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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.

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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,

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