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OPEN

Gastrointestinal Bleeding and Anticoagulant or Antiplatelet Drugs: Systematic Search for Clinical Practice Guidelines

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Abstract: Gastrointestinal (GI) bleeding is a frequently encountered and very serious problem in emergency room patients who are currently being treated with anticoagulant or antiplatelet medications. There is, however, a lack of clinical practice guidelines about how to respond to these situations. The goal of this study was to find published articles that contain specific information about how to safely adjust anticoagulant and antiplatelet therapy when GI bleeding occurs.

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Abbreviations: ASA = acetylsalicylic acid, COX-2 = cyclooxygenase-2, GI = gastrointestinal, NSAID = nonsteroidal anti-inflammatory drug, PPI = proton-pump inhibitor, SSRI = selective serotonin reuptake inhibitor.

INTRODUCTION

Gastrointestinal (GI) bleeding is frequently encountered in emergency room patients who are currently being treated with anticoagulant or antiplatelet medications for an underlying medical condition. It is a serious problem, especially in the elderly and/or multimorbid patients, and it presents the emergency room physician with a dilemma. On the one hand, any anticoagulant and antiplatelet treatment should be discontinued to help stopping the acute bleeding. On the other hand, discontinuing this type of therapy can significantly increase the risk for cardiovascular or cerebrovascular complications because of the underlying disease.

The number of patients who are being prescribed anticoagulant or antiplatelet therapy to either treat or prevent cardiovascular and cerebrovascular diseases is increasing.[1–4] The downside of these therapies, however, is that they increase the risk for life-threatening bleeding, most of which occur as GI or intracerebral bleeding.[5] The relative risk for upper GI bleeding, in particular, increases up to 10% in patients being treated with these therapies, and the annual risk for upper GI bleeding occurring in such patients is 1.5% to 4.5%.[6–8] This complication puts affected patients into an acutely life-threatening situation because the mortality from GI bleeding ranges from 1% to 13%.[9–11]

Given how often this life-threatening situation is encountered in emergency rooms, there is a surprising lack of data with respect to the problem. We found only 2 controlled studies that have investigated whether or when the use of anticoagulant or antiplatelet medications should be resumed after GI bleeding has ceased.[12,13] Results of the 2 studies do not provide a consistent guideline with respect to adjusting medications. The timeframe for resuming therapy was anywhere between 20 and 90 days after GI bleeding had stopped.[12,13] Results of one of the studies indicated that permanently stopping anticoagulant therapy in patients being treated with warfarin greatly increases the risk for thromboembolic events and even death.[12,13]

The goal of this study was to find published information that provided specific advice about how to safely adjust anticoagulant and antiplatelet therapy when GI bleeding occurs.

METHODS

Because there were no clinical practice guidelines currently available to emergency room physicians, our team was looking for relatively recent articles that might provide, if not explicit guidelines, at least some kind of advice that addressed

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how to best respond to a situation of GI bleeding in patients taking anticoagulant or antiplatelet drugs. No ethical approval was necessary to conduct the study because no patient data were collected or analyzed.

Overview of Study Design

The study consisted of a series of searches in the medical literature on 2 Internet websites using the terms ''gastrointestinal hemorrhage,'' ''cardiovascular diseases,'' ''guideline,'' ''platelet aggregation inhibitors,'' and ''anticoagulants'' as single terms or as PubMed MeSH terms to provide a list of titles for articles that might contain the type of clinical practice information we were seeking. The search included articles published through March 2013. The list of articles retrieved in the searches was then screened to narrow the set of entries to those that met 2 sets of criteria and eliminate entries that did not satisfy the goal of the study.

The first set of criteria was designed to ensure a focus on practical guidelines rather than general research in the areas of GI bleeding or cardiovascular therapies, that the entries comprised a relatively homogeneous study population in terms of genetic and lifestyle characteristics to which any guidelines might apply, the entries represented the results of relatively recent research, and consistency with respect to the terminology used in the articles. The second set of criteria was designed to narrow the set of eligible entries to ones that mentioned some guidelines, advice, suggestions, or otherwise relevant information about clinical practices.

A third stage of review eliminated articles that did not contain specific recommendations with respect to how to adjust therapeutic regimens for GI bleeding and concurrent cardiovascular conditions. After a set of articles had been identified that most closely matched all criteria, the relevant information in each article was analyzed in detail and compared with that in other articles to determine how many actual guidelines exist and are useful. At least 2 members of the investigating team reviewed each entry at all stages of the selection process.

Data Sources and Searches

The initial Internet searches were on the PubMed website, first using the term ''Gastrointestinal hemorrhage,'' followed by an advanced search with the terms ''Cardiovascular diseases AND Gastrointestinal hemorrhage,'' ''Cardiovascular diseases AND Gastrointestinal hemorrhage AND guideline,'' and ''Cardiovascular diseases AND platelet aggregation inhibitors OR anticoagulants AND guideline.'' The second set of searches was on the Google website using the same search terms in the same order. The articles gleaned from all of these searches were collated and the duplicate entries deleted.

Study Selection

1 To test the initial set of criteria that would be used to screen articles at this stage, a pilot set of 100 titles and their associated abstracts were reviewed by I.K.G. and one of the coauthors. If necessary, the criteria were modified. If no abstract was available for an article but the title appeared to be relevant, we obtained the full text of the article for review.
2 All remaining titles and their associated abstracts were then screened by I.K.G. and one of the coauthors using the initial set of selection criteria in a predetermined sequence. First, articles that were clearly not guideline articles were eliminated. Second, all articles that were not written in English were eliminated. Third, all articles published >5 years prior to March 2013 were eliminated. Fourth, all articles that did not originate in Europe, the United States, or Canada were eliminated. Again, if no abstract was available for an article, but the title appeared to be relevant, we obtained the full text of the article for review.
3 To test the criteria that would be used for screening the smaller and more focused group of articles in the next stages of the study, the full texts of a pilot set of 10 papers from this group were read and discussed by I.K.G. and one of the coauthors of this study.
4 The full texts of all remaining articles were then screened by I.K.G. and one of the coauthors of this study. Upon initial reading of the texts, any articles found to not meet the initial selection criteria were eliminated. Then articles that did not mention any information about patient care or whose focus was obviously non-GI-related hemorrhaging were eliminated.

Data Extraction and Quality Assessment

In their evaluations of the full texts of the articles, the reviewers noted whether an article contained information about how to proceed with respect to stopping, continuing, or adjusting dosages of specific anticoagulant or antiplatelet drugs in use at the time of GI bleeding, with respect to the use of other types of interventions for GI bleeding, and with respect to whether to resume specific anticoagulant or antiplatelet drugs after GI bleeding had stopped, and if so, when and at what dosages. The results of the 2 investigators were compared. Any differences that could not be resolved were referred to EB, MS, or the primary author of this study.

Data Synthesis and Analysis

The clinical practice advice in the remaining articles was evaluated again in detail and compared by 2 of the coauthors and the findings summarized. The 4 finally relevant articles were identified by both searches, PubMed and Google.

RESULTS

The combined results for searches of the PubMed and Google sites were 81 320 articles after eliminating duplicate entries. However, despite the large number of articles initially identified on those sites, almost no articles contained operationally useful recommendations with respect to strategies for reducing or eliminating the use of anticoagulant and antiplatelet drugs when GI bleeding is present in patients. Of the initial 49 020 articles originally extracted from PubMed, only 56 articles remained eligible for further assessment; of the 32 300 articles originally extracted from the Google site, only 20 articles remained eligible for further assessment.

After reading the full text of all eligible articles, 59 were excluded because they were found to not meet the initial selection criteria, did not mention information about patient care, or discussed situations of non-GI-related hemorrhaging. Among the 17 remaining articles that provided some type of information about patient care in a case of GI hemorrhaging, gastroenterology guidelines tended to primarily focus on the bleeding-associated risk for patient, and cardiovascular guidelines tended to focus on the risk that is associated with

discontinuing anticoagulant or antiplatelet therapy. After evaluating the specific guidelines or suggestions, 8 articles were eliminated because they contained very general information that was not considered useful from a clinical practice standpoint. Only 4 of the 9 remaining articles were found to contain useful advice for an emergency room setting, only 1 of which focused on the interaction between cardiovascular medications and GI hemorrhaging. The specific recommendations of these 4 articles are summarized in Table 1. One of those articles featured a combined cardiovascular and GI focus,[14] and 3 of them clearly revealed a GI focus.[15–17]

Guidelines With a Combined Cardiovascular and GI Focus

Our search identified 1 article published by the British Society of Gastroenterology that addressed both cardiovascular and GI aspects of managing anticoagulant and antiplatelet therapy in patients undergoing endoscopic procedures.[14] In this article, some concrete advice is provided about how to proceed in an actual emergency situation. It is clearly stated that an acute GI hemorrhage in patients on anticoagulant or antiplatelet medications is a high-risk situation and that the immediate risk to the patient from a hemorrhage may outweigh the risk of thrombosis that might occur if anticoagulant or antiplatelet therapy is stopped. It should be noted that patients need to be assessed on an individual basis because it is not possible to provide unequivocal guidance to cover all of the possible situations that might be encountered in patients. It should also be noted that endoscopy should be attempted as soon as safely possible after immediate consultation between the patient's cardiologist and the specialist doing the endoscopy.

Early therapeutic endoscopic intervention may achieve hemostasis with minimal or no cessation of anticoagulant or antiplatelet therapy and should be the first goal if possible. This recommendation is stated as an evidence grade IV, recommendation grade C. For patients with high-risk conditions who are being treated with warfarin, the article states that warfarin can be discontinued either with or without the substitution of heparin, depending on the severity of the hemorrhaging and the risk of discontinuing anticoagulant therapy. For the patient being treated with clopidogrel, the recommendation is not to discontinue the medication without discussing the action with a cardiologist beforehand. There is a high risk of acute myocardial infarction or death in patients with coronary stents if clopidogrel is discontinued, particularly if it is discontinued soon after the stent has been implanted and for up to 1 year after implantation. If clopidogrel therapy must be discontinued, the action should be limited to a maximum of 5 days because the risk of stent thrombosis increases after this interval. The latter recommendation is stated as an evidence grade III, recommendation grade B.

Guidelines With a GI Focus

Eight of the 17 articles were associated with a gastroenterology society or association or provided international consensus information about a specific GI situation, but most of them provided little operational advice with respect to concurrent cardiovascular conditions.[15–22] Only 3 of the articles provided some concrete guidance with respect to adjusting anticoagulant and antiplatelet therapies in situations of GI bleeding,[15–17] and their results are summarized in Table 1.

American College of Gastroenterology guidelines for managing patients with a bleeding ulcer[15] also provide advice about how to handle anticoagulant or antiplatelet therapies, specifically with respect to therapy management, when to resume therapy that has been suspended, and the need to differentiate between primary and secondary prevention when prescribing low-dose aspirin therapy. When bleeding occurs, the guidelines recommend that acetylsalicylic acid (ASA) or any nonsteroidal anti-inflammatory drug (NSAID) should be stopped. For long-term prevention of recurring bleeding ulcers, the recommendation is that in patients with NSAID-associated bleeding ulcers, the need for NSAIDs should be carefully assessed and, if possible, NSAIDs should not be resumed. In patients who must resume NSAIDs, a cyclooxygenase-2 (COX-2)-selective NSAID at the lowest effective dose along with a daily proton-pump inhibitor (PPI) is recommended. This is stated as a strong recommendation. In patients with low-dose

TABLE 1. Recommendations Available According to the Results of a Review of >81 000 Articles Culled From the Published Literature in 2013 on Topics Related to GI Bleeding in Patients Taking Anticoagulant and Antiplatelet Drugs

Guideline Source	Is Long-Term Use of ASA/NSAID Permissible?	Is ASA and PPI Preferred to Clopidogrel?	Stop Anticoagulant and Antiplatelet Medications During Acute Bleeding?	Is the Use of ASA Permissible Again After Bleeding Stops?*	Is the Use of Clopidogrel Permissible Again After Bleeding Stops?
DSGH†	Yes, but add a PPI	Yes	Yes	Yes, 24 h after bleeding stops, but add a high-dose PPI	Yes, 3 d after bleeding stops
ACG‡	Yes, but add a PPI	Not discussed	Yes	Yes, 1–7 d after bleeding stops	Not discussed
ICG§	Yes, but add a PPI	Yes	Yes	Yes, as soon as possible after bleeding stops	Not discussed
BSG‖	Not discussed	Not discussed	Yes	Not discussed	Yes, 5 d after bleeding stops

ACG = American College of Gastroenterology, ASA = acetylsalicylic acid, BSG = British Society of Gastroenterology, DSGH = Danish Society for Gastroenterology and Hepatology, GI = gastrointestinal, ICG = international consensus guidelines, NSAID = nonsteroidal anti-inflammatory drug, PPI = proton-pump inhibitor.

* When cardiovascular risk outweighs gastrointestinal bleeding risk.

† Laursen et al.[16]

‡ Laine and Jensen.[15]

§ Barkun et al.[17]

‖ Veitch et al.[14]

ASA-associated bleeding ulcers, it is suggested that the need for ASA should be assessed. If ASA had been prescribed for secondary prevention (ie, in the case of established cardiovascular disease), the ASA should be resumed in most patients as soon as possible after bleeding ceases (ideally within 1–3 days, and certainly within 7 days). Long-term daily PPI therapy should also be provided in this situation. If ASA had been prescribed for primary prevention (ie, no established cardiovascular disease), antiplatelet therapy should probably not be resumed in most patients. This recommendation is, however, conditional, depending on the actual circumstances for each patient (Table 1).

The Danish Society for Gastroenterology and Hepatology guidelines for managing bleeding gastroduodenal ulcers[16] recommend suspending treatment with ASA, clopidogrel, NSAIDs, and selective serotonin reuptake inhibitors (SSRIs) in the presence of a bleeding ulcer. They note that platelet function in normal subjects is inhibited for up to 5 days after the withdrawal of clopidogrel or aspirin, but presumably for a shorter time in bleeding patients. Consequently, treatment with both drugs can be suspended for up to 24 hours until the bleeding has stopped and the situation has stabilized. In the case of patients with bleeding peptic ulcers who require secondary cardiovascular prophylaxis, the recommendation is to resume ASA again as soon as the cardiovascular risk outweighs the GI risk. Low-dose ASA can be resumed after 24 hours if there is no longer any sign of bleeding and a high-dose intravenous PPI is given along with it. They recommend unnecessary NSAID intake be discontinued. They note that treatment with clopidogrel or other thienopyridines in patients with coronary stents can be resumed after 3 days, but if there is any doubt whether this is the appropriate approach, a cardiologist should be consulted. They also note that treatment with an SSRI can be resumed after 5 days. For patients in need of long-term treatment with ASA or a NSAID, the recommendation is to prescribe prophylactic treatment with a PPI at standard dosage. In patients who need antiplatelet therapy for conditions other than coronary stents, the recommendation is a PPI in combination with 75 mg ASA as the preferred therapeutic choice rather than monotherapy with clopidogrel (Table 1).

Biondi-Zoccai et al[23] mention that prematurely stopping antiplatelet therapy is the most significant risk factor for stent thrombosis among patients with coronary stents. Therefore, continuing with ASA treatment is important because the risk of developing arterial thrombosis almost doubles when ASA treatment is stopped in patients for whom this type of treatment is the most appropriate choice. Sung et al[24] mention that the mortality rate is lower in patients who are on a low-dose ASA regimen combined with a high-dose intravenous PPI after an endoscopic procedure for a bleeding ulcer; there is no statistically significant increase in the rebleeding rate. A set of international consensus guidelines for managing patients with nonvariceal upper GI bleeding[17] states that in patients who are receiving anticoagulants, the recommendation is to correct the coagulopathy but not to delay endoscopy. In patients who are being treated with low-dose ASA, the ASA therapy should be resumed as soon as the risk for cardiovascular complication is thought to outweigh the risk for a hemorrhage. In patients who need antiplatelet therapy for conditions other than coronary stents, a PPI in combination with 75 mg ASA should be the preferred therapeutic choice rather than monotherapy with clopidogrel. These guidelines note that clopidogrel alone has a higher risk for a recurrence of bleeding than does ASA combined with a PPI in patients who require cardiovascular prophylaxis and who also previously had a bleeding ulcer. For patients who have either current upper GI bleeding or a history of bleeding ulcers and who require a NSAID, the recommendation is to use a PPI together with a COX-2 inhibitor rather than to use COX-2 inhibitors alone to reduce the risk of recurring bleeding. They, however, note that even treatment with a traditional NSAID and a PPI is still associated with a clinically significant risk of a recurring bleeding ulcer.

All 8 articles suggested temporarily suspending anticoagulant and antiplatelet therapy in a situation that involved acute bleeding and, in the case of high-risk patients (eg, patients with critical coronary artery disease and coronary stents), suggested that the treatment plan should be discussed between specialists in the 2 medical disciplines.[15–22]

Guidelines With a Cardiovascular Focus

In the 8 of the 17 articles identified as containing relevant cardiovascular guidelines, only minimal information is provided about how to proceed with anticoagulant or antiplatelet therapy in a situation of acute GI bleeding.[25–32] In fact, none of them explicitly mention directions for addressing situations involving GI bleeding. The article that provides the most information about handling an acute bleeding situation is the European Society of Cardiology guideline for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.[26] Here it is stated that major bleeding events such as GI, retroperitoneal, intracranial, or other severe blood loss requires the interruption and neutralization of both anticoagulant and antiplatelet treatment if bleeding cannot be controlled by other appropriate interventions. In this situation, neither anticoagulant nor antiplatelet agents should be reintroduced until strict control of the hemorrhage has been achieved for at least 24 hours. The guideline, however, also mentions that it may not be necessary to interrupt treatment with antithrombotic agents if complete control of the hemorrhage can be achieved with local measures. It is further suggested that in clinical practice, the risk of discontinuing antithrombotic medications must be weighed against the risk of a thrombotic event, particularly if the patient has a stent implant. The opinion at this time is that discontinuing antiplatelet and antithrombotic drugs leads to an increased risk of ischemic events, particularly stent thrombosis after percutaneous coronary intervention.

DISCUSSION

What we find in this study is that, with one exception, neither current gastroenterology nor cardiology guidelines focus on the interaction between the therapies being prescribed for GI bleeding and cardiovascular conditions. So, in an emergency situation, there are only a few operationally useful recommendations in the published literature with respect to strategies for modifying prescribed therapeutic regimens to address the risks related to both the hemorrhage and the underlying disease. This creates the very real possibility of an adverse outcome that could have been prevented if there had been adequate and clearly presented information available about how to adjust anticoagulant and antiplatelet therapies in these situations.

Even in the 17 articles that we found to offer some type of guideline, only minimal information and advice is provided. Although it is generally recommended that anticoagulant and antiplatelet therapies be discontinued in the case of acute, life-threatening GI bleeding, particularly for patients with an underlying complex cardiovascular disease, and that the clinicians in

the respective medical specialties should discuss the patient's situation immediately, there is no clear advice about how to proceed after the episode of acute bleeding. The lack of clear clinical practice guidelines further complicates patient care in an emergency room setting because the extra time needed for clinicians in the respective medical specialties to discuss each individual patient's situation can delay critically needed emergency care and therefore be detrimental to patient outcome. It is obvious that clinical practice guidelines play a crucial role in patient management. Therefore, we recommend that current clinical practice guidelines be expanded to include specific advice about how to adjust therapeutic regimens in patients with GI bleeding. The guidelines should clearly state in what situations the use of a specific anticoagulant or antiplatelet drug should be suspended, in which situations specific medications should be resumed after the GI hemorrhage has stopped (preferably providing precise timeframes and dosages for resuming the drugs), and the level of risk for any particular action.

Nevertheless, it must be mentioned that patients often exhibit a poor adherence to gastroprotective agents when using NSAIDs or low-dose ASA. This fact also seems to critically contribute to the incidence of GI bleeding, since a significant proportion of patients using NSAID and ASA with a high risk for GI bleeding had not received prophylaxis with gastroprotective agents before ulcer bleeding. These bleeding episodes might be preventable with better adherence to gastroprotective agent use.[33] Only about 24% of elderly and often multimorbid patients taking NSAIDs also receive also a coprescription for gastroprotective agents.[34]

Current guidelines recommend testing for *Helicobacter pylori* infection among users of low-dose ASA who are at high risk for developing ulcers. A recent study demonstrated that the long-term incidence of recurrent ulcer bleeding with ASA use is low after *H pylori* infection is eradicated. This demonstrates that the eradication of *H pylori* might be an important factor in the prevention of GI bleeding, in particular, in high-risk patients.[35]

A completely new player affecting the risk for GI bleeding are the new-generation oral anticoagulants, which include thrombin and factor Xa inhibitors. These drugs are more and more frequently used, especially in older and multimorbid patients. Although little is known about whether these drugs increase patients' risk for GI bleeding, it seems these new-generation oral anticoagulants cause an increased risk of GI bleeding compared with standard care.[36]

As limitations of the study must be recognized that we were able to provide only minimal information about appropriate therapeutic strategies. Relevant information might be missing because the study did not include articles that were written in languages other than English or that originated from a geographic area outside Europe, Canada, and the United States. The strength of the study, however, is that this study is the only known global search for relevant articles in the published literature. The pool of eligible articles was restricted so that it encompassed a fairly homogeneous study population genetically and culturally, which enabled a comparison of the recommendations that we did find. Limiting the articles to ones written in English reduced the risk of errors in translation and ensured a consistent use of terminology across the articles.

We realize that providing precise advice about how to proceed both at the time of the emergency and in the days following cessation of GI bleeding might be difficult. Therefore, there should be a discussion and ultimately a consensus among gastroenterologists and cardiologists with respect to the benefit-risk ratios for specific types of emergency situations. For example, it is necessary to answer questions such as the following: ''What are the risks (stated as percentages) for a patient with upper GI bleeding who is being treated with clopidogrel, and after how many days should clopidogrel be resumed?'' Ultimately, it might be necessary to conduct clinical trials to further define and answer these types of questions.

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