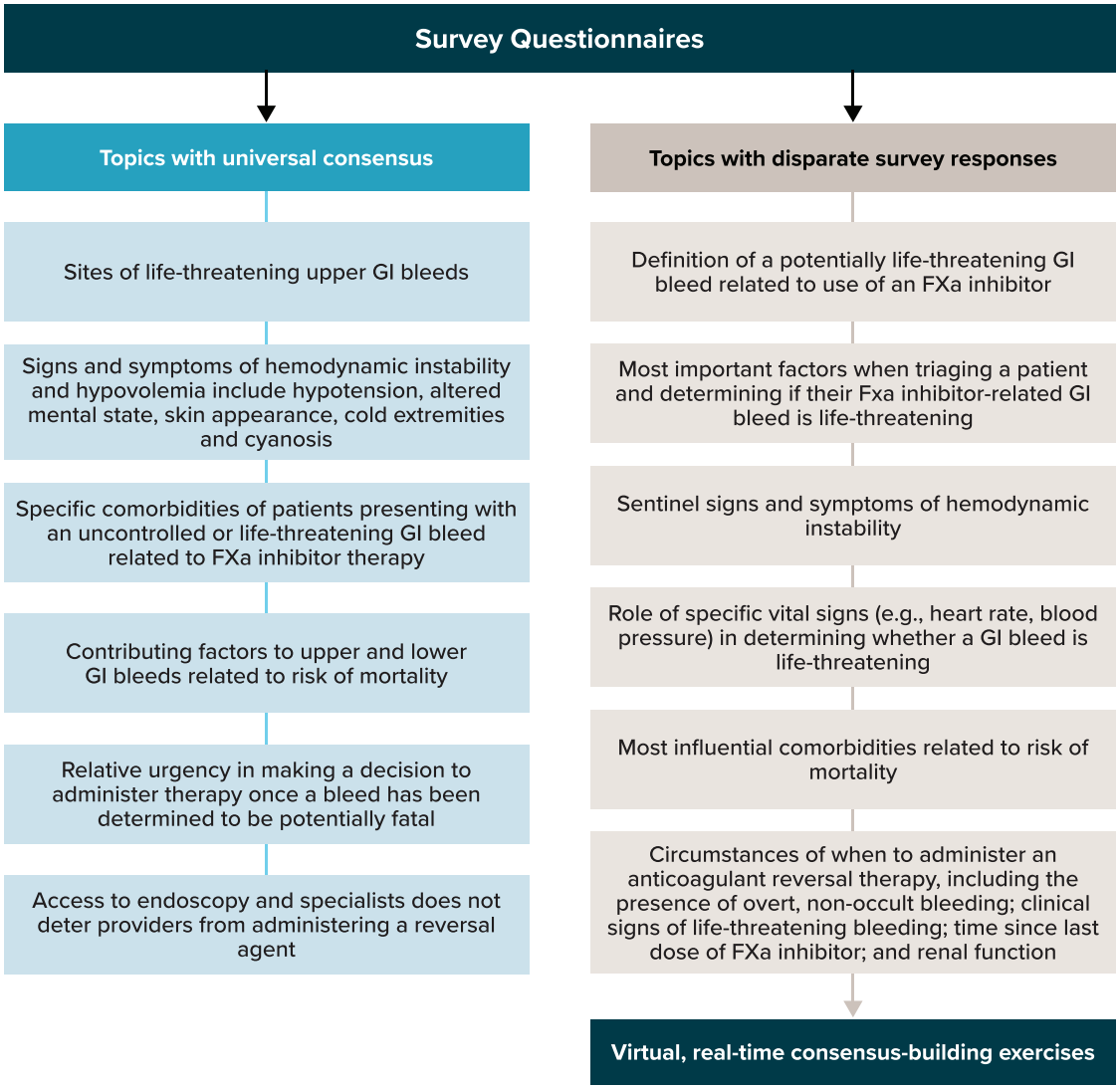

FIGURE 1 Topics explored by the Delphi panel. FXa, factor Xa; GI, gastrointestinal.

representation in emergency medicine (n = 3), gastroenterology (n = 3), surgery (n = 1), and vascular medicine (n = 1). The multinational panel included panelists from Germany (n = 1), Switzerland (n = 1), the United Kingdom (n = 2), and the United States (n = 4). Each panelist had a minimum of 10 years in practice, and half had more than 20 years in practice. The 8 panelists reported treating 581 patients (cumulatively) for a GI bleed within the previous 12 months.

3.2 | Delphi panel

Topics explored by the Delphi panel, along with the consensus status for each topic, are presented in Figure 1. Approximately half of the topics reached universal consensus during the questionnaire phase. The remaining topics with disparate survey responses were discussed in the consensus-building exercises. We have synthesized the findings from all topics into 4 key areas: a definition and clinical signs of FXa inhibitor–related, life-threatening GI bleeds; signs and symptoms of hypovolemia and hemodynamic instability; factors related to risk of mortality in patients presenting with a life-threatening GI bleed related to FXa inhibitor therapy; and decision-making considerations for the administration of FXa inhibitor reversal therapy.

3.2.1 | Definition and clinical signs of FXa inhibitor–related, life-threatening GI bleeds

Panelists derived a nuanced definition of FXa inhibitor–related, life-threatening GI bleeds, whereby "potentially life-threatening" GI bleeding should be determined on the basis of hemodynamic instability, individual patient characteristics, signs of shock, and clinical judgment. Hypovolemia and hemodynamic instability were considered the most important indicators to determine whether a GI bleed is life-threatening among patients who take an FXa inhibitor. Furthermore, universal consensus was achieved regarding sites where life-threatening GI bleeds more frequently occur. Upper GI bleeds

(ie, esophageal, gastric, and duodenal) were considered potentially more fatal than lower GI bleeds (ie, colonic, jejunal, and ileal), which aligns with the findings of previous research.[32,33]

3.2.2 | Signs and symptoms of hypovolemia and hemodynamic instability

A summary of the panelists' consensus on key signs and symptoms of hypovolemia and hemodynamic instability in the setting of GI bleeding is presented in Figure 2. In the final consensus discussions, panelists agreed that hemodynamic instability is characterized by objective signs of shock in the presence of overt, non-occult bleeding. Panelists unanimously agreed that, in patients presenting with an FXa inhibitor–related GI bleed, overt bleeding (eg, hematemesis and rectal bleeding) and altered mental state are the clearest signs and symptoms of hemodynamic instability in the context of hypotension and tachycardia. However, panelists also agreed that altered mental state is a subjective sign of hemodynamic instability that is subject to potential confounding factors. Altered mental status has been shown to increase short-term mortality in older patients[34] and therefore may also be sign of a life-threatening GI bleed in the setting of DOAC use; however, the inherent subjectivity and lack of baseline mental status in many patients with GI bleeding limits its generalizability as a clinical predictor.

Panelists agreed that the amount of blood loss, rate of blood loss, blood pressure, and heart rate of patients can be used to identify hypovolemia and hemodynamic instability from an FXa inhibitor–related, potentially life-threatening GI bleed. However, evaluating only 1 sign or symptom is an incomplete assessment, and panelists agreed that the shock index is a more reliable metric. Because the amount of blood loss is difficult to assess due to variability in body size, the panelists agreed that a more relevant parameter is the percentage of total blood volume lost. Panelists emphasized the importance of considering key patient characteristics and suggested referring to the definition of hemorrhagic shock in the Advanced Trauma and Life Support Scale by the American College of Surgeons (ATLS),[35] which correlates blood loss to body responses (a scale of mild, moderate, severe, and life-threatening hemorrhagic shock levels).[36]

> "Age, body size and mass, comorbidities, and comedications are important to consider when estimating total blood volume, which is nearly impossible to estimate. You can refer to ATLS definition of hemorrhagic shock, as it correlates blood loss to body responses." (ID 5)

> "What is more relevant is percentage of total blood volume lost versus the amount of blood lost itself. And this is hard to estimate." (ID 7)

Panelists also agreed that the rate of blood loss should be considered a primary cause of the signs or symptoms of hypovolemia and hemodynamic instability. Although the rate of blood loss can be difficult to measure, it can be estimated by measuring the number of blood products that a patient receives; however, this method largely depends on the physician's decision to transfuse. Importantly, response to transfusion is difficult to interpret, as transient responders may still be at a high risk of hemodynamic decompensation.

> "The rate of blood loss is not indicative but rather causative of hemodynamic instability and hypovolemia." (ID 4)

Panelists unanimously agreed that hypotension is the clearest objective sign of hypovolemia and that systolic blood pressure of <90 mm Hg is an important sign of both hypovolemia and hemodynamic instability from an FXa inhibitor–related, potentially life-threatening GI bleed. Panelists also agreed that tachycardia, indicated by a heart rate >100 beats/min, may potentially be a sign of hypovolemia and hemodynamic instability from an FXa inhibitor–related potentially life-threatening GI bleed, but this must be interpreted in context. Patients experiencing clinically significant or life-threatening GI bleeding who are also taking rate-altering drugs, such as beta blocker therapy and calcium channel blockers, may not be tachycardic. Other signs and symptoms of hypovolemia and hemodynamic instability agreed upon by the panelists included cold extremities, cyanosis, diaphoresis, pallor, and delayed capillary refill time.

3.2.3 | Factors related to risk of mortality

Factors that contribute to life-threatening GI bleeding include individual patient characteristics, such as comorbidities. Panelists agreed that the most influential comorbidities related to risk of mortality are heart failure, kidney disease, and malignancy. There was universal consensus regarding contributing factors to upper and lower GI bleeding that are related to the risk of mortality, which included peptic ulcer disease; gastric injury from nonsteroidal anti-inflammatory drugs; esophagogastric varices; tumors (benign or malignant) of the esophagus, stomach, or small bowel; kidney disease; and liver disease.

3.2.4 | Decision-making considerations for the administration of FXa inhibitor reversal therapy

Panelists agreed that there is relative urgency in the decision to administer FXa inhibitor reversal therapy once a GI bleed has been determined to be potentially fatal. There was consensus among panelists that key considerations for the administration of reversal therapy include hypovolemia and hemodynamic instability, overt bleeding, and the amount of time elapsed since the last dose of an FXa inhibitor. There was unanimous agreement that FXa inhibitor reversal should be considered immediately after initial emergency department evaluation if a patient has obvious hypovolemia and hemodynamic instability, massive overt bleeding, and the time since the last dose of an FXa inhibitor is known. Furthermore, if the time since the last dose of an FXa inhibitor is unknown, panelists agreed that reversal therapy should be

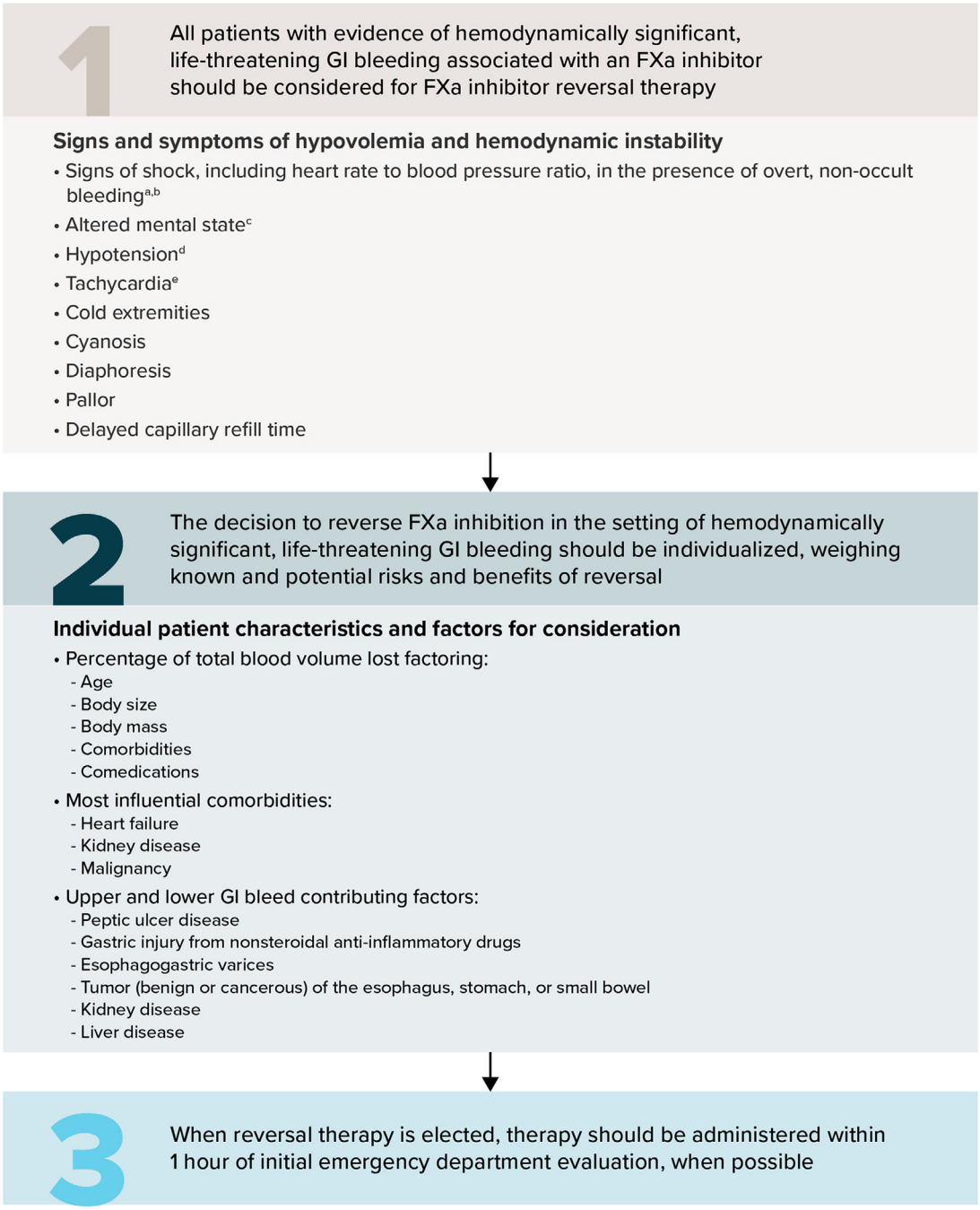

FIGURE 2 Stepwise decision-making approach to the administration of FXa inhibitor reversal therapy. (A) Amount of blood loss should be determined as a percentage of total blood volume. (B) Rate of blood loss is causative of hypovolemia and hemodynamic instability and can be estimated by the amount of blood products received. (C) Altered mental state is a subjective sign of hemodynamic instability that is subject to potential confounding factors. (D) Systolic blood pressure of <90 mm Hg is a clear sign of hemodynamic instability and hypovolemia. (E) Heart rate >100 beats/min is indicative of hemodynamic instability and hypovolemia but must be interpreted in the context of rate-altering drugs. FXa, factor Xa; GI, gastrointestinal.

administered if the patient is exhibiting signs of hemodynamic instability and overt bleeding and, if available in a timely manner, laboratory assays show that the concentration of an FXa inhibitor remains at a therapeutic level. Last, due to the half-life (rivaroxaban, 5–9 h; apixaban, ~12 h) and renal clearance of FXa inhibitors,[13,15] renal function should be a key driver in the decision to administer reversal therapy after 18 h have elapsed since the last FXa inhibitor dose. On the basis of these considerations, the panel derived and agreed on a staged approach to FXa inhibitor reversal therapy, which is presented in Figure 2.

4 | LIMITATIONS

A limitation of the Delphi technique used in the present study is that the results are based on the clinical experiences and responses of the 8 panelists. However, these results reflect unique patient populations and diversity in reported resource availability and utilization, treatment methods, and treatment duration, which depend on GI bleeding severity. The results of this study may aid in decision-making for clinicians treating patients experiencing FXa inhibitor–related, life-threatening GI bleeding and provide actionable insights to inform guidelines for the treatment of this patient population.

5 | DISCUSSION

In the present study, we conducted a Delphi panel exercise to define and contextualize life-threatening GI bleeding related to FXa inhibitor use and derive a consensus-based, clinically oriented approach to the administration of FXa inhibitor reversal therapy. A strong consensus emerged for most topics covered by the panel, and panelists agreed that the determination of potentially life-threatening GI bleeding should be based on hemodynamic instability, signs of shock, consideration of individual patient characteristics, and clinical judgment. Additionally, panelists unanimously agreed that FXa inhibitor reversal therapy should be administered if the patient is exhibiting signs and symptoms consistent with life-threatening GI bleeding, including hypovolemia, hemodynamic instability, and overt bleeding. To guide clinicians in the emergency department setting, the panel developed a stepwise decision-making approach to administering specific FXa inhibitor reversal therapy, such as andexanet alfa (Figure 2).

Hypovolemia and hemodynamic instability were considered the most important sequalae of life-threatening GI bleeds that contribute to mortality among patients who take an FXa inhibitor. Furthermore, the panelists agreed that a systolic blood pressure of <90 mm Hg and a heart rate of >100 bpm are indicative of hypovolemia and hemodynamic instability, which is supported by previous studies.[37,38] However, panelists agreed that evaluating singular signs and symptoms is an insufficient assessment approach and suggested the use of the shock index,[39] which is calculated by using both metrics, as a potentially more useful tool in this setting. Aligning with this recommendation, the shock index has been used for early identification of significant bleeding,[40,41] and some studies have shown that it may be useful to evaluate and organize care for patients with GI bleeding.[42] Furthermore, although other widely used risk assessment tools (eg, Rockall score and Glasgow-Blatchford score) incorporate heart rate and blood pressure, they require input of additional risk factors that require additional time to collect,[43] but the shock index is a simple tool that can be used quickly for risk stratification in the emergency department setting. In addition to their support of hypovolemia, hemodynamic instability, and the shock index, panelists in the present study highlighted the importance of using clinical judgment and considering individual patient characteristics when determining whether a GI bleed is potentially life-threatening.

The panel's focus on hypovolemia and hemodynamic instability as key objective signs of potentially life-threatening GI bleeding aligns with the definition used in the ACG-CAG guidelines for acute GI bleeding,[23] ACG guidelines for acute lower GI bleeding,[22] and the ANNEXA-4 trial of andexanet alfa.[44] Furthermore, and in agreement with the ACG-CAG guidelines that recommend DOAC reversal be considered in patients with a life-threatening GI bleed, panelists recommended considering FXa inhibitor reversal in patients with evidence of a hemodynamically significant bleed who are taking an FXa inhibitor. However, important factors distinguish the ACG-CAG guidelines from the results of the present Delphi panel. Here, panelists focused on clinical features of potentially life-threatening GI bleeding and highlighted the shock index as a useful tool in this setting. Overall, the Delphi panel arrived at a clinically oriented and pragmatic approach to guide decision-making in the emergency department setting that aims to administer anticoagulant reversal earlier than typical clinical trial end point definitions of life-threatening GI bleeding (ie, before the patient experiences "a decrease in hemoglobin of greater than 5 g/dL, requiring transfusion of greater than or equal to 5 units of packed red blood cells, or causing death"). The panel specifically minimized reliance on hemoglobin or transfusion thresholds to define life-threatening GI bleeding because of the inherent time requirements and clinical practice variability in obtaining these datapoints during the individualized care of a patient with GI bleeding. Although they recognized and acknowledged the contribution of these datapoints to the overall assessment of a patient with GI bleeding, the expert panel agreed that comorbidities and other clinical considerations can also contribute to the assessment of an anticoagulant-associated GI bleed as being life-threatening, with or without fulfilling laboratory or packed red blood cell transfusion thresholds.

In summary, we convened an expert panel to provide a definition of life-threatening GI bleeding related to FXa inhibitor use and inform clinical decision-making when FXa inhibitor reversal therapy may be warranted. The panel agreed that hypovolemia and hemodynamic instability are the most important predictors of life-threatening GI bleeds among patients receiving FXa inhibitor therapy. Additionally, panelists recommended that potentially life-threatening GI bleeding be determined using clinical judgment, taking into consideration hemodynamic instability, signs of shock, and individual patient characteristics. To support the evaluation and treatment of this patient population, panelists derived an approach to the administration of FXa inhibitor reversal therapy, with consensus that all patients with evidence of a hemodynamically significant bleed associated with an FXa inhibitor should be considered for FXa inhibitor reversal therapy. Panelists agreed that this decision should be individualized and recommended reversal therapy within 1 h of initial emergency department evaluation, when possible.

AUTHOR CONTRIBUTIONS

Anna Hundt Golden, Mark Price, Bruce Koch, and Mary J. Christoph substantially contributed to the conception or design of this research. Anna Hundt Golden, Jon Russo, and Mark Price substantially contributed to the acquisition and analysis of data for this work. All authors

substantially contributed to the interpretation of data for this work. Anna Hundt Golden, Mark Price, Bruce Koch, and Mary J. Christoph substantially contributed to the drafting of the manuscript. All authors critically revised the manuscript for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work by ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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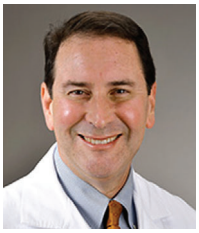

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