REVIEW

GASTROINTESTINAL BLEEDING IN PATIENTS UNDER ANTICOAGULANT AND ANTIPLATELET THERAPY – THE OPTIMAL APPROACH

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Abstract: *Gastrointestinal bleeding is one of the most common pathologies in patients who present to the emergency department, especially in those under anticoagulant or antiplatelet therapy. This therapy is fundamental in preventing and treating cardiovascular and cerebrovascular diseases in a wide spectrum of patients. When a bleeding event occurs, any anticoagulant or antiplatelet treatment should be interrupted. This interruption could significantly increase the risk of thromboembolic complications. Besides, clinicians should weight very carefully the moment and the circumstances for resuming the anticoagulant therapy depending on the severity of the bleeding, patients' comorbidities, drug interactions, thromboembolic and hemorrhagic risks. It is a serious problem and a decision difficult to make, considering that there is a lack of clinical practice guidelines about how to approach these situations.*

Introduction

Gastrointestinal bleeding is one of the most common pathologies in patients who present to the emergency department. There is an increasing in the prescription of prescription of anticoagulants and antiplatelets worldwide, especially in the elderly and multimorbid patients, in order to prevent or treat cardiovascular and cerebrovascular diseases [1]. It is commonly known that the main downside of these therapies is represented by the hemorrhagic risks, the majority being with gastrointestinal or cerebral origin. When a bleeding event occurs, any anticoagulant or antiplatelet treatment should be interrupted, but this interruption could significantly increase the risk of thromboembolic complications [2]. Acute gastrointestinal (GI) bleeding represents a life-threatening situation, particularly in patients under anticoagulants or antiplatelets. Hence, it is a real challenge for the clinician to appreciate the moment and the circumstances for resuming the anticoagulant therapy depending on several factors, such as the severity of the bleeding, patients' comorbidities, drug interactions, thromboembolic and hemorrhagic risks. Given the fact that there is a lack of clinical practice guidelines and limited data about an optimal approach of these situations, we aimed to find information in published

literature that provided specific and clear advice and recommendations regarding how to adjust anticoagulant and antiplatelet therapy when GI bleeding occurs, as safe as possible.

GASTROINTESTINAL BLEEDING IN PATIENTS UNDER ANTICOAGULANT/ANTIPLATELET THERAPY

General considerations

Anticoagulant drugs such as vitamin K antagonists (VKAs) (e.g., warfarin, acenocoumarol) and direct oral anticoagulants (DOACs) (e.g., apixaban, dabigatran, edoxaban, and rivaroxaban), also antiplatelet drugs such as the P2Y12 receptor inhibitors (clopidogrel, prasugrel, and ticagrelor), and acetylsalicylic acid (ASA) are approved and widely used for the treatment of deep venous thrombosis or pulmonary embolism, for stroke prevention in non-valvular atrial fibrillation, and for managing patients with ischemic heart disease or with valvular heart disease [3]. Taking into account their predictable pharmacodynamics with their rapid onset of action, the smaller number of drug or food interactions, the lack of required monitoring and dose adjustments, their safety profile, DOACs have become more appealing and the preferred oral anticoagulants over warfarin [4].

GI bleeding has a major impact on morbidity and mortality, being a frequent complication both in patients under oral anticoagulation and in patients under antiplatelet therapy. VKAs, particularly warfarin, are strongly associated with major haemorrhage, including intracranial, GI, genitourinary and respiratory, but the GI tract is the most common bleeding site. One study reported that GI bleedings occur in approximately 4.5% of patients who take oral anticoagulant treatment with VKAs [5]. Furthermore, among VKAs users, it seems that almost 8-15% present with acute upper GI bleeding, and 7% with lower GI

bleeding, respectively [6]. Also, endoscopic findings revealed that proportion of VKA users who present with non-variceal acute upper GI bleeding is similar to that noticed in patients without anticoagulants, with peptic ulcer being the main cause of bleeding [2]. However, warfarin exposure does not seem to significantly increase the GI bleeding mortality, when compared to intracranial haemorrhage [7]. As preferred alternative, DOACs proved a reduced bleeding risk and lower rates of hospitalizations and blood transfusions by contrast with warfarin [4][8]. However, new oral anticoagulants were associated with an increase in gastrointestinal bleeding [4]. Initially, literature reported an increased risk of bleeding in DOACs when compared to warfarin (dabigatran and rivaroxaban especially), which has raised some caution in their use [9][10]. Evidence showed an increased rate of GI bleed associated with rivaroxaban, but, on the other hand, apixaban proved the most advantageous safety profile, by comparison with both rivaroxaban and dabigatran [10][11]. Nevertheless, more recent studies and meta-analysis highlighted that there was no significant difference between DOACs and VKAs in terms of GI bleeding, even more, they seem to have lower rates of blood transfusion of hospitalization [8][12]. Additionally, while among patients with atrial fibrillation there was no difference noticed, in patients with venous thromboembolism, the risk of GI bleeding was considerably lower when using DOACs vs. VKAs [4][12][13].

Antiplatelet therapy represents the cornerstone of treatment in patients with acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI) with stenting, aspirin, clopidogrel, ticagrelor and prasugrel being the most commonly prescribed [14]. Aspirin, like other nonsteroidal anti-inflammatory drugs, induce both topical and systemic mechanisms which promote gastric or duodenal ulcer formation. In

addition to other factors including age, comorbidities, corticosteroid or multiple NSAIDs use, that increase gastric acid secretion and contribute to weakening the mucosal barrier and ulcer formation, the antiplatelet effects of aspirin amplifies the risk of GI bleeding [15]. The antiplatelet effects of clopidogrel could delay the ulcer healing and predispose patients with gastric ulcers to hemmorhage [16]. Even so, it seems that clopidogrel is preferred in patients with previous GI bleeding considering that aspirin is not only ulcerogenic, but also increases bleeding when it occurs. For instance, the largest head-to-head comparison of aspirin and clopidogrel named CAPRIE trial (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events), compared 9,546 patients using aspirin 325 mg daily with 9,553 patients using clopidogrel 75 mg daily. Although aspirin and clopidogrel have been considered to prove similar efficacy and strength of recommendation in guidelines, the trial reported a significantly higher incidence of any GI bleeding (2.66% vs. 1.99%) and severe upper GI bleeding (0.7% vs. 0.5%) in patients under aspirin vs. patients under clopidogrel [17]. Even if studies have not assessed post endoscopic procedural bleeding risk, a meta-analysis of 5 randomized controlled trials (RCTs) reported a lower risk of GI bleeding in patients taking P2Y12 inhibitor monotherapy vs. ASA monotherapy [18]. Moreover, clopidogrel showed superior impact on reducing the primary endpoint of stroke, myocardial infarction, or vascular death (absolute event rate of 5.32% for clopidogrel vs. 5.83 % for aspirin), and a lower rate of hospitalization for ischemia or bleeding (12.4% vs. 13.6%). Prasugrel and ticagrelor are also approved for the treatment of acute coronary syndrome, but when compared to clopidogrel, they both showed a higher incidence of major bleeding (prasugrel 2.4% vs. clopidogrel 1.8%; ticagrelor 4.5% vs. clopidogrel 3.8%) [19][20].

GUIDELINE STRATEGY IN THE SETTING OF ACUTE GI BLEEDING

An acute GI hemorrhage in patients under anticoagulant or antiplatelet medications represents a high-risk situation and the immediate risk of bleeding might outweigh the risk of thrombosis which could occur if anticoagulant or antiplatelet therapy is interrupted. Hence, it is crucially that endoscopy to be performed as soon as safely possible after immediate consultation between a gastroenterologist and a cardiologist, considering that every patient needs to be assessed on an individual basis. The American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) convened an international and multidisciplinary working group to create an accurate, comprehensive and pragmatic guideline after thorough assessment of published literature to provide clinical practice in the periendoscopic period.

PATIENTS USING VKAs

In case of a significant acute GI bleeding such as haematemesis, maelena or severe hematochezia, the risk of hemmorhage might outweigh a thrombotic event, hence, the correction of coagulopathy (defined as an international normalized ratio [INR] >1.5 and/or a prothombin time prolonged by >3 s) and cessation of VKA might be beneficial [21]. Taking into account the advantages of an early endoscopy when acute upper GI bleeding occurs, literature suggests that endoscopy should not be postponed to correct coagulopathy in patients with a INR≤2.5, while in patients

with supra-therapeutic INR values, endoscopy should be postponed until the coagulopathy is partially or completely corrected [22].

According to the American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG), in the setting of acute GI bleed, it is recommended as follows: 1) for patients on warfarin who are hospitalized or under observation with acute GI bleeding, should plead against fresh frozen plasma (FFP) administration (conditional recommendation, very low level of evidence); 2) for patients on warfarin who are hospitalized or under observation with acute GIB, should not reach a recommendation for or against prothrombin complex concentrate (PCC) administration; 3) for patients on warfarin who are hospitalized or under observation with acute GIB, PCC administration compared with FFP administration is recommended (conditional recommendation, very low certainty of evidence); 4) for patients on warfarin who are hospitalized or under observation with acute GIB (upper and/or lower), recommends against the use of vitamin K (conditional recommendation, very low certainty of evidence) [23]. Furthermore, two studies pointed out that coagulopathy related to VKAs does not have a negative impact on bleeding outcomes if anticoagulation is promptly reversed. Thus, Choudari et al. reported similar rates of rebleeding and mortality between 52 GI bleeders on warfarin (INR at presentation 1.5–6.0) who received (FFP) to decrease the INR value to 1.5–2.5 before urgent endoscopy and 50 matched controls who did not use warfarin [24]. In a retrospective study, Irwin et al. reported that 128 patients with upper GIB and a supratherapeutic INR ($\geq$3.0) on warfarin had a significantly lower 30-day mortality when compared to 135 matched controls

who were not on warfarin (6.3% vs. 15.5%, respectively); it is to be mentioned that 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]. Therefore, the decision to use PPCs (or FFP if unavailable) should be based on the clinical assessment of the severity of bleeding at presentation. Excepting a minor hemmorhage (which not causes anaemia) and a INR value $\leq$5, in all patients VKAs should be interrupted and vitamin K should be administered, given orally (1–5 mg) or IV at low-dosage (1–2.5 mg) [2]. When it comes to critical cases such as haemodynamic instability or active bleeding, it is recommended that coagulation factors to be administered and PCC rather than FFP, regardless of the INR value [26]. After the PCC infusion, the INR should be measured at 30 minutes and if the value remains $\geq$1.5, then another dose of PCC should be administered; after 6-8 hours, the INR value needs to be measured again, and then daily, as long as the patient's status is critical [21][27]. Once the transfused factors have been cleared and the INR has normalized, in order to prevent a so called "rebound coagulopathy", an IV co-administration of vitamin K is required [26][27]. In haemodynamycally stable patients, with no active bleeding and with therapeutic INR values, IV administration of vitamin K alone might be an option, while for an effective haemostasis in case of elective endoscopy setting, supratherapeutic INR values imply co-administration of PCCs or FFP [26].

Besides, in case of elective endoscopy setting, ACG and CAG suggests, regarding anticoagulant interruption vs continuation, as follows: 1) for patients on warfarin undergoing elective/planned endoscopic GI procedures, warfarin should be continued, as opposed to temporarily interrupted (1–7 days) (conditional recommendation, very

low level of evidence); 2) for patients on warfarin, who hold warfarin in the peri-procedural period for elective/planned endoscopic GI procedures, it is recommended against bridging anticoagulation (conditional recommendation, low level of evidence) [23]. Depending on the severity of the bleeding and considering the risk of interrupting anticoagulant therapy, in patients with high risk conditions, warfarin could be discontinued with or without the substitution of heparin [28].

VKAs resumption

In terms of the appropriate timing of VKAs resumption after endoscopy, data is limited, and practical guidelines do not provide accurate and specific information. For instance, ACG and CAG could not reach a recommendation for or against resuming warfarin the same day vs 1-7 days after the endoscopic procedure in patients whose warfarin was interrupted and who are undergoing elective endoscopy [23].

However, when deciding, it is essential not only to consider the thrombotic risk and the risk of a delayed bleeding associated with the endoscopic procedure, but also to achieve an adequate haemostasis. Thus, observational studies recommend the resumption of VKA therapy as soon as possible if the risk of a cardiovascular complication outweighs the risk of bleeding.

Several studies focused on the comparison between patients who resumed vs. patients who did not resumed anticoagulants after a GI bleeding. One consistent study compared 653 patients who resumed warfarin at different intervals after bleeding (<7 days, 7-15 days, 15-21 days, 21-30 days, >30 days) vs. 676 patients who did not resume warfarin after a GI bleeding. Qureshi et al. reported no increase in

rebleeding, a reduction of thromboembolic events and a considerably lower mortality rate among patients who resumed warfarin [29]. Specifically, patients who resumed warfarin within 7 days showed a risk of rebleeding almost twice higher than patients who resumed anticoagulation after 30 days and no significant decrease in thromboembolism. Additionally, patients who resumed warfarin in less than 30 days following a GI bleeding proved a lower mortality when comparing to those who resumed warfarin in more than 30 days. Also, the incidence of rebleeding was similar for all groups of patients who resumed warfarin >7 days after the GI bleeding, meaning that the second week after GI bleeding could be appropriate to resume VKAs in the vast majority of cases [29]. In a retrospective cohort study, Witt et al. compared 260 patients who resumed warfarin with 182 who did not and highlighted that warfarin resumption was associated with a >10-fold lower risk of thrombotic events (0.4% vs. 5.5%), a >3-fold lower risk of death (5.8% vs. 20.3%) and a rebleeding risk of 10% vs. 5.5% [5]. Thereby, although the currently available evidence is poor and limited on this regard, it seems that the second week (between 7-30 days) represents an optimal time for VKAs resumption following a GI bleeding in most cases.

PATIENTS USING DOACs

Specific data and clinical experience for an optimal management of GI bleeding in DOACs users are still deficient and reversal strategies are not completely defined and validated yet. Though, it is necessary to envisage that, in contradistinction to VKAs, the clearance of DOACs is quicker and more efficient in the absence of renal failure, they have shorter half-life and the

routine laboratory tests are not reliable to measure their anticoagulant effect [30].

Regarding DOACs reversal, treatment options include gastric lavage and oral charcoal, nonspecific pro-haemostatic agents, specific molecular antidotes, haemodialysis or "watch and support" strategy [2]. "Watch and support" strategy requires the exact time of the last DOAC intake and, in case of clinically significant acute GI bleeding, DOACs should be temporary suppressed, along with aggressive supportive measures, such as fluid replacement and transfusion in order to preserve haemodynamic stability and enhance renal excretion [2]. Gastric lavage and oral charcoal could be considered if DOACs have been ingested within 2–3 h and haemodialysis, a very effective strategy in patients with renal failure, could only be used to reduce the plasma concentration of dabigatran rapidly and efficiently (65% at 2–4 h) [2][31][32]. As nonspecific pro-haemostatic agents activated and non-activated PCCs and rFVIIa might be helpful, although the evidence is limited. Recently, several practice guidelindes suggest that, when immediate haemostatic support is needed, the administration of either activated PCC (FEIBA) or 4F-PCC could be considered, but 4F-PCC is commonly preferred because of its lower prothrombotic activity [33]. Specific molecular antidotes for DOACs are represented by fully humanized anti-body fragment (Fab) directly binding to dabigatran (Idarucizumab) and a truncated form of enzymatically inactive factor Xa, which binds to and inhibits factor Xa inhibitors (Andexanet alfa), but they are still under assessment, in early phases of clinical trials in humans [34].

According to ACG and CAG, PCC should not be administered in patients on DOACs who are hospitalized or under observation with acute GI bleeding (conditional recommendation, very low certainty of evidence). Also, for patients on dabigatran who are hospitalized or under observation with acute GIB, it is suggested against the administration of idarucizumab and for patients on rivaroxaban or apixaban against the administration of andexanet alfa (conditional recommendation, very low certainty of evidence) [23]. Furthermore, in the elective endoscopy setting, ACG and CAG suggest temporarily interrupting DOACs rather than continuing (conditional recommendation, very low certainty of evidence) [23].

DOACs resumption

Given the rapid action of onset and half-life of DOACs, the thrombotic risk associated with their interruption is anticipated to be lower than with interruption of warfarin. Thereby, the optimal period of temporary DOACs cessation before endoscopic should be between 1 and 2 days, excluding the day of the procedure [35]. One relevant study is represented by the prospective PAUSE cohort study which provides a standardized protocol for DOACs interruption, complete follow-up, and valid outcome assessment [36]. According to this study, before the endoscopic procedures consisting in colonoscopies, gastroscopies, flexible sigmoidoscopies with and without biopsy or polypectomy, the duration of DOACs cessation was 2.0±0.5 days, including the day before the procedure and the day of the procedure in most of the cases. The DOACs resumption after the endoscopic procedure was around 1.9±1.5 days and with hemostasis achieved, the complete period of DOACs cessation was 3.9±1.6 days in the periendoscopic period. There were only 8.1% of patients who interrupted DOACS for more than 2 days before the endoscopic procedure. Furthermore, Douketis et al. reported very low incidence rates of mortality and 30-day

thromboembolic with temporary DOAC interruption [36].

In patients who are undergoing elective endoscopic GI procedures, ACG and CAG could not reach a specific recommendation for or against resuming the DOAC on the same day of the procedure vs 1–7 days after the procedure [23]. In one study, Radaelli et al. compared the risk of bleeding based on the timing of DOACs resumption, by evaluating 529 patients who interrupted DOAC therapy for an elective endoscopic procedure (among who 327 presented a low bleeding risk procedure and 202 a high bleeding risk procedure), with 18 patients receiving low-molecular-weight heparin (LMWH) bridging therapy, followed then for 30 days [37]. The study showed a bleeding risk of 2.3% in patients who resumed the DOACs between days 0-3 vs. a bleeding risk of 11.5% in patients who resumed the DOACs after day 3. Even more, the use of bridging coagulation might have increased the bleeding risk in patients who resumed the DOACs after day 3 [37]. Additionally, Radaelli et al. reported thromboembolic events in one patient of 477 who resumed DOACs on days 0-3 vs. in one patient of 52 who resumed DOACs after day 3.

According to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines, in patients under DOACs therapy with a moderate GI bleeding or worse, it is recommended to stop the DOAC and resume between 7–15 days after the event, while in patients with a very high thrombotic risk, including a mechanical heart valve, cardiac assist device or CHA2DS2-VASc score ≥4 should benefit from earlier resumption (first week) [14][38].

Therefore, specific evidence focused on DOACs resumption following a GI bleeding is still lacking. However, it seems that LMWH bridging therapy is not necessary in most of the cases and DOACs resumption should be delayed after the first week following the bleeding event, requiring much caution.

PATIENTS USING ANTIPLATELET THERAPY

When dealing with the decision of continuation vs. interruption of ASA therapy, it is of crucial importance to weight very careful cardiovascular benefit of secondary preventive ASA therapy and the potential risk of further GI bleeding with continued ASA therapy.

The pharmacodynamic effect of ASA consists in irreversible inhibition of platelet cyclooxygenase 1, which mediates thromboxane synthesis. After the ingestion of ASA, thromboxane synthesis normalizes by 7–10 days, thus, stopping ASA in patients with GI bleeding would have minor impact on the initial clinical course, considering the persistent antiplatelet effect of ASA in the first two days [39][40]. In patients with upper GI bleeding, current guidelines recommend performing endoscopy within 24 hours, and in patients with lower GI bleeding diagnostic testing is recommended within 24-36 hours [41][42]. Moreover, usually hemostasis occurs before endoscopy or at the time of the procedure when active bleeding is identified. Hence, the initial cessation of ASA after presentation should not have major impact on either bleeding or cardiovascular clinical outcomes if resuming when endoscopic hemostasis is established.

Regarding reversal of antiplatelet with platelet transfusion, for patients on antiplatelet agents who are hospitalized or under observation with acute GI bleeding without thrombocytopenia, ACG and CAG recommend against platelet transfusions (conditional recommendation, very low level of evidence) [23]. Platelet administration for reversal effect of antiplatelet agents in patients with severe

GI bleeding was suggested by previous guidelines but it is strongly necessary to take into consideration the possibility of thrombotic events with an infusion of functional platelets in patients under antiplatelet therapy with higher cardiovascular risk, together with potential risks related to the transfusion of blood products [43]. For instance, one cohort study compared 204 patients with GI bleeding using antiplatelet agents, without thrombocytopenia, who received platelet transfusion with a matched control group of 204 patients who did not receive. In this study, Zakko et al. reported a significant increase in mortality and the lack of benefit in decreasing further hemorrhage in patients with GI bleeding with platelet transfusion vs. those who did not receive transfusion [43].

Regarding holding vs. continuing ASA, one relevant study, a double-blinded, randomised controlled trial (RCT), assessed patients using ASA for secondary cardiovascular protection with high-risk peptic ulcer bleeding, requiring endoscopic treatment [44]. The RCT included 156 patients with upper GI bleeding on aspirin for secondary prevention and randomized to continuing low dose of ASA or placebo for 8 weeks of the study. Recurrent upper GI bleeding occurred more frequently in the group treated with ASA (10.3% vs. 5.4%) while the 8-week mortality rate attributable to cardiovascular, cerebrovascular, and GI complications was significantly higher in the placebo group (1.3% vs. 12.9%). However, the need for blood transfusions was similar between both groups, implying relatively mild recurrent bleeding events. In addition, the study reported no significant differences between the two groups regarding thrombotic events at 30 days (3/78 vs. 9/78, pleading for early ASA resumption). Taking into account the downward trend in the mortality rate among patients with myocardial infarction who continued ASA therapy and the considerable decrease in mortality among patients with high-risk ulcer bleeding who

resumed ASA immediately after endoscopic hemostasis, ACG and CAG guidelines recommend: 1) to continue rather than interrupt aspirin therapy; 2) in case of interruption at clinical presentation, it is suggested rapid resumption within 24 hours of successful endoscopic hemostasis [23].

Furthermore, for patients on dual antiplatelet therapy (DAPT) (P2Y12 inhibitor [clopidogrel, prasugrel, or ticagrelor and ASA 81–325 mg/dL) for secondary cardiovascular prevention who are undergoing elective endoscopic GI procedures, ACG and CAG suggest temporary interruption of the P2Y12 inhibitor while continuing ASA (conditional recommendation, very low certainty of evidence); it is to be mentioned that this recommendation applies only to elective procedures and not in emergency situations [23]. Nevertheless, for patients on monotherapy with ASA 81–325 mg/dL for secondary cardiovascular prevention, it is recommended against interruption of ASA (conditional recommendation, very low certainty of evidence) [23]. Literature showed that in case of standard biopsies or diagnostic endoscopy the risk of clinically significant bleeding is low enough that there is not necessary to interrupt ASA. One prospective observational study reported bleeding events in 0 of 142 patients who continued ASA vs. one patient of 61 who held ASA [45]. Additionally, one RCT which compared clopidogrel with ASA in patients undergoing duodenal and antral biopsies, none of the 280 biopsies on ASA induced bleeding events [46]. Accordingly, the ESGE guideline and expert consensus paper of the ESC, suggest that patients on aspirin or DAPT for secondary prevention with upper gastrointestinal bleeding should continue aspirin or DAPT if endoscopy shows no active bleeding [38][47]. On the other hand, in patients with active bleeding it is strongly recommended a three-day interruption of aspirin and, in case of DAPT, to continue P2Y12 inhibitor and interrupt aspirin for three days [38][47].

Also, the ESC DAPT guideline recommends to consider shortening the DAPT duration and switching to DAPT consisting of aspirin with clopidogrel [14]. The ACG guideline suggests continuing aspirin for secondary prevention in case of acute lower GI bleeding and in patients on DAPT, it is recommended to interrupt the P2Y12 inhibitor for a maximum of 7 days while aspirin should be continued. In patients who suffered from an acute coronary syndrome within 90 days or who received a coronary stent within 30 days DAPT should be continued (strong recommendation, low quality evidence) [42].

For patients on single antiplatelet therapy with P2Y12 inhibitor agents who are undergoing elective endoscopic GI procedures, ACG and CAG could not reach a recommendation for or against temporary interruption of the P2Y12 inhibitor, whereas the currently available evidence reported no significant increase in bleeding risk among patients who interrupted a P2Y12 inhibitor for an elective endoscopic procedure [23].

Regarding the optimal timing of P2Y12 inhibitor resumption after endoscopy, for patients who are undergoing elective endoscopic GI procedures whose P2Y12 inhibitor was interrupted, ACG and CAG could not reach a recommendation for or against resuming P2Y12 inhibitor on the same day of the procedure vs 1–7 days after the procedure [23].

In addition to all measures mentioned above, in patients with upper GI bleeding, ESGE guideline recommends immediate initiation of high-dose intravenous proton pump inhibitors (PPIs) (strong recommendation, high quality evidence) and continuing the infusion until 72 hours post-endoscopy. In patients under DOACs or antiplatelet therapy, PPIs reduce the risk of upper GI bleeding, hence, it is recommended to consider continuing the treatment with oral PPIs after discharge when DOAC or antiplatelet therapy is reinitiated [38].

CONCLUSIONS

Currently, although there are several specific advices that could be generally followed, the evidence considering the management of antithrombotic agents in patients with GI bleeding is insufficient and future studies are necessary in order to provide accurate and standardized recommendations for an optimal approach.

Author Contributions:

R.I.D. conceived the original draft preparation. R.I.D., L.B.G., A.I.N., M.M. and C.C.D. were responsible for conception and design of the review. R.I.D., A.G.P., L.B.G. and C.C.D. were responsible for the data acquisition. R.I.D, was responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. R.I.D., L.B.G., A.I.N., M.M. and C.C.D. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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