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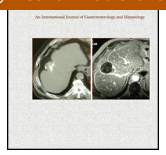

Review Article

Management of anticoagulation in patients with acute gastrointestinal bleeding

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ABSTRACT

Acute gastrointestinal bleeding represents the most common adverse event associated with the use of oral anticoagulant therapy. Due to increasing prescription of anticoagulants worldwide, gastroenterologists are more and more called to deal with bleeding patients taking these medications. Their management is challenging because several issues have to be taken into account, such as the severity of bleeding, the intensity of anticoagulation, the patient's thrombotic risk and endoscopy findings. The recent introduction into the marketplace of new direct oral anticoagulants, for whom specific reversal agents are still lacking, further contributes to make the decision-making process even more demanding. Available evidence on this topic is limited and practice guidelines by gastroenterology societies only marginally address key issues for clinicians, including when and how to reverse coagulopathy, the optimal timing of endoscopy and when and how to resume anticoagulation thereafter. The present paper reviews the evidence in the literature and provides practical algorithms to support clinicians in the management of patients on anticoagulants who present with acute gastrointestinal bleeding.

1. Background

About 2% of the population in developed countries receive vitamin K antagonists (VKAs) (e.g., warfarin, acenocoumarol), mainly for the prevention of thromboembolism in patients with atrial fibrillation (AF) or mechanical heart valves (MHV) or for the treatment of deep venous thrombosis/pulmonary embolism. These drugs are increasingly prescribed worldwide, mostly due to the increasing age of the population [1,2]. In Italy, the use of warfarin has almost doubled during the last 10 years [3].

The burden of oral anticoagulants has also been recently broadened by the introduction of new oral anticoagulants, also named direct oral anticoagulants (DOACs), which directly inhibit either thrombin (dabigatran, Pradaxa®, BoehringerIngelheim, Ingelheim, Germany) or the activated coagulation factor X (rivaroxaban, Xarelto®, Bayer AG, Leverkusen, Germany; apixaban, Eliquis®, Bristol-Myers Squibb, New York, NY, USA). DOACs have been approved in Europe as alternatives to VKAs for preventing strokes and embolic events in patients with non-valvular AF, for thrombo-prophylaxis after major orthopaedic surgery and for the prevention/treatment of deep venous thrombosis and pulmonary embolism. Another direct inhibitor of the activated coagulation factor X (edoxaban, Lixiana®, Daiichi-Sankyo, Tokyo, Japan) is currently under regulatory review in Europe [4]. These agents, which are characterized by a predictable anticoagulant effect at fixed doses, overcome some of the VKAs pitfalls such as their narrow therapeutic window, the need for frequent monitoring and dose adjustments as well as the interaction with foods and/or other drugs.

The proportion of patients with AF who take DOACs relative to VKAs currently is 1/10–15 but this proportion will likely increase as more and more patients shift from VKAs to DOACs [5–7].

Both VKAs and DOACs present an inherent risk of bleeding:

Warfarin users present an incidence of major haemorrhage (including intracranial, gastrointestinal [GI], genitourinary and respiratory sites) of 1–3% per person-year [8–13], but figures as high as 7% per person-year have been reported in some observational studies [14–16]. The GI tract represents the most common

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bleeding site, with an age-standardized incidence rate of 5.8 per 1000 person-year [17], i.e., an approximately three-fold increased risk as compared with the general population [18]. The proportions of acute GI bleeders who take VKAs are 8–15% and 7% for upper [19–21] and lower GI bleeding, respectively [22]. The spectrum of endoscopic findings in VKA users who present with non-variceal acute upper GI bleeding is similar to that observed in patients taking no anticoagulants, with peptic ulcer being the main cause of bleeding [23]. VKAs-related GI bleeding events are associated with long hospitalization, relevant resource utilization, and a 30-day mortality of up to 15% [24,25]. However, in stark contrast to intracranial haemorrhage, warfarin exposure does not seem to significantly increase the GI bleeding mortality, which is mainly affected by patient's comorbidities [26]. A recent observational study carried out in two large community-based cohorts of patients with AF confirm that the mortality rates of patients with a major GI haemorrhage were not significantly different between patients on- versus off-warfarin therapy [27].

With respect to DOACs, the risk of GI bleeding is uncertain and reported incidences are heterogeneous. Initial evidence from AF registration trials [28,29] and a meta-analysis [30] showed an increased risk of bleeding as compared with warfarin at least for dabigatran and rivaroxaban. Conversely, a more recent and comprehensive meta-analysis of 11 phase III randomized controlled trials (RCTs), found no significant difference in the overall incidence of major GI bleeding between DOACs and VKAs. Interestingly, when trials were grouped according to the indication for anticoagulant therapy, the risk of GI bleeding in patients with venous thromboembolism was significant lower with DOACs vs. VKAs, whereas no difference was found among AF patients [31]. Actually, postmarketing data suggest that in the real world practice setting the observed GI bleeding risk with dabigatran in AF patients is higher than that experienced using warfarin [32]. With respect to available data on bleeding outcomes, a small retrospective study found that GI bleeders on DOACs received fewer transfusions as compared with those on warfarin; no difference was reported in terms of mortality and duration of hospital stay [33].

Acute GI bleeding in patients taking anticoagulants raises several difficulties related to the balance between thrombotic risks, associated with drug discontinuation or reversal, and haemorrhagic risks. Gastroenterologists who manage such patients have largely varying attitudes and an overall scarce knowledge of this topic as recently reported in a national Italian survey [34]. This might be related to several factors, such as the paucity of studies addressing the issue of acute GI bleeding in anticoagulated patients and the absence of RCTs comparing different management strategies. Moreover, practice guidelines by GI professional societies only marginally address this topic as they mostly focus on the management of anticoagulants in patients undergoing elective procedures [35–38]. This paucity of data is even more relevant for DOACs.

The current paper exclusively focuses on the appropriate management of VKAs and DOACs in acute GI bleeders, putting aside management practices common to all GI bleeders.

2. Pre-endoscopic management: anticoagulation reversal

2.1. Patients on VKAs

VKA discontinuation and correction of coagulopathy is recommended in VKA users who present with a clinically significant acute GI bleeding (haematemesis, maelena, severe haematochezia causing acute aenemia) as the risks of continued bleeding are supposed to outweigh those of thrombotic events [39–41]. The evidence documenting that an early intervention to correct VKA-related coagulopathy improves patient outcomes is limited. In a national audit from the UK that involved 4478 upper GI bleeders from 212 centres, coagulopathy (defined as an international normalized ratio [INR] >1.5 and/or a prothombin time prolonged by >3 s) was the strongest clinical predictor of failed endoscopic haemostasis [42]. Hence, it is inferred that pre-endoscopic correction of coagulopathy may be beneficial for most GI bleeders on VKAs. Two studies showed that VKAs-related coagulopathy at presentation does not have a negative impact on bleeding-related outcomes, provided that anticoagulation is promptly reversed: (i) in a prospective study by Choudari et al., 52 GI bleeders on warfarin (INR at presentation, 1.5–6.0) who received fresh frozen plasma (FFP) to decrease the INR value to 1.5–2.5 before urgent endoscopy had rebleeding and mortality rates similar to those observed in 50 matched controls who did not take warfarin [43]; (ii) in a retrospective study, 128 upper GI bleeders with a supratherapeutic ($\geq$3.0) INR on warfarin had a significantly lower 30-day mortality as compared with 135 matched controls who were not taking warfarin (6.3% vs. 15.5%, respectively; $p = 0.03$). Almost all patients (95%) received at least one drug to reverse anticoagulation before endoscopy, and 47% of them normalized their INR within 24 h [25].

2.1.1. Timing of endoscopy

The optimal target INR for endoscopic therapy to be safe and effective has yet to be determined. In the above-mentioned study by Choudari et al. [43], endoscopic haemostasis was reported to be as effective in warfarin users (after obtaining INR levels of 1.5–2.5) as in controls but the number of patients with attempted endoscopic treatment was small ($n = 23$). Conversely, no data exist on the safety and efficacy of endoscopic therapy in GI bleeders without previous correction of supratherapeutic INR. Considering the recognized benefits of early endoscopy in acute upper GI bleeding, various authors have recommended that endoscopy should not be postponed to correct coagulopathy in patients with a INR $\leq$2.5 [38]. In patients with supra-therapeutic INR values, endoscopy should preferably be postponed until the coagulopathy is partially or completely reversed.

2.1.2. Treatment options for VKA reversal

Treatment options for VKA reversal include administration of vitamin K, FFP, prothrombin complex concentrate (PCC) and recombinant activated factor VIIa (rFVIIa) [39].

Vitamin K acts by promoting the synthesis by the liver of new functional clotting factors II, VII, IX and X. In bleeding patients, the intravenous (IV) route is preferred over the oral one because it allows a more rapid correction of the INR [44]. IV vitamin K is associated with an estimated 3/100 000 risk of anaphylaxis; thus, a slow infusion over a minimum of 30 minutes is advised to minimize this risk. Following IV infusion of 5–10 mg vitamin K, the INR begins to decrease within 2–4 h and usually reaches a normal range within 24 h [39]. Lower doses may fail to normalize the INR by 24 h, especially in patients with more prolonged INR values, and therefore may be inappropriate in bleeding patients [45,46]. Vitamin K is not ideal for urgently reversing anticoagulation but it provides a sustained correction of the coagulopathy, which lasts beyond that provided by short half-lived FFP and PCC. As the response to vitamin K may vary among subjects and warfarin has a much longer duration of action than vitamin K, INR testing every 12 h is advised until the INR stabilizes within normal values. A repeat dose of 5–10 mg may be considered whenever INR values remain elevated [46].

FFP consists of the fluid portion of human blood frozen within 8 h after collection. FFP is widely available, contains vitamin K-dependent clotting factors and has been the standard of care for urgent reversal of warfarin coagulopathy for years in the absence of RCTs. The recommended dose is an IV infusion of 15 mL/kg,

corresponding to about 3–4 units of plasma (one unit = 250 mL) in the average adult weighing 70 kg. The large infusion volume of FFP increases the duration necessary to correct coagulopathy and puts patients at risk of fluid overload. Other significant limitations associated with FFP, when urgent reversal is needed, include the prolonged time needed to match blood group and to thaw and transport the units. FFP may also be associated with transfusion-related acute lung injury and carries a risk, albeit minimal, of infection transmission as most FFP products are not virally inactivated. Time to effect of FFP is 10 min, but it takes a few hours for partial reversal of INR and at least 9 h for complete reversal (i.e., INR < 1.5) [47].

PCCs are pharmacological products that contain lyophilized inactivated concentrates of factors II, IX, and X, with variable amounts of factor VII, derived from the cryoprecipitate supernatant of large plasma pools after at least one viral inactivation step to minimize the risk of pathogen transmission. Variations in factor VII concentrations among available PCCs have led to classify them as either three- or four-factor complexes (3F-PCC or 4F-PCC, respectively). The factors provided by PCC products are generally not activated and require activation by the clotting cascade. To prevent the activation of these factors, most PCC contain heparin and natural coagulation inhibitors (protein C, protein S). There is one activated PCC (aPCC) product available (FEIBA®, factor VIII inhibitor bypassing activity) which contains mostly activated factor VII and mainly inactivated forms of factors II, IX and X. Two 3F-PPCs (Uman Complex D.I®, Kedrion S.p.a, Italy and Prothromplex TIM 3®, Baxter, Austria) and two 4F-PPCs (Confidex®, CSL Behring, Germany and Pronativ®, Octapharma, Italy) are currently available in Italy and all are licensed for urgent reversal of VKAs. The PCCs are standardized according to their factor IX content and they are administered IV, usually at the dose of 25–50 IU of factor IX/Kg, depending on baseline INR. Main advantages of PCCs over FFP include a prompt reconstitution into a small volume (20 mL for about 500 IU) at bedside and administered regardless of the patient's blood type with a rapid IV infusion over 20–30 min and a faster INR correction [48,49]. In a recent RCT that included 202 VKA users with acute major bleeding (52% of whom from the GI tract), 4F-PCC was non-inferior to FFP for haemostatic efficacy in the first 24 h but it was superior to FFP for rapid INR lowering (62.2% vs. 9.6% of patients in the 4F-PCC and FFP group, respectively, achieved an INR $\leq$1.3 within 30 min of the end of infusion) [50]. In a large prospective cohort study that included 822 patients with VKA-associated major bleeding events, the use of PCC and of vitamin K in accordance with established guidelines was associated with a significant decrease in seven-day mortality, particularly among patients with intracranial haemorrhage, where timing of reversal strongly impacts on outcomes [51]. A recent prospective non-randomized comparative study that included 40 upper GI bleeders on warfarin with an INR >2.1 showed that patients who received 4F-PCC had almost normalized their INR at 2 h (INR, 1.53), while those who had received FFP had a INR of 2.41 at 6 h following infusion. No patient in the PCC group had active bleeding at endoscopy, compared with 7 in the FFP group (0% vs. 35%, $p < 0.01$). The need for endoscopic haemostasis and the length of stay in the emergency department were significantly lower in the PCC group than in the FFP group [52]. Three-factors PCC may be less effective than 4F-PPC for warfarin reversal, as supratherapeutic INR may remain prolonged due to the persistent deficiency of factor VII [53,54]. Thus, where available, 4-PCCs should be preferred over 3F-PCCs for acute reversal of oral VKAs [55]. With respect to safety issues, in a retrospective cohort study of 314 warfarin users, serious adverse events 7 days after anticoagulation reversal were significantly more frequent with FFP vs. 4F-PCC (19.5% vs. 9.7%, $p = 0.014$) [56]. Of note, significantly more patients experienced heart failure possibly related to volume overload in the FFP group, whereas there was no difference in the rate of thromboembolic events. A recent meta-analysis of 27 studies (seven studies with 3F-PCC and 20 with 4F-PCC, 1032 patients overall) showed that the incidence of thromboembolic events was 0.7% (95% confidence interval [CI], 0.0–2.4) and 1.8% (95% CI, 1.0–3.0) in patients treated with 3F-PCCs and 4F-PCCs, respectively. This suggests that a low but quantifiable risk of thromboembolism exists in VKA users who receive PCCs for anticoagulation reversal, this risk being acceptable when compared with the bleeding risks [57].

Recombinant factor VIIa (rFVIIa) is a biotechnology product that is structurally similar to the native FVIIa and enables haemostasis by activating the extrinsic pathway. Evidence supporting the effectiveness of rFVIIa for the rapid correction of prolonged INR values and the treatment of VKA-associated bleeding is confined to case reports and small case series [58]. However, for urgent reversal of anticoagulation the use of both rFVIIa and FEIBA has been correlated with an unacceptably high risk of thromboembolism. None of these agents is licensed for this indication and their routine use should be avoided until better quality evidence supporting its effectiveness and safety becomes available [59,60].

2.1.3. Practical management strategies

An algorithm for the management of acute GI bleeders on VKAs is proposed (Fig. 1). In all patients, except those with minor rectal bleeding and a INR <5, VKAs should be stopped and vitamin K should be administered.

The decision to use PPCs (or FFP if unavailable) should be based on the clinical assessment of the severity of bleeding at presentation, although the INR value, the timing of endoscopy, and the patient thrombotic risk are other relevant factors to be considered.

In critical patients who are actively bleeding with persistent or intermittent haemodynamic instability, coagulation factors should be administered even in the case of therapeutic INR ranges and 4F-PCC rather than FFP should be used [39,41]. Whenever 4F-PCC is not available, 3F-PCC should be used. The INR should be measured 20–30 min following the end of PCC infusion and, if it remains $\geq$1.5, another dose of PCC should be administered [49]. The INR should be measured again after 6–8 h and then daily while the situation remains critical. IV co-administration of vitamin K is necessary to prevent a "rebound coagulopathy", which occurs 12–24 h after INR normalization once the transfused factors have been cleared (the half-life of warfarin is 20–60 h, exceeding by far those of PCC [6–8 h] and of FFP [1.5 h–2 d]) [61].

For patients who are not actively bleeding and who are haemodynamically stable, IV administration of vitamin K alone may represent an option in patients with therapeutic INR values. In the case of supratherapeutic INR values, the co-administration of PCCs or FFP could be considered whenever endoscopy is scheduled within 6–12 h in order to allow for effective haemostasis.

In the case of minor GI bleeding (e.g., self-limited scanty haematochezia not causing anaemia), there is no need for urgent anticoagulation reversal; vitamin K, given orally (1–5 mg) or IV at low-dosage (1–2.5 mg) may be considered if INR values are $\geq$5.

2.2. Patients on DOACs

Some differences between DOACs and VKAs are important to understand the adequate management of bleeding in DOACs users [62]: (i) in the absence of renal or hepatic failure, the clearance of DOACs and the subsequent loss of anticoagulation is rapid and predictable, occurring gradually over 12–24 h; (ii) currently, no specific reversal agent of DOACs are available for clinical use even though the shorter half-life of DOACs compared with VKAs makes this unavailability less critical; (iii) routine laboratory tests are not reliable to measure the anticoagulant effect of DOACs. Although a normal prothrombin time (PT) and a normal activated partial thromboplastin time (aPTT) are advocated as useful tool to exclude

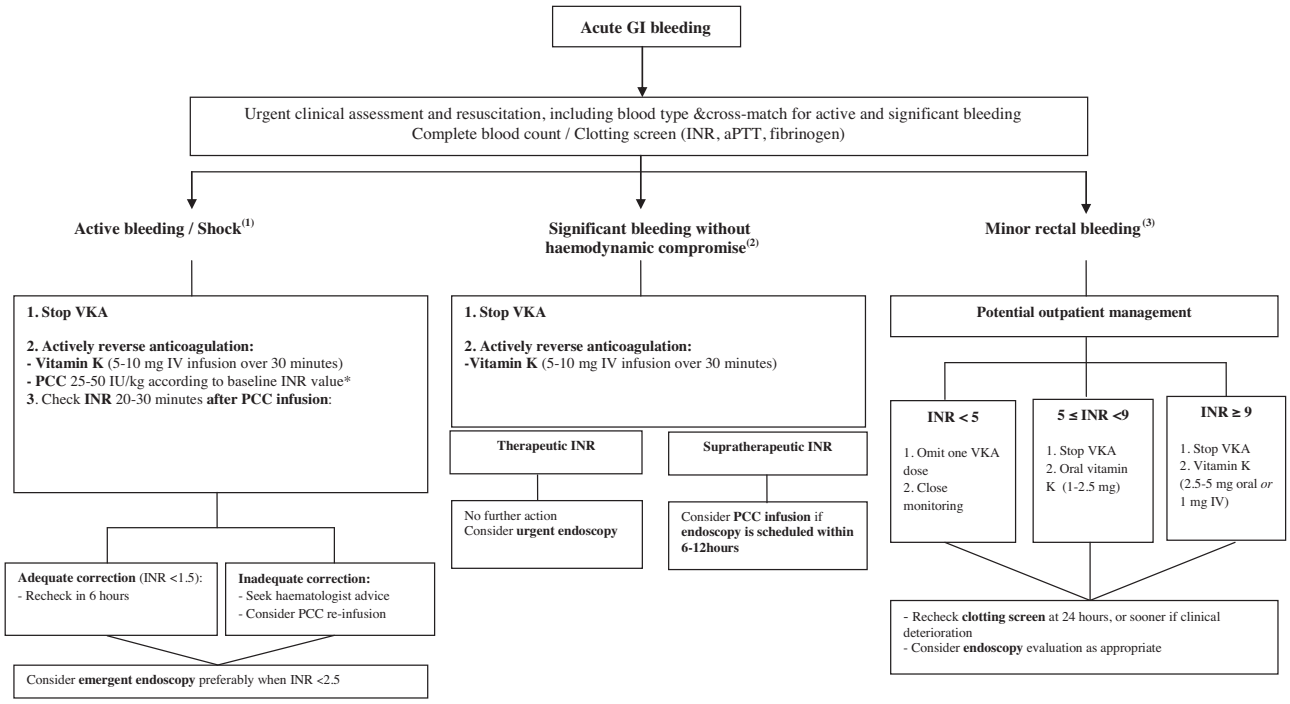

Fig. 1. Proposed management algorithm for acute gastrointestinal bleeders on vitamin K antagonists. aPTT, activated partial thromboplastin time; PCC, prothombin complex concentrate; INR, international normalized ratio; IU, international unit. *Administer 15 mL/kg FFP only if PPC is unavailable. (1) Overt acute GI bleeding (haematemesis, maelena, haematochezia), with shock or persistent/intermittent haemodynamic instability. (2) Overt acute GI bleeding but no haemodynamic compromise. (3) Scanty, self-limited haematochezia, with neither anaemia nor haemodynamic compromise.

the anticoagulant effect of rivaroxaban and dabigatran, respectively [63], these coagulation assays may be normal at trough drug levels. With respect to apixaban, both the PT and aPTT may be normal in the presence of clinically relevant on-therapy drug concentrations [64].

There are no published clinical trials or other high-quality evidence addressing the management of GI bleeding on DOACs, the clinical experience is still limited and no reversal strategies have yet been fully validated; thus, most current recommendations are based on experts' opinion or laboratory end-points [65–68].

2.2.1. Treatment options for DOAC reversal

Watch and support – In the case of clinically significant acute GI bleeding, DOACs should be temporary withheld. Given their relatively short half-lives, time is the most important antidote for DOACs, along with aggressive supportive measures, such as fluid replacement and transfusion as needed in order to preserve haemodynamic stability and enhance renal excretion. In order to adequately plan a watch and support strategy, it is important to inquire about the exact time of the last DOAC intake.

Gastric lavage and oral charcoal may be considered if DOACs have been ingested within 2–3 h, to prevent further absorption. In an in vitro experiment by van Ryn et al. [69], more than 99.9% of dabigatran was adsorbed by activated charcoal. This has not been tested in patients and no similar study has been reported for rivaroxaban or apixaban. However, the use of charcoal seems reasonable, particularly in the case of a recent dabigatran overdose.

Non specific pro-haemostatic agents, including activated and non-activated PCCs and rFVIIa may act as reversal agents and play a role in the treatment of serious bleeding, but supporting evidence is mostly limited to healthy human volunteers, animal models and *in vitro* studies [70]. Recently, a few small case series provided some evidence for these proposed reversal agents in actively bleeding patients: bleeding was effectively controlled with activated PCC (FEIBA) and 4F-PCC, while results were less consistent with 3F-PCC and rFVIIa [71]. According to recent practice guidelines [68], the administration of either activated PCC (FEIBA) or 4F-PCC may be considered in a patient with life-threatening bleeding if immediate haemostatic support is required. However, usually, 4F-PCC is preferred to FEIBA due to its lower potential prothrombotic activity and wider prompt availability. Vice versa, there is no place for the use of vitamin K or FFP as antidotes against DOACs; scanty data in animal models indeed argue against their use [72].

Specific molecular antidotes for DOACs are in the early phases of clinical trials in humans; these include a fully humanized antibody fragment (Fab) directly binding to dabigatran (idarucizumab, Boehringer Ingelheim) and a truncated form of enzymatically inactive factor Xa, which binds to and inhibits factor Xa inhibitors (Andexanet alfa, Portola Pharmaceuticals, San Francisco, CA, USA) [73]. Lastly, a small, water-soluble, cationic molecule (Arapazine, Perosphere, Danbury, CT, USA) has been recently synthesized to specifically bind to all DOACs, as well as unfractionated heparin and low-molecular-weight heparin [74]. In the future, these molecules might represent an option for the management of ongoing life-threatening bleeding events in DOAC users.

Haemodialysis can be used to reduce the plasma concentration of dabigatran rapidly and efficiently (65% at 2–4 h), and it is considered the most effective strategy for dabigatran-associated bleeding in patients with renal failure; however, it is not effective for other DOACs (rivaroxaban, apixaban, and edoxaban) that are bound to plasma proteins in higher proportions than dabigatran [75,76].

2.2.2. Practical management strategies

An algorithm for the management of acute GI bleeders on DOACs is proposed (Fig. 2).

If the patient is haemodynamically stable and/or responds sufficiently to resuscitation, it is advisable to simply observe the patient closely and defer endoscopy for 12–24 h, thus allowing for drug clearance and normal haemostatic functions to resume. The theoretical advantage of this approach is that endoscopic therapy may

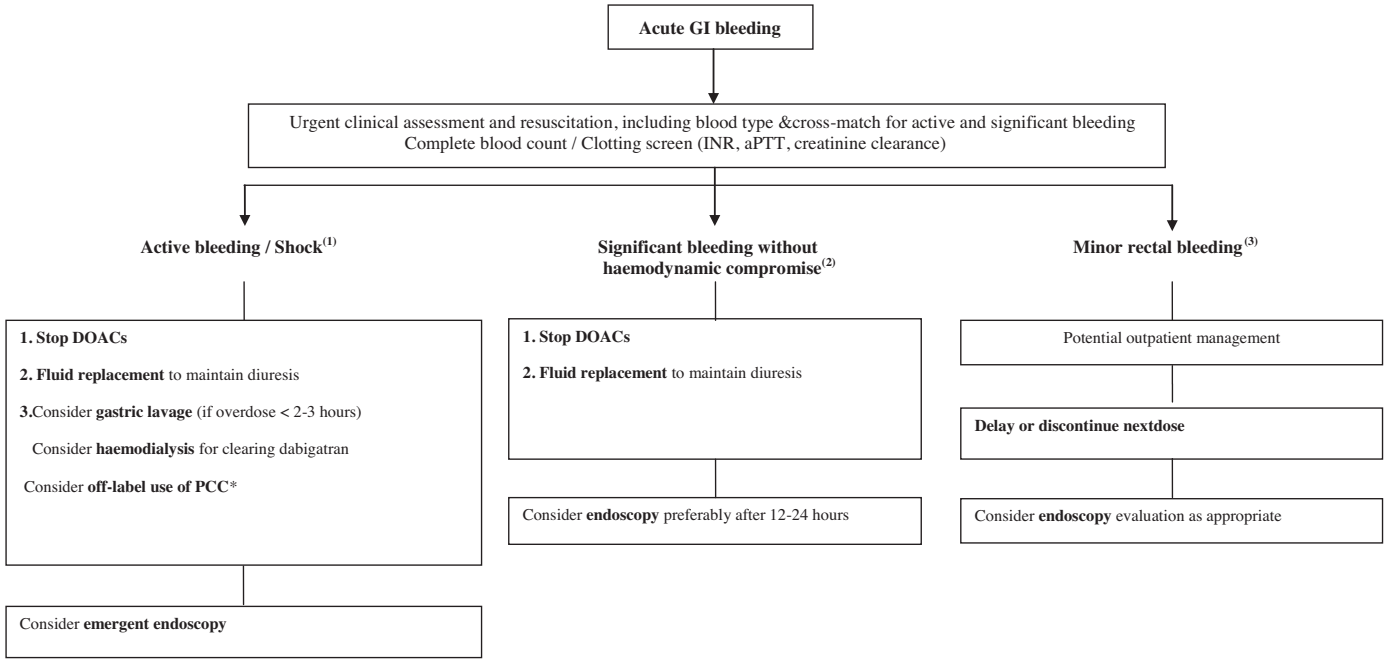

Fig. 2. Proposed management algorithm for acute gastrointestinal bleeders on direct oral anticoagulants (DOACs). aPTT, activated partial thromboplastin time; INR, international normalized ratio; PCC, prothombin complex concentrate; aPCC, activated prothombin complex concentrate. *Preferably 4F-PCC or aPCC, if available. (1) Overt acute GI bleeding (haematemesis, maelena, haematochezia), with shock or persistent/intermittent haemodynamic instability. (2) Overt acute GI bleeding, but no haemodynamic compromise. (3) Scanty, self-limited haematochezia, with neither anaemia nor haemodynamic compromise.

be easier and safer to perform in a patient who is not fully anticoagulated.

Conversely, for actively bleeding patients with persistent or intermittent haemodynamic instability, emergent endoscopy may be appropriate. In this case, the use of non-specific pro-haemostatic agents to accelerate anticoagulation reversal may be considered. Practice guidelines [68] recommend the use of such reversal agents in patients with life-threatening bleeding but no reversal strategy for DOACs has yet been validated. In a recent survey among haematology specialists on current DOACs reversal practices, factor concentrates (activated PCCs and rFVIIa) were prescribed in 41% of dabigatran-associated bleedings [77].

Awaiting more data on the clinical effectiveness of these strategies in bleeding patients and the availability of DOACs reversal agents, the current treatment approach may depend on the resources and experience of each centre.

3. Post-endoscopic management

3.1. VKAs resumption

Data from observational studies consistently favour the resumption of VKAs after a major bleeding event; evidence about the timing of VKA resumption is limited.

Three studies compared patients who resumed or did not resume anticoagulants after GI bleeding. A retrospective cohort study compared 260 patients who resumed warfarin and 182 who did not [78]; after adjustment for potential confounders, warfarin resumption was associated with a >10-fold lower risk of thrombotic events (0.4% vs. 5.5%; hazard ratio [HR], 0.05; 95% CI, 0.01–0.58) and a >3-fold lower risk of death (5.8% vs. 20.3%; HR, 0.31; 95% CI, 0.15–0.62) while the risk of rebleeding was similar (10% vs. 5.5%; HR, 1.32; 95% CI, 0.05–3.57). A prospective cohort study included 208 consecutive patients admitted for GI bleeding while on systemic anticoagulation (73% warfarin, 13% DOACs, 8% low-weight molecular heparin and 6% unfractionated heparin); 121 of these resumed anticoagulation at discharge. Overall, during a 90-day follow-up period, a thromboembolic event was observed in 4% of the patients, whereas 14% of them were readmitted for GI bleeding. At multivariate analysis, anticoagulation resumption was independently associated with a lower risk of thromboembolism (HR, 0.121; 95% CI, 0.006–0.812), but not with a significantly increased risk of rebleeding (HR, 2.17; 95% CI, 0.86–6.67) or death (HR, 0.63; 95% CI, 0.21–1.89) [79]. Quereshi et al. [80] compared 653 patients who resumed vs. 676 patients who did not resume warfarin after GI bleeding. Resumption of anticoagulation was associated with a reduction of thromboembolic events (HR, 0.71; 95% CI, 0.54–0.93) and no increase in rebleeding (HR, 1.18; 95% CI, 0.94–1.10). Mortality was significantly lower among patients who resumed anticoagulation (HR, 0.67; 95% CI, 0.56–0.81; $p < 0.0001$).

The ideal timing to restart anticoagulation has been poorly studied. GI practice guidelines do not specifically address this issue and basically suggest resuming anticoagulation as soon as the risk for cardiovascular complications is thought to outweigh the risk for bleeding [38]. The only available data come from the abovementioned study by Quereshi et al. [80]. In that study, 653 patients resumed warfarin at various intervals after bleeding (<7 days [$n = 62$], 7–15 days [$n = 51$], 15–21 days [$n = 58$], 21–30 days [$n = 53$] and >30 days [$n = 429$]). Mortality was lower in patients who resumed warfarin <7 days, 7–15 days and 15–21 days vs. >30 days following GI bleeding ($p < 0.05$ for all comparisons). Patients who resumed warfarin within 7 days had an approximately two-fold higher risk of rebleeding and a non-significant decrease in thromboembolism as compared with patients who resumed anticoagulation after 30 days. The incidence of rebleeding was similar for all groups of patients who resumed warfarin >7 days following bleeding, suggesting that the second week following GI bleeding could be appropriate to resume VKAs in a majority of patients. Nevertheless, the study does not provide a stratification of patients on the basis of their risks of bleeding or thrombosis.

Based on this limited evidence, VAKs should be resumed and the ideal timing lies between 7 and 30 days after the bleeding event, likely in the second week for most patients.

3.2. DOACs resumption

Data about DOACs resumption after GI bleeding are lacking. It can be hypothesized that the principles adopted for VKAs could be extended to DOACs but caution is required as, unlike warfarin, DOACs induce anticoagulation within a few hours and no specific antidotes are currently available. The pharmokinetics of DOACs make the role of heparin bridge therapy unnecessary in most cases, but also call for prudence in DOACs resumption, which should probably be deferred after the first week following the bleeding event.

4. Areas of uncertainty

To date, there is limited information on the management of patients with MHV and GI bleeding. With respect to anticoagulation reversal, ACC/AHA guidelines issued in 2008 raised some concerns on the safety of administering PCC due to potential thromboembolic complications, including valve thrombosis, as well as high-dose (5–10 mg) IV vitamin K due to potential "warfarin resistance" [81]. Low-dose (1–2.5 mg) IV vitamin K combined with FFP was recommended in the case of major bleeding. However, there is no evidence that bleeders with or without MHV should be treated differently; accordingly, the updated ACC/AHA guidelines recommend PCC as a reasonable alternative to FFP when urgent reversal is required [82]. With respect to VKAs resumption, MHV patients should be considered at high risk of thromboembolic complications. In particular, prolonged anticoagulation withdrawal is a major risk factor for prosthetic valve thrombosis, a serious complication associated with significant morbidity and mortality [83]. Hence, it might be advisable to resume VKAs early in the second week (ideally on day 7) considering heparin bridge therapy until INR reaches the therapeutic level. For MHV patients at highest thrombotic risk (mitral MHV, multiple MHVs, MHV with prior stroke or AF, and MVH implanted within 6 months) a potential role for heparin bridge therapy starting 72 h after endoscopy may be advocated, provided that the haemostasis is established and the risk of rebleeding is low.

Another issue is the timing of anticoagulant resumption in patients with clinically significant GI haemorrhage and no source of bleeding identified at endoscopy. In these patients, the timing should be decided based on estimates of the individual risks of rebleeding and thrombosis.

Lastly, in patients for whom the endoscopist is not fully confident in the achievement of haemostasis, no clear-cut recommendations on anticoagulant therapy resumption can be made. In such cases, a "second look" endoscopy might be indicated, although its role should be better evaluated.

Conflict of interest

None declared.

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