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Consensus document of the Spanish Society of Digestives Diseases and the Spanish Society of Thrombosis and Haemostasis on massive nonvariceal gastrointestinal bleeding and direct-acting oral anticoagulants

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ABSTRACT

Introduction: there is limited experience and understanding of massive nonvariceal gastrointestinal bleeding during therapy with direct-acting oral anticoagulants.

Objectives: to provide evidenced-based definitions and recommendations.

Methods: a consensus document developed by the Spanish Society of Digestives Diseases and the Spanish Society of Thrombosis and Haemostasis using modified Delphi methodology. A panel was set up of 24 gastroenterologists with experience in gastrointestinal bleeding, and consensus building was assessed over three rounds. Final recommendations are based on a systematic review of the literature using the GRADE system.

Results: panelist agreement was 91.53 % for all 30 items as a group, a percentage that was improved during rounds 2 and 3 for items where clinical experience is lower. Explicit disagreement was only 1.25 %. A definition of massive nonvariceal gastrointestinal bleeding in patients on direct-acting oral anticoagulants was established, and recommendations to optimize this condition's management were developed.

Conclusion: the approach to these critically ill patients must be multidisciplinary and protocolized, optimizing decisions for an early identification of the condition and patient stabilization according to the tenets of damage control resuscitation. Thus, consideration must be given to immediate anticoagulation reversal, preferentially with specific antidotes (idarucizumab for dabigatran and andexanet alfa for direct factor Xa inhibitors); hemostatic resuscitation, and bleeding point identification and management.

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INTRODUCTION

Massive nonvariceal gastrointestinal bleeding (MNVGIB), while uncommon, is a life-threatening condition that requires accurate, early recognition and well-defined management to limit mortality (1). Direct-acting oral anticoagulants (DOACs) (2) are an alternative to vitamin K antagonists (VKAs) that is increasingly used because of its net clinical benefit in patients with atrial fibrillation (AF) with moderate-to-high thromboembolic risk (3). No wide experience or solid evidence is available on the management of patients on DOACs with severe or massive gastrointestinal bleeding (GIB). This document attempts to establish a number of definitions, descriptions and recommendations to narrow down the major areas of interest in the management of MNVGIB in patients on a DOAC. Furthermore, it attempts to gain insight on the level of agreement extant in a representative group of Spanish gastroenterologists with GIB experience using the contents herein developed.

METHODS

The study design adopted involved an expert consensus using a modified Delphi methodology with a prior pertinence and relevance assessment phase for the initial questionnaire, and stepwise delivery of evidence to panelists. The researcher coordinator group was set up with six gastroenterology —appointed by the Spanish Society of Digestive Diseases (SEPD)— and one hematology —appointed by the Spanish Society of Thrombosis and Haemostasis (SETH)— specialists.

The study was carried out from July 2021 to March 2022 and had three well-differentiated phases: 1) systematic review (SR) of the literature; 2) initial questionnaire development; and 3) a Delphi study proper including quality of evidence (QoE) assessment for each item, as well as their grade of recommendation (GoR), according to the Grading of Recommendations, Assessment, Development and

Evaluation (GRADE) system (https://www.gradeworkinggroup.org/).

The literature search was conducted in the PubMed and Cochrane Library databases, supplemented as necessary with other databases, and had its last update in March 2022. The search strategy and terms (in English) may be looked up in the supplementary material.

Questionnaire building involved the development by the investigators —in an individual, anonymous fashion— of a list of areas of interest whose pertinence and relevance were judged prior to developing a definitive proposal (Fig. 1). Only questions directly related to MNVGIB in patients on DOACs were considered, and generic questions were thus deleted. The final proposal was reviewed members of the SEPD Scientific Committee.

A panel was set up for the Delphi study with 24 Spanish gastroenterology specialists who were selected using the following criteria: 1) active clinical practitioner, 2) reconciled experience in GIB management, 3) work in responsibility positions, 4) various geographic areas. Participants remained anonymous throughout the process. During the first round they were given the questionnaire in RedCap format (4) for scoring every item with one of four possible options: agree (A); disagree (D); neither agree nor disagree (NAND); no answer/don't know (NA/DK). They were also instructed to provide any comments they might deem pertinent. After responses were received the researcher coordinator group revised the writing in the proposal, which was resubmitted in the second round together with the results obtained in round 1 plus a summary of the evidence available for each and every item. In the third round the definitive questionnaire was submitted for final voting together with the evidence, QoE and GoR as described in the GRADE manual (5). Response changes from one round to the next were considered relevant ≥ 20 %. Level of agreement was expressed as the percentage of panelists who opted for each of the four possible response options (A, D, MNVGIB, NR/DK) in the third round.

RESULTS

Figure 2 shows the results of the literature search. The references of all 278 originals finally included in the evidence review may be looked up in the supplementary

material.

Regarding all 30 items as a group the panelists agreed in 91.53 % of cases (D: 1.25 %; NAND: 4.72 %; NR/DK: 2.50 %). The results obtained for each item in each round are detailed in the supplementary material.

Items in the final writing, agreement results obtained, QoE, GoR, and summary of the evidence.

1	Gastrointestinal bleeding is the type of major bleeding (MB) most commonly associated with anticoagulant therapy, including DOACs, which entails an increase in morbidity and mortality, and in resource use.
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong.
2	MNVGIB in anticoagulated patients is a severe MB event that is life-threatening because of rapid, abundant blood loss, which clinically manifests with shock, oligoanuria, confusion or letargy, and requires transfusion of 2 or more red blood cell concentrates (RBCCs) during early resuscitation.
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).
	QoE: low. GoR: weak.

GIB is the major bleeding type most commonly seen in patients on anticoagulants, including DOACs (6-9), and represents significant care burden (10,11), morbidity (9-11), mortality (6,8,9,11,12), and resource use (6,9,10,13). The concept of MB in patients receiving antithrombotic therapy is well defined by the International Society on Thrombosis and Haemostasis (ISTH) (14,15). According to this classification, in case of MNVGIB we would be facing a serious DOAC-linked, life-threatening MB in the gut, with a nonvariceal origin, meeting the criteria of massive bleeding. These criteria include hemodynamic instability, shock, and copious blood loss, which could be clinically assessed and its severity estimated (16) based on transfusion requirements (17). When only early resuscitation is considered, these requirements may oscillate between 2 (1) and 4 (17) RBCC units, whereas 10 may be passed when considering the first 24 hours (18-20).

3	All DOACs are associated with an increased risk for major gastrointestinal

	bleeding when used in standard doses and for most common indications; risk magnitudes differ amongst DOACs though, with worse profiles for rivaroxaban 20 mg/24 h, dabigatran 150 mg/12 h, and edoxaban (60 mg/24 h), and a better profile for apixaban (5 mg/12 h).
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).
	QoE: moderate. GoR: weak.
4	Additional major risk factors associated with GIB development in patients on DOACs include: concomitant anti-inflammatory or antiplatelet drug use, age ≥ 75 years, renal failure (RF) (creatinine clearance < 50 mL/min), advanced liver disease, a history of ulcer disease or GIB, potentially bleeding pre-extant lesions in any gut segment, and a HAS-BLED score ≥ 3.
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).
	QoE: low. GoR: strong.
5	In order to reduce gastrointestinal bleeding risk in patients on DOACs the following is recommended: 1. Suppress or modify risk factors whenever possible. 2. Adjust DOAC dosage in case of RF, according to instructions in each drug's prescribing information. 3. Prescribe gastroprotection using proton-pump inhibitors (PPIs) in patients with a history of ulcer disease or upper GIB. 4. Also consider gastroprotection with PPIs in patients requiring standard DOAC doses at risk of gastrointestinal bleeding.
	Agree: 95.83 %. (D: 0 %; NAND: 4.17 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong for items 1, 2 and 3; weak for item 4.

Meta-analyses (MAs) of registration randomized clinical trials (RCTs) suggested that major GIB was more common with DOACs versus VKAs (21,22), which has not been confirmed in real-world studies (23-29). However, a differential GIB risk according to each specific DOAC has been acknowledged. An early MA reported that rivaroxaban and high-dose dabigatran or edoxaban significantly increased GIB risk as opposed to apixaban (22), which has been later confirmed (30-36). Risk factors for GIB in these patients include: age (37-41), RF (42), a history of peptic ulcer (40), antiplatelet drugs

(37,40,43,44), liver disease (45) —DOACs would only be formally contraindicated for Child-C stage (46)— or HAS-BLED ≥ 3 (47,48). DOAC-related GIB prevention includes patient selection according to each drug's indications and contraindications, use of lower doses for some DOACs in patients with RF, modifiable risk factor correction, and gastroprotection prescription (49,50).

6	Any patient suspected of MNVGIB should be preferentially referred to a center with institutionalized management protocols for massive bleeding, with around-the-clock intensive care unit (ICU) services, and on-site surgery, radiology, hematology, and gastroenterology teams —at least on-call endoscopy teams— trained in endoscopic hemostasis techniques and appropriately supported by a nursing staff.
	Agree: 95.83 %. (D: 0 %; NAND: 4.17 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong.
7	Before being taken to hospital, patients suspected of MNVGIB should receive: 1. Oxygen to sustain saturation at > 92 %. 2. Any support measures available before referral (venous access, crystalloid infusion, etc.), provided their arrival in hospital is not delayed.
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).
	QoE: low. GoR: strong.
8	In order to optimally manage patients with massive GIB in general, and MNVGIB in particular, it is advisable that a multidisciplinary team be set up in every hospital to adapt the various multidisciplinary protocols and fast circuits. Besides gastroenterologists, it is recommended that cardiologists, hematologists, emergency and intensive care specialists, anesthetists, surgeons, interventionist radiologists, and others be also included.
	Agree: 95.83 %. (D: 0 %; NAND: 4.17 %; NR/DK: 0 %).
	QoE: low. GoR: strong.

A patient with MNVGIB must be taken as fast as possible (51-53) to a hospital with adequate medical resources to provide advanced stabilization, multidisciplinary care, and complex diagnostic testing, including therapeutic GI endoscopy procedures

(1,54-56). Healthcare team multidisciplinarity and presence of protocols are key to facilitate rapid, right decision-making, including criteria for massive transfusion (MT), anticoagulation reversal, and diagnostic testing indications and timing (1,17,19,54-61).

9	In case of massive, active GIB only manifesting as hematochezia or rectorrhagia with hemodynamic instability, CT angiography is suggested to pinpoint the bleeding site as a prior step to endoscopic or radiological intervention planning.
	Agree: 83.33 %. (D: 4.17 %; NAND: 12.50 %; NR/DK: 0 %).
	QoE: low. GoR: strong.

Severe bleeding exclusively manifesting as abundant, overt hematochezia/rectorrhagia may originate in the upper GI tract. The likelihood of this ranges from 11 % to 15 % (62,63). Gastroscopy represents an option to exclude such possibility once stabilization has been ensured (1), but guidelines suggest that patients with persistent active bleeding should undergo CT angiography, and gastroscopy should only be indicated when CT angiography fails to identify the bleeding source (64,65).

10	While useful to predict severity in case MNVGIB is suspected, pre-endoscopic prognostic scales should never prevail over clinical judgement.
	Agree: 95.83 %. (D: 0 %; NAND: 4.17 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong.

Nonsystematic clinical criteria are inadequate to decide whether a GIB patient can be discharged from the emergency room (66). Several prognostic scores are useful for upper GIB (67, 68), including the Glasgow-Blatchford score (69), a modified version of the latter (70), the Rockall score, in its pre-endoscopic version (71), AIMS65 (72), or MAP(ASH) (73). Several scores have also been described for lower GIB (74-78), but their results are poorer when compared to upper GIB (79).

11	The initial assessment of any patient on anticoagulation with a DOAC with suspected MNVGIB should consider the factors associated with persisting anticoagulant activity: 1. Drug-dependent factors (type, dosage, prescribed regimen, and time of last dose).

	2. Concomitant drug therapies that may interfere in DOAC pharmacokinetics. 3. Patient comorbidities (renal function, liver function).
	Agree: 95.83 %. (D: 0 %; NAND: 4.17 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong.

Persisting anticoagulant activity must always be assessed during patient care, considering any factors that may reduce drug clearance as well as factors that may add to the effect (80, 81). Once the involved DOAC, its dosing and time of last dose are known the drug's half-life must be taken into account: 12-17 h for dabigatran, 5-9 h for rivaroxaban, 8-15 hours for apixaban, and 6-12 h for edoxaban (82). Its main routes of excretion must also be considered. Renal elimination is predominant for dabigatran (80-85 %) but not so for direct factor Xa inhibitors (25-50 %) (54, 80), where any potential impairment of liver function must also be factored in.

12	Routine, systematic placement of a nasogastric tube (NGT) is not recommended for patients with MNVGIB.
	Agree: 87.50 %. (D: 8.33 %; NAND: 4.17 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong.
13	In patients with MNVGIB endotracheal intubation is not systematically indicated but should be considered, together with early mechanical ventilation, when there is evidence of increased respiratory effort, severe hypoxemia, marked acidosis, reduced level of consciousness, or massive/abundant hematemesis.
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong.

Routine use of NGTs for GIB ceased to be recommended long ago (83-86). In MNVGIB it may be exceptionally used as a prior step to endotracheal intubation in cases the latter is needed to reduce aspiration risk (1). Furthermore, the International Consensus Group guidelines (55) carry since their first edition in 2013 (87) the ongoing recommendation of placing a NGT in selected patients since findings may be of

prognostic value, a stance not shared by other guidelines such as ESGE 2021, which advises against its routine use in patients with upper nonvariceal GIB (56) based on an observational study (OS) (88), a SR (89), and a RCT (90).

Nor is prophylactic endotracheal intubation indicated, as it is associated with a higher risk for cardiopulmonary events and mortality (91-94). Intubation should be held in reserve for patients requiring adequate airway control, persistent hematemesis, agitation or encephalopathy (56), or early mechanical ventilation for increased respiratory effort, hypoxemia, acidosis, and reduced consciousness (1,95).

14	In patients with MNVGIB, stabilization in all cases, and intubation when applicable, should occur before their being transferred to undergo diagnostic testing or endoscopic, radiological interventions.
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong.

Endoscopy should only be performed in stable patients (56,96,97). Overall, it is recommended within 24 hours (55,56); moving up endoscopy within the first 12 hours provides no benefit (96,98). Even in patients with a higher risk of death or rebleeding "urgent" endoscopy (within 6 hours) is not superior to "early" endoscopy (within 6 to 24 hours) (99). Similar assurance should be obtained prior to patient transfer to undergo other procedures such as CT angiography (1,65) or colonoscopy (65,100).

15	In any patient with suspected MNVGIB it is recommended: 1. That a venous access be early, primarily obtained: preferentially two peripheral large-caliber accesses (G14-G18 or larger), or using intraosseous access in case of impossible venous access. 2. That patient stabilization be initiated with an initial bolus of 500 mL of crystalloids over less than 15 minutes, which may be repeated as needed, to be followed by administration of smaller volumes of balanced solutions at body temperature (e.g., Ringer's lactate) to sustain hemodynamics in the setting of hypotensive resuscitation while awaiting urgently requested blood derivatives.
	Agree: 95.83 %. (D: 0 %; NAND: 4.17 %; NR/DK: 0 %).
	QoE: moderate. GoR: weak.

16	In patients with MNVGIB, particularly when intensively transfused, it is advisable to avoid hypothermia by regulating room temperature, using thermal blankets, and pre-warming solutions and blood products.
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong.

Appropriate patient resuscitation requires a rapidly-obtained, large-caliber venous access, preferably two (95,101). If impossible, consideration must given to osseous access (57,58). Resuscitation must adhere to the tenets of hemostatic resuscitation, with the earliest possible administration of blood products (RBCCs, platelets and plasma), and restricting high-volume crystalloid use (58,59), which is associated with further pulmonary and systemic complications (102), and contribute to hyperchloremic acidosis and hypothermia (103) with coagulation impairment (104,105). Hypothermia is a serious complication in these patients, particularly in those subjected to MT (1,17,57-59), so room temperature must be adjusted, thermal blankets should be used, and fluids and blood should be warmed before administration (1,17,18,58)

17	Resuscitation of MNVGIB patients on DOACs must ensue in the right setting (ICU, resuscitation areas, bleed units, etc.) under 3 principles: 1. Principle of damage control resuscitation, with special priority given to bleeding cause management. 2. Principle of hypotensive resuscitation, such that systolic blood pressure will not exceed 80-100 mmHg. 3. Principle of hemostatic resuscitation, including early use of blood products and derivatives until the cause of bleeding is resolved, and in case of DOAC use assessing the need for reversal.
	Agree: 83.33 %. (D: 0 %; NAND: 12.50 %; NR/DK: 4.17 %).
	QoE: low, items 1 & 2; moderate, item 3. GoR: strong.

So-called damage control resuscitation, which includes permissive hypotension, early administration of blood products (hemostatic resuscitation), and surgery to stop bleeding and contamination for trauma patients (106,107), has demonstrated a reduction in mortality in patients with severe bleeding (108) as well as in case of GIB (109). In the setting of MNVGIB in patients on DOACs, the damage control concept

includes anticoagulation reversal (54,61), bleeding source location, and the procedures (mainly endoscopic) for bleeding control, which also entails reduced mortality (110). Hemostatic resuscitation must be compliant with MT protocols, considering RBCC, plasma and platelets transfusion, as this is the regimen most closely resembling whole blood replacement, thus contributing to early coagulopathy correction and greater survival (59).

18	Notwithstanding the required assessment of each individual patient, in MNVGIB the transfusion of RBC concentrates should be based on a restrictive protocol (initiate if Hb < 7 g/dL; objective: 7-9 g/dL); a higher value (initiate if Hb < 8 g/dL; objective: 8-10 g/dL) may be considered in patients with ischemic heart disease.
	Agree: 95.83 %. (D: 4.17 %; NAND: 0 %; NR/DK: 0 %).
	QoE: low. GoR: strong.

The restrictive approach is generally considered appropriate for GIB patients who require a transfusion (96,111-113). A MA confirmed the decreased mortality associated with this approach, albeit this effect could not be ascertained in the nonvariceal bleeding subgroup (113). No differences in mortality are observed between transfusion started when Hb < 7 g/dL and transfusion started when Hb < 8 g/dL (114). Guidelines generally recommend higher Hb levels for patients with ischemic heart disease (56,115,116). Recommendations for lower GIB are similar (64,65).

19	Hospitals should have their own transfusion protocols in case of massive GIB, in compliance with the guidelines provided by the Department of Hematology and Hemotherapy. General transfusion guidelines include the following, and should be used considering any adaptations applicable according to specific patient profiles: 1. Initial administration of 2-4 RBCCs. 2. Transfuse platelets (1 pool = 5 platelet units) if platelet count is equal or inferior to 50,000 platelets/dL. 3. Transfuse plasma (start dose, 15 mL/kg of fresh frozen plasma). 4. Transfuse 3-4 g of fibrinogen.

	5. In further transfusions until patient stabilization, depending on each hospital's protocol, a transfusion ratio of one plasma unit and one platelet unit for every two RBCCs (1:1:2) or even for each RBCC (1:1:1), attempting to draw near or mimic complete blood replacement.
	Agree: 45.83 %. (D: 4.17 %; NAND: 37.50 %; NR/DK: 12.50 %).
	QoE: low. GoR: weak.

Guidelines and publications on MT are unanimous about recommending institutional protocols (1,17,59,117-121), as these contribute to reducing mortality in these patients (122,123). In trauma patients protocols using a 1:1:1 proportion for plasma, platelets and RBCCs, compared to RBCC transfusion alone, have demonstrated a reduction in mortality and number of RBCCs eventually administered (108), and their extrapolation to MGIB is likely reasonable (1) provided MT protocols can prevent the development of a coagulopathy (121). Another study considers the 1:1:2 strategy more appropriate in the non-trauma setting (124). This same opinion is advocated in the HEMOMAS document, which considers that no differences have been demonstrated between the 1:1:1 and 1:1:2 strategies (17).

20	In case of MNVGIB in a patient on a DOAC the latter must be discontinued, as must any antiplatelets if present, and such discontinuation may be later discussed with the specialists who prescribed anticoagulation/antiaggregation and the Department of Hematology.
	Agree: 95.83 %. (D: 0 %; NAND: 4.17 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong.
21	In case of MNVGIB in a patient on a DOAC who took it within the past two hours, gastric lavages with activated charcoal to preclude absorption are not feasible in practice, both because of the demanding setting of unstable patient resuscitation and the difficulties they would add to diagnostic-therapeutic endoscopy subsequently.
	Agree: 70.83 %. (D: 8.33 %; NAND: 8.33 %; NR/DK: 12.50 %).
	QoE: very low. GoR: weak.

Any anticoagulants must be immediately discontinued, as well as any antiplatelets should these be associated with treatment (50,54,57,61,80,125,126). While there is a

theoretical possibility of activated charcoal administration to reduce intestinal residual drug absorption if the DOAC was dosed within the past two hours, this in practice is exceptional in patients on DOACs, and is only indicated for toxicity after massive drug intake, usually in the setting of a suicide attempt (127). Anyway, the theoretical potential benefit of gastric lavage is balanced out by subsequent impairment of endoscopic visualization (128,129) and, most particularly, the risk GIB management entails with hemodynamic instability.

22	In case of MNVGIB in a patient on a DOAC, if significant drug levels are thought to be present in the plasma (depending on last dosing, elimination profile, potential comorbidities or interactions, and available lab test results), anticoagulation reversal should be immediately started according to each individual center's protocol.
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).
	QoE: moderate. GoR: strong.

MNVGIB represents a medical emergency that, by definition, jeopardizes life (1,55); therefore, hemodynamic stabilization and attempting anticoagulation reversal as soon as possible are the first measures in management. In guidelines, the general consensus is that, besides DOAC discontinuation, in case of serious/life-threatening bleeding drug-specific reversal agents should be administered if available (idarucizumab for dabigatran, andexanet alfa for direct factor Xa inhibitors), with prothrombin complex concentrates (PCCs) as second-line option (56,64,126,130-135). Actions to revert anticoagulation from care onset are an absolute priority together with resuscitation maneuvers (1,50,54,61,80,130,135-138).

23	In case of MNVGIB in a patient receiving the direct thrombin inhibitor dabigatran the drug's anticoagulant effect may be evaluated (with no detriment to any immediate anticoagulation reversal decisions in critical cases) as follows: 1. By assessing plasma dabigatran concentration using diluted thrombin time or ecarin clotting time. 2. Alternatively, the presence or absence of any significant anticoagulant effects of dabigatran may be inferred using activated partial

	thromboplastin time (aPTT) and thrombin time (TT) while considering dosage, time from last dose, drug half-life, and creatinine clearance (80-85 % of excretion is renal). 3. Normal TT excludes the drug's presence in the blood, whereas normal aPTT does not, but does rule out higher levels.
	Agree: 75.00 %. (D: 0 %; NAND: 12.50 %; NR/DK: 12.50 %).
	QoE: low. GoR: strong.
24	In case of MNVGIB in a patient on treatment with a direct factor Xa inhibitor, anticoagulant effects may be assessed (with no detriment to any immediate anticoagulation reversal decisions in critical cases) as follows: 1. Specifically, assessing plasma drug levels using a specifically calibrated anti-factor Xa assay. This test is not available in every hospital. 2. Measuring anti-Xa activity (as used to measure heparin levels) may provide some information. Absence of activity excludes clinically relevant drug levels. 3. Whether significant anticoagulant effects are present may be fathomed considering the dose administered and time elapsed since last administration (rivaroxaban has a half-life of 5-9 hours; apixaban of 8-15 hours, and edoxaban of 6-11 hours), and both renal and liver function (renal excretion of all three drugs is secondary [< 35 %] hence they may accumulate when liver function is severely impaired).
	Agree: 66.67 %. (D: 0 %; NAND: 16.67 %; NR/DK: 16.67 %).
	QoE: low. GoR: weak.

Usual hematology testing offers no substantial information on the anticoagulant effect of DOACs, and changes only develop in case of an associated coagulopathy (54,139). Plasma dabigatran measurement is often unavailable, particularly for rapid usage (54). While no ideal assay exists, diluted TT or ecarin clotting time may be recommended as they offer sound information on plasma dabigatran concentration (137,139-141). Should these tests be unavailable TT and aPTT may be used bearing in mind drug dosage, time from last dose, and renal function (140). Normal TT levels practically rule out the drug's presence (54,139). For direct factor Xa inhibitors the anticoagulant

effect may be specifically assessed using calibrated anti-FXa assays (139-141), although these are unfortunately unavailable more often than not (141). Alternatively, measuring anti-Fxa activity (used to determine heparin levels) may offer guidance on the presence of direct FXa inhibition (139,140). If the latter is also unavailable, then the anticoagulant effect may be estimated based on drug type, half-life, renal excretion, and potential interactions.

25	In case of MNVGIB in a patient receiving the direct thrombin inhibitor dabigatran where activity remains ongoing: 1. Reverse anticoagulation with idarucizumab, which should be done immediately in critical cases. 2. If fewer than 4 hours have elapsed since dabigatran was last dosed, and the patient's clinical status allows, consider hemodialysis or hemofiltration. 3. Should idarucizumab be unavailable, consider PCCs as an alternative. 4. If bleeding remains active after the first block of blood products in the massive transfusion protocol, or bleeding is endoscopically or surgically uncontrollable, consider administering factor VIIa.
	Agree: 91.67 %. (D: 0 %; NAND: 0 %; NR/DK: 8.33 %).
	QoE: low. GoR: strong, items 1 & 2; weak, items 3 & 4.

Idarucizumab is a humanized monoclonal antibody fragment against dabigatran that serves as a specific antidote for this direct thrombin inhibitor (50,126,135). In its registration study a median 2.5 hours to bleeding cessation was observed in patients with GIB, with a thrombotic event rate of 4.8 % at 30 days, and a death rate 18.8 % (142). Subsequent SR & MAs suggest a benefit in patients requiring emergency surgery, with severe bleeding and intracranial hemorrhage (143-145). Another MA describes a thrombotic event rate of 3.3 % (146).

26	Regarding factor Xa inhibitor reversal in a patient with MNVGIB on such an agent, should effects be deemed to persist: 1. If available, anticoagulation reversal may be attempted using andexanet alfa, a specific agent for factor Xa inhibitor reversal approved for rivaroxaban and apixaban, which should be used off-label

	for edoxaban. 2. PCCs may be used when andexanet alfa is unavailable. 3. In cases of active bleeding beyond completion of the MT protocol's first-block blood products usage, or of bleeding uncontrollable with surgical or endoscopic management, consideration of factor VIIa administration is recommended.
	Agree: 87.50 %. (D: 0 %; NAND: 4.17 %; NR/DK: 8.33 %).
	QoE: low. GoR: strong for item 1 & 2; weak for item 3.

Andexanet alfa recombinant modified human factor Xa decoy protein that binds factor Xa inhibitors and acts as universal factor Xa reversal agent (49). In its main study it demonstrated good to excellent hemostasis in 82 % of patients, mortality at 30 days was 14 %, and thrombotic events developed in 10 % (147), a rate a subsequent MA estimates at 10.6 % (146). Another MA supports its use, and the use of idarucizumab, to revert bleeding and reduce mortality risk (144). The Anticoagulation Forum (135) guidelines recommend using andexanet alfa (high-dose, 800 mg administered as an initial bolus at a rate of 30 mg/min, followed by continuous infusion at 8 mg/min for 120 min) in case of major GIB. It is particularly recommended for life-threatening bleeding events (126).

27	In DOAC-treated patients with MNVGIB DOAC indication and dosage should be discussed on a multidisciplinary basis at anticoagulation restart (carefully considered, with an exacting assessment of the benefit-risk ratio), bearing the following in mind: 1. Concomitant use of other medications such as anti-inflammatory or antiplatelet drugs. 2. Patient age. 3. Presence of chronic alcohol or other substance abuse. 4. Presence of additional risk factors and comorbidities. 5. Bleeding location. 6. Type of bleeding lesion (treatable, multiple angiodysplasia of the GI tract, any untreatable cause, unidentified cause).
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).

	QoE: low. GoR: strong.
28	In DOAC-treated patients with MNVGIB, once bleeding is under control the timing of anticoagulation restart, if indicated, must be decided on an individual basis: 1. Restart by day 7 from bleeding onset, even sooner, should thrombotic risk make it advisable, with any individualized adjustments that may be needed to decrease bleeding risk. 2. Most patients can restart anticoagulation within fifteen days after bleeding stops.
	Agree: 95.83 %. (D: 4.17 %; NAND: 0 %; NR/DK: 0 %).
	QoE: low. GoR: strong.
29	When DOACs are not appropriately restarted after GIB, patients have a higher risk of thrombosis and greater morbidity and mortality, whereas in those who restart anticoagulation there is a favorable balance between thrombosis, mortality risk and rebleeding risk.
	Agree: 100 %. (D: 0 %; NAND: 0 %; NR/DK: 0 %).
	QoE: low. GoR: weak.

Once hemostasis has been achieved consideration should be given to restoring anticoagulation therapy to counter increased thrombotic risk after prolonged anticoagulant withdrawal (61), a risk that must be balanced against that of recurrent bleeding (56,65,80,148), reassessing DOAC indication and dosage —apixaban and dabigatran 110 mg show a better risk profile versus other DOACs and doses (138)— as well as the concomitant use of other bleeding-risk contributors such as antiplatelet or anti-inflammatory drugs (61). Most patients can restart anticoagulation therapy within approximately two weeks (149), and studies suggest that restart delays are associated with an increased risk of thrombosis and mortality (150-152). A SR and MA concludes that restart is advisable at 7 to 14 days after GIB, regardless of therapy (151). Different OSs, including MAs, suggest a lower risk of thrombosis when anticoagulation is restarted (153-158), even though there is a small increase in non-fatal GI bleeding events (156,159,160), as well as a reduction in all-cause mortality (153,155-157).

30	Systematic, prospective data collection about MNVGIB events in patients on

	DOAC anticoagulation, as well as their follow-up (for at least six months in order to include delayed mortality) is recommended.
	Agree: 91.67 %. (D: 0 %; NAND: 4.17 %; NR/DK: 4.17 %).
	QoE: moderate. GoR: strong.

MNVGIB in patients on a DOAC represents a high-risk scenario where ongoing monitoring is key to assess bleeding relapse, thrombotic events, and mortality. A minimum follow-up of 6 months seems adequate to identify delayed mortality and other events beyond in-hospital or 30-day outcomes (161,162). In addition, having information available on the characteristics and course of said events by setting up a multicenter registry would be extremely useful.

DISCUSSION

This study addresses a clinical challenge, namely caring for a critical patient with MNVGIB in a scenario —anticoagulation with a DOAC— where early decisions may and must be made in order to save the patient's life. No robust studies are available on the specific subject of MNVGIB; more abundant is the literature addressing MT (17). This original is based on three generic items: massive bleeding, nonvariceal GIB, and DOAC-associated GIB. Most results are extrapolations that prompt caution, hence we set out to develop a state-of-the-art consensus paper rather than a set of clinical practice guidelines. Together with various recommendations, a number of definitions and descriptive positionings are offered. When it came to define the limits of the issue at hand we opted for integrating the concept of life-threatening bleeding, typical of the anticoagulation setting (14,15), with the concepts of unstable critically-ill patient from loss of blood volume and of significant, early transfusion requirements. Our goal was to offer a clinical criterion that may be used from resuscitation onset, focusing on the severe GIB with hemodynamic instability at the emergency room scenario.

A peculiarity of this study is its not being based on questions posed after reviewing the evidence available but on the definition of a range of issues identified as challenges from a clinical standpoint, on which evidence is then systematically sought. The panel's formulation evolved according to three drivers of improvement: clinical practice orientation, knowledge provided by the review, and finally QoE scoring. Hence the

relevance of the fact that items where significant opinion shifts occurred are precisely those with a lower baseline clinical understanding of the scenario under consideration. Importantly, in cases where high agreement was eventually not obtained the cause was no significant, explicit disagreement but rather an increase in NAND or NR/DK responses, a reflection of uncertainty within a clinical setting where both experience and evidence are inadequate. In this regard item 19 is of particular note as fewer than half of panelists agreed, but only one of them expressed disagreement, very likely because of the difficulties of using hemostatic resuscitation criteria for patients with MNVGIB on a DOAC.

The need for a multidisciplinary approach is one of the most widely considered items. Indeed, the problem posed by MNVGIB, specifically by DOAC-associated MNVGIB, can never be considered an issue for any given specialty, not even gastroenterology. Decisions must be made at presentation, hence there is no room for variability according to treating professional. As a consequence, protocolized care is inevitable. It is here that the primary message resides: MNVGIB in a patient on DOACs requires very early recognition and efficient care, as well as resuscitation, which must meet the criteria of individualized stabilization under the tenets of damage control. For DOAC-related MNVGIB several damage control tools are available: achieve hemostasis with anticoagulation reversal, including antidote use, hemostatic resuscitation, and bleeding site identification and management. None of this can be achieved with delayed decisions.

Topics to receive greater attention towards the future include the growing importance of lower GIB (8,163,164) and the increasing frequency of Dieulafoy lesions, arteriovenous malformations, and tumors as sources of GI bleeding (165,166). However, the most relevant research field should aim at increasing available evidence for the management of these patients, particularly regarding the evolution and usage of drugs capable of anticoagulation reversal. To this end setting up registries will surely help, as suggested in the panel's last item. DOAC antidotes must be assessed in clinical trials including a control arm, which is absent in the registration studies leading to their approval. The high cost of these drugs and their potential adverse effects should be considered before prescription.

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To conclude, MNVGIB in patients on DOACs represents a relevant, complex, but addressable issue when various strategies are integrated to converge into the management of these patients. Approaches include multidisciplinary protocolization, early recognition, and efficient resuscitation under the tenets of damage control, including immediate anticoagulation reversal preferentially using specific antidotes, hemostatic resuscitation, and bleeding site identification and management.

KEY POINTS

MNVGIB in patients on a DOAC requires a protocolized, multidisciplinary approach. Management includes early identification, anticoagulation reversal, and damage control.

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ANNEX 1. RESEARCHERS

Members of the Massive and Severe Gastrointestinal Hemorrhage (MASGIH) Group of the Spanish Society of Digestives Diseases (SEPD) and the Spanish Society of Thrombosis and Haemostasis (SETH)

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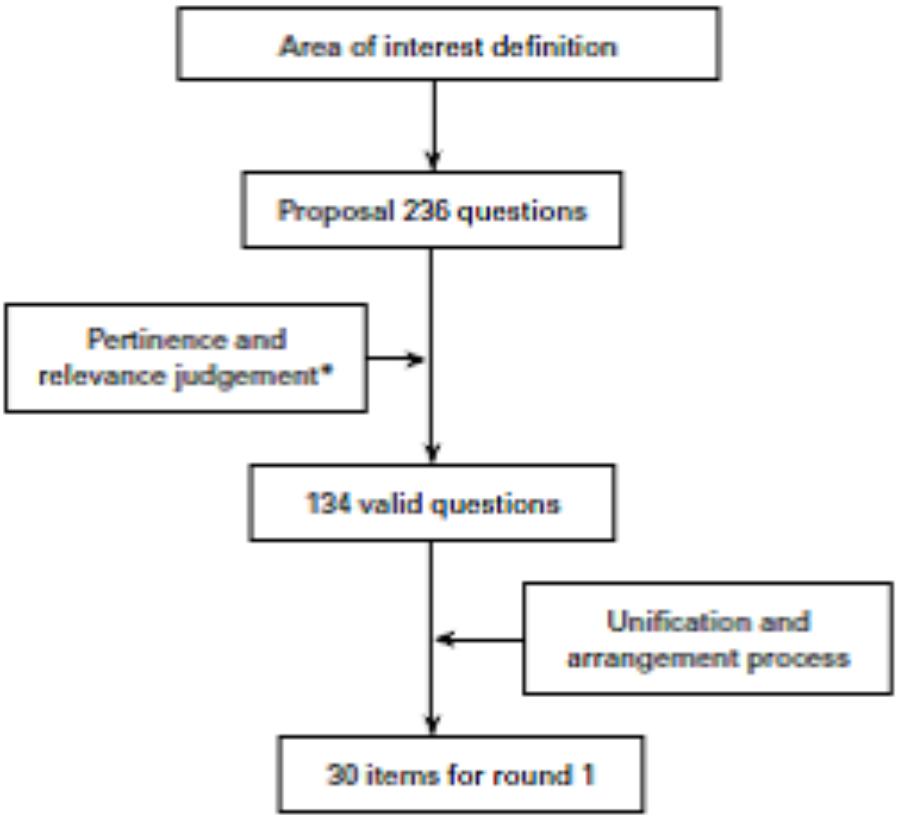

Fig. 1. Delphi panel questionnaire-building process.

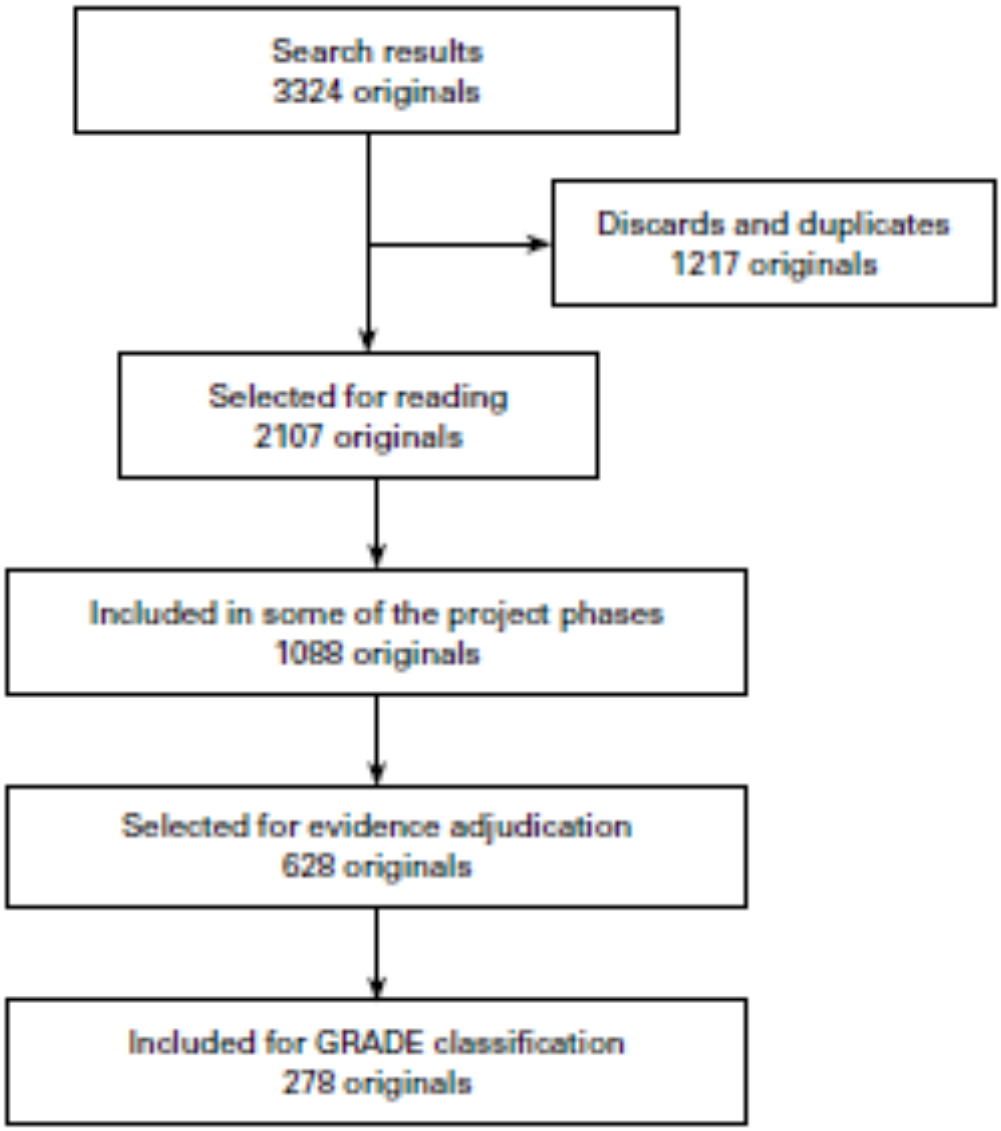

Fig. 2. Results of the literature search.