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REVIEW

Gastroenterological Perspectives on Acute Cardiac Care — the Management of Patients with Implanted Coronary Stents Following an Acute Coronary Syndrome

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ABSTRACT

Cardiovascular and digestive diseases frequently share the same risk factors such as obesity, unhealthy diet, or several social behaviors, and the increasing prevalence of patients with overlapped cardiovascular and digestive symptoms is a challenging problem in the daily practice. Patients with gastro-esophageal reflux disease can exhibit various forms of chest pain that can be very similar to angina. Furthermore, antithrombotic therapies used for preventive or curative purposes in patients with cardiovascular diseases are frequently associated with gastrointestinal side effects including bleeding. At the same time, in patients with coronary stents presenting to the emergency department with chest pain, angina triggered by stent thrombosis or restenosis should be differentiated from angina-like symptoms caused by a gastrointestinal disease. The aim of this review was to present the complex inter-relation between gastroesophageal diseases and angina in patients on dual antiplatelet therapy following an acute coronary syndrome, with a particular emphasis on the role of anemia resulting from occult or manifest gastrointestinal bleeding, as a precipitating factor for triggering or aggravating angina.

Keywords: dual antiplatelet therapy, gastrointestinal bleeding, recurrent angina

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INTRODUCTION

The increasing prevalence of patients with overlapped cardiovascular and digestive symptoms has become a challenging problem in the daily practice.[1,2] Cardiovascular and digestive diseases frequently share the same risk factors such as obesity, unhealthy diet, or several social behaviors. Furthermore, antithrombotic therapies used for preventive or curative purposes in patients with cardiovascular diseases are frequently associated with gastrointestinal side effects including bleeding.[3] Patients with gastro-esophageal reflux disease (GERD) can also exhibit various forms of chest pain that can be very similar to angina.[4] Therefore, the complex relationship between gastrointestinal diseases and acute chest pain has been

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extensively studied in order to reduce the mortality risk associated to chest pain with unknown etiology.[5–7]

In patients with acute chest pain, initiation of an adequate diagnostic strategy is essential for elucidating the etiology of chest pain. Due to the devastating consequences of misdiagnosing an acute coronary syndrome (ACS), the first diagnostic approach should be oriented towards the confirmation or exclusion of a significant coronary artery disease (CAD) as the source of the chest pain. In the eventuality that CAD has been ruled out, the next step of evaluation is frequently represented by upper digestive endoscopy for diagnosing a possible gastrointestinal disease as the source of the pain. Such gastrointestinal etiology of angina-like symptoms could be represented by GERD, gastritis, or gastro-duodenal ulcer.[5] However, due to the low prevalence of mucosal findings in patients with GERD, endoscopy is nowadays considered of limited value in patients with non-cardiac chest pain.[6,7] In many cases with endoscopy-negative non-cardiac chest pain, the etiology of the angina-like symptoms can be functional or psychiatric.[3]

It has also been shown that patients with severe GERD-related symptoms had an increased risk of developing atrial fibrillation (AF), and treatment with proton pump inhibitors may facilitate conversion to sinus rhythm. However, the current studies did not succeed to demonstrate the casual relationship between GERD and AF.[8]

The use of dual antiplatelet therapy (DAPT), consisting in clopidogrel plus low-dose aspirin, significantly reduced cardiovascular mortality in patients suffering an acute myocardial infarction (AMI) and in those undergoing a percutaneous coronary intervention (PCI), however with the cost of increasing the rate of gastrointestinal (GI) events, including bleeding.[3,9,10] Therefore, the management of patients with cardiovascular diseases who are on DAPT and present recurrent chest pain mimicking angina can be challenging in many clinical settings.[11]

The aim of this review was to present the complex inter-relation between gastroesophageal diseases and chest pain in patients on dual antiplatelet therapy following an acute coronary syndrome, with a particular emphasis on the role of anemia resulting from occult or manifest gastrointestinal bleeding, as a precipitating factor for triggering or aggravating angina.

DUAL ANTIPLATELET THERAPY IN ACUTE CARDIAC CARE

Selection of the most appropriate antiplatelet therapy in acute cardiac care depends largely on the clinical setting. Platelet inhibition is one of the main pharmacologic treatment goals in patients presenting with ACS. This is realized through inhibition of both the thromboxane A2-dependent route (by administration of aspirin) and adenosine diphosphate P2Y12 receptor inhibition (by administration of ticagrelor, clopidogrel, or prasugrel).[12] According to current guidelines and recommendations of the European Society of Cardiology (ESC), patients undergoing PCI for an ACS should be initiated with DAPT as soon as the diagnosis is established, if no contraindications are present.[13]

The optimal dosage of aspirin therapy to maximize the platelet inhibition with minimized bleeding risk is not well established so far. Currently, a loading dose of 150–300 mg oral aspirin is recommended in post-PCI patients; however, recent trials evidenced that single intravenous administration of 250 or 500 mg of aspirin is superior in terms of thromboxane inhibition, with no increased bleeding risk compared to the administration of 300 mg of oral aspirin.[14] Administration of 180 mg loading dose ticagrelor along with aspirin, continued with 90 mg twice daily is recommended irrespective of the previous antiplatelet therapy. In a large clinical trial which included 18,624 patients with ACS, ticagrelor was associated with significantly lower rates of major adverse cardiovascular events (such as cardiovascular death rates, myocardial infarction, and stroke), without a significant increase in major bleedings (11.6% vs. 11.2%, p = 0.43) compared to clopidogrel in a loading dose of 300 to 600 mg continued with 75 mg daily.[15]

The only P2Y12 inhibitor investigated in large clinical trials in patients who received thrombolytic therapy for an ST-elevation myocardial infarction (STEMI) was clopidogrel. Administration on top of aspirin in this patient category was associated with lower adverse ischemic event rates, with no significant increase in major bleedings, thus a 300 mg loading dose, continued with 75 mg daily is recommended in patients younger than 75 years.[16,17] For those older than 75 years, there is no sufficient data about the safety and benefits of clopidogrel, thus the decision of a loading dose and further administration should be made individually, assessing the bleeding risk.[13]

In patients who present indication for oral anticoagulation (OAC), adding DAPT to OAC significantly increased bleeding events, hence an additional bleeding risk assessment (using HAS-BLED or ABC scores) is essential for establishing the duration of triple therapy.[18] Administration of 600 mg clopidogrel loading dose, continued with 75 mg daily is currently recommended in the setting of an ACS.[13]

INTERACTION BETWEEN PROTON PUMP INHIBITORS AND ANTIPLATELETS IN THE CURRENT ERA – MYTH OR REALITY?

A large number of clinical trials investigated the lowest efficient dose for platelet inhibition to minimize the rate of hemorrhagic complications, as gastrointestinal bleedings are among the most frequently reported adverse events in patients taking DAPT, and multiple sub-studies of these trials demonstrated the efficiency of proton pump inhibitors (PPI) in reducing gastrointestinal bleeding risk for patients under antiplatelet therapy.[20] Thus, current ESC Guidelines recommend the administration of PPIs in combination with DAPT.[13,22,23]

The question of pharmacological interaction between antiplatelet drugs and PPIs arose from the fact that both clopidogrel and PPIs are metabolized by the liver through cytochrome P450 or CYP enzymes. Pharmacologic studies suggested that omeprazole and esomeprazole inhibit isoenzyme CYP2C19 (which is used for the metabolic activation of clopidogrel), leading to decreased antiplatelet activity of clopidogrel in concomitant administration. This inhibition may be even augmented in some genetic variations of the CYP2C19 isoenzyme.[24–26]

In a randomized double-blind study, Furtado *et al.* evidenced a significant decrease in inhibition of platelet activity (26.3 ± 32.9% to 17.4 ± 33.1%, p = 0.025) at one week follow-up when 20 mg omeprazole twice daily was added to 75 mg clopidogrel therapy in patients with stable coronary artery disease.[28] In an observational study on a general population of 2.9 million subjects, a 1.16-fold increase (95% CI: 1.09–1.24) of myocardial infarction was observed in patients with PPI therapy regardless of clopidogrel use.[29] A systematic review carried out by Sherwood *et al.*, which analyzed 6 observational studies, concluded that the concomitant use of clopidogrel and pantoprazole (HR: 1.38, 95% CI: 1.12–1.70), lansoprazole (HR: 1.29, 95% CI: 1.09–1.52), or esomeprazole (HR: 1.27, 95% CI: 1.02–1.58) is associated with higher risk of cardiovascular events.[30]

The COGENT study, a randomized double blind, placebo-controlled trial, which included 3,761 patients undergoing stent implantation for ACS or stable coronary artery disease, analyzed and compared the safety and efficacy of 75 mg clopidogrel administration versus concomitant administration of clopidogrel and 20 mg omeprazole. A significant reduction in the rate of gastrointestinal clinical events was observed at the 180-day follow-up in patients in whom omeprazole was added, compared to the placebo group (1.1% vs. 2.9%, p <0.001). Adversely, no significant increase was recorded in terms of adverse cardiovascular events in the group of patients who received omeprazole versus the placebo group (4.9%, 95% CI: 3.4–6.4% vs. 5.7%, 95% CI 4–7.3%, p = 0.98).[22] However DAPT with ticagrelor or prasugrel is associated with higher bleeding risk compared to clopidogrel, and there are no randomized studies so far to investigate the risks and benefits of the concomitant use of these antiplatelet agents with PPIs.

Currently, the data obtained from randomized controlled trials is lacking convincing clinical evidence to support the negative effect of PPIs in patients with indication for DAPT.

GASTROINTESTINAL SIDE EFFECTS OF DUAL ANTIPLATELET THERAPY

Two major gastrointestinal side effects have been described in relation to antithrombotic therapy: angina-like symptoms caused by mucosal damage, which is more frequent in the upper digestive tract, and bleeding, which can occur from the upper or lower digestive tract. The mechanisms of gastric mucosal damage caused by aspirin involve the systemic inhibition of cyclooxygenase (COX-1 and COX-2) and consequently gastric prostaglandin synthesis, as well as local inflammatory reaction mediated by cytokines.[31] Additionally, clopidogrel delays the healing of the gastric mucosa via impairment of angiogenesis, leading to an increased risk of a gastrointestinal bleeding episode in comparison with aspirin alone.[32–34]

The effect of DAPT, or generally antithrombotic drugs, on the lower digestive tract is not very well known. Unlike the upper digestive tract, where endoscopic lesions are easily detected using endoscopy, and the effectiveness of preventive strategies such as proton pump inhibitors use or *Helicobacter pylori* eradication has been well demonstrated, the effects of DAPT on the lower digestive tract are less well known. The most important and largest study investigating the bleeding risk of DAPT (CHARISMA) did not offer data regarding the site of bleeding.[32] Recent data suggest that bleeding from the small and large intestine associated with antithrombotic drugs plays a significant role in hospital readmission rate or increased mortality.[35,36]

In a retrospective Chinese study investigating the etiology of gastrointestinal bleeding in 114 patients with a first episode of bleeding while on DAPT, the incidence of upper (53.5% vs. 51.3%) and lower (46.5% vs. 48.7%) gastrointestinal bleeding was similar irrespective of DAPT use, but a much higher proportion of the DAPT group had no source of bleeding identified even after an extensive workup, underling that patients are more prone to bleed from an occult lesion.[37]

A prospective Japanese study based on endoscopy (n = 319) proved that the association of low-dose aspirin with thienopyridines was associated with a significantly lower risk of digestive bleeding (OR: 2.2, 95% CI: 1.1–4.5).[38] Nevertheless, data sustaining that bleeding risk associated to gastrointestinal endoscopic procedures in patients under DAPT are scarce and poor-quality, and do not sustain the cessation of clopidogrel for endoscopic procedures.[39,40] On the other hand, in patients with lower gastrointestinal bleeding, antiplatelet drugs are more prone to be related to recurrent bleeding in comparison with patients on warfarin or OACs.[41]

STENT THROMBOSIS AND ANTIPLATELET THERAPY

Patients having implanted coronary stents represent a distinct population with specific risks. For instance, patients with history of stent thrombosis are at high risk for recurrent thrombotic events. It has been demonstrated that clopidogrel is associated with significantly higher rates of recurrent stent thrombosis compared to ticagrelor or prasugrel. Therefore, the administration of ticagrelor or prasugrel is recommended over clopidogrel in patients presenting with an ACS in the context of a stent thrombosis, and this therapy should be maintained for a long term.[15,42] The optimal duration of DAPT should be assessed based on validated risk scores such as the PRECISE-DAPT (at the moment of stent implantation) or DAPT score (after one year of uneventful DAPT), which evaluate the ischemic and bleeding risk of patients with stent implantation and offer guidance for DAPT duration.[43,44]

ETIOLOGY OF ACUTE CHEST PAIN IN PATIENTS WITH CORONARY STENTS

Acute chest pain is one of the most frequent complain of patients presenting at the emergency department, and approximately 20–25% of these patients are diagnosed with an ACS.[45]

In patients with coronary stents presenting to the emergency department with chest pain, angina triggered by stent thrombosis or restenosis should be differentiated from angina-like symptoms caused by a gastrointestinal disease.

Other frequent etiologies of chest pain include musculoskeletal, pulmonary, gastrointestinal, and psychiatric diseases.[46] In emergency settings, it is paramount to rule out the major life-threatening conditions that may represent the underlying cause for acute chest pain. These pathologies include acute myocardial infarction, aortic dissection, pulmonary artery embolism, tension pneumothorax, and Boerhaave syndrome.[47] Physical examination, recording of a 12-lead electrocardiogram (ECG), clinical chemistry (hemoglobin, white blood cell count, troponin, myoglobin, creatine-kinase levels), and imaging studies such as echocardiography, chest X-ray, or computed tomography angiography are essential for a quick and accurate diagnosis.[46]

Patients who underwent PCI with coronary stent implantation are still at risk of developing recurrent ischemic events, and approximately 30–35% of these patients return complaining about chest pain. The underlying cause of acute chest pain is mostly represented by acute stent thrombosis, incomplete revascularization, in-stent restenosis (ISR), or the progression of non-culprit atheromatous lesions.[48,49] Despite the fact that the rate of ISR has been significantly reduced in the drug-eluting stent (DES) era, it still represents a major issue for the healthcare system.[50] A large number of these patients present an ACS with subsequent ECG and laboratory changes. In a clinical trial which analyzed 110 patients with clinically manifested ISR at a follow-up of minimum one year, Marino *et al*. stated that 62.7% of the patients presented with an ACS.[51] ACS as clinical presentation remains unchanged irrespective of stent type, as Magalhaes *et al*., in a study on 909 subjects, reported similar rates in patients with implanted bare metal stent (BMS) and first- and second-generation DES (67.8% vs. 71% vs. 66.7%, respectively, p = 0.47).[52] A high rate of post-PCI chest pain is also recorded in patients with stable CAD. In a study which included 167 patients who underwent elective PCI for stable CAD, Chang *et al*. reported an incidence of 41.9% of post-PCI chest pain.[53]

ANEMIA FOLLOWING GASTROINTESTINAL BLEEDING – A PRECIPITATING FACTOR FOR POST-STENTING ANGINA

In patients with implanted stents, a significant precipitating factor for developing recurrent ischemic events is represented by anemia that can result from occult or manifest gastrointestinal bleeding. Figure 1 summarizes the approach of patients with implanted coronary stents presenting with chest pain and the role of anemia as precipitating factor for developing angina.

A recent study conducted by Giustino *et al.* in patients on DAPT for an implanted DES revealed that compared to patients with normal hemoglobin levels, those with anemia presented significantly higher rates of major adverse

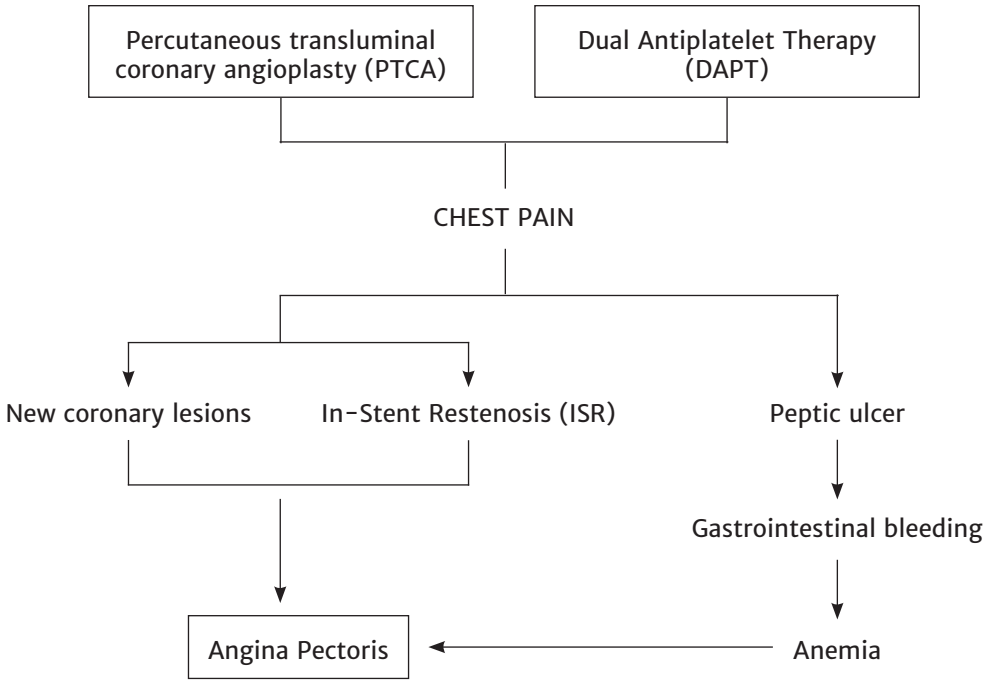

FIGURE 1. The approach of patients with implanted coronary stents presenting with chest pain and the role of anemia as precipitating factor for developing angina

cardiovascular events (9.5% vs. 5.6%, p <0.0001), all-cause mortality (4.0% vs. 1.4%, p <0.0001), as well as major bleeding events (11.8% vs. 7.7%, p <0.0001).[54] Patients on DAPT are at an increased risk of developing both upper and lower gastrointestinal bleeding events, which can subsequently lead to serious anemia in this fragile population.[55,56] In a recent large cohort study which included 27,707 patients, Gonzalez-Perez *et al.* concluded that 73% of patients with upper gastrointestinal bleeding and 23% of those with lower gastrointestinal bleeding, being on antiplatelet therapy for a serious coronary event, needed hospitalization.[57] In an observational study which included 122 patients, DAPT was associated with a significant decrease of hemoglobin levels (1.6, 95% CI: 1.2–1.8, p <0.001) and an increased prevalence of anemia after DAPT (9.1% vs. 45.9%).

MANAGEMENT OF GASTROINTESTINAL BLEEDING IN PATIENTS WITH CORONARY STENTS

In case of hemorrhage in a patient on DAPT, with a recently implanted coronary stent, a life-threatening complication could occur if the therapy is interrupted. The standard attitude, after adequate resuscitation, is prompt endoscopic hemostasis within the gastrointestinal tract, and good facilities and specialists should be available to provide this.[58] In case of patients with coronary stents, whenever it is deemed necessary to temporarily discontinue antiplatelet therapy, this should be limited to the P2Y12 inhibitor, but aspirin should be continued.

Even if there is no good-quality prospective study to evaluate the optimal time for cessation of therapy, the P2Y12 inhibitor should be restarted within a maximum of 5 days due to the high risk of stent thrombosis after this time, and to obtain the most suitable balance between hemorrhage and thrombosis risk.[59] A retrospective study in elective or acute settings of PCI reported a frequency of 10.2% of bleeding complication within 1 year after the procedure, with no increase in mortality risk.[60] Dual antithrombotic therapy had a higher risk than single therapy for rebleeding in the lower digestive tract. In a retrospective study (adjusted HR 1.8, p <0.05), 46% of all patients had rebleeding, and the overall mortality rate was 13% within 5 years after hospitalization.[36]

There are published data indicating no significant differences in the cardiovascular outcomes and safety between post-PCI patients on DAPT continuing antiplatelet monotherapy with aspirin and experiencing a gastrointestinal hemorrhage, even if, in terms of recurrent bleeding, antiplatelet monotherapy remains beneficial.[61] One of the most important known risk factors for gastrointestinal bleeding in the upper digestive tract in patients on aspirin

therapy is a history of complicated or uncomplicated ulcer, that increases the risk two or three times.[3,21] Patients who need continuous combined antithrombotics present two concomitant important risk factors, while standard preventive therapy with PPI does not influence the risk of lower endoscopic bleeding sources. Despite guideline recommendations for gastroprotective therapy in patients with dual antiplatelet therapy, only 60% of patients who required protective therapy were on PPIs in studies involving a Romanian population.[3,19] The results are very similar with studies published elsewhere, sustaining the relatively low adherence to protective therapy in patients with bleeding risk.[62] Nonetheless, a recent meta-analysis sustains that all gastroprotective therapies reduced further bleeding (OR: 0.68, p <0.0001), blood transfusion (OR: 0.75, p = 0.0003), further endoscopic intervention (OR: 0.56, p <0.0001), or surgery (OR: 0.72, p <0.0001), but did not significantly reduce mortality (OR: 0.90, p = 0.31), supporting the importance of careful assessment of good balance between ischemic and bleeding risk in cardiac patients.[63]

HELICOBACTER PYLORI – A SILENT ENEMY IN PATIENTS WITH CORONARY STENTS

The interaction between aspirin and *H. pylori* infection in the upper digestive tract is not fully understood, some studies sustaining an increased risk for bleeding in infected patients on treatment with aspirin, while others do not support this association.[64,65] The possible causes of discordant results could be the inhomogeneous nature of these studies, being conducted in populations with various genetic backgrounds or different characteristics of the *H. pylori* infection. Apart from decreased prostaglandin synthesis influencing the local protective mechanisms of the gastric mucosa, the damaging mechanism initiated by aspirin involves the role of inflammatory cytokines.[66] This mechanism acts synergistically with the *H. pylori* infection, leading to the accumulation of inflammatory infiltrate in the gastric mucosa and increased acid secretion, at least in the first stages of infection.[67] Adding P2Y12 inhibitors to aspirin can favor the lesion of the gastric mucosa and promotes bleeding from any other type of mucosal lesions in patients after PCI, further increasing the risk of bleeding.[68]

On the other hand, *H. pylori* has been suggested to be a possible contributor to CAD progression, both via inducing a systemic inflammation or via direct aggression on the vessel wall, with a possible role even in ACSs.[69–71] Despite the controversial results of different studies taking into account the complex gastric and extragastric effects of *H. pylori* infection in the human body, the infection should be carefully assessed in cardiac patients with coronary stents on DAPT.[72,73] The possible preventive role of *H. pylori* infection assessment in a cardiac population which required combined antithrombotic therapy has not been clarified so far, due to differences in infection prevalence worldwide, as well as to differences in population characteristics in terms of genetic background or specific environmental factors.[27,28,67] The majority of published work supports the beneficial effect of adding PPI to a combined antiplatelet therapy for gastro-duodenal lesions, with a more important effect in the population characterized by a high frequency of *H. pylori* infection.[74] At the same time, the childhood acquisition of *H. pylori* infection increases the burden of ulcer history, which further increases the risk of bleeding complications at adult age in patients with CAD who require DAPT. This interrelation seems to be related to mucosal scar vulnerability and, probably, to the lack of any effective therapy for *H. pylori* eradication in patients with previous ulcers.[3,21]

CONCLUSIONS

In conclusion, DAPT significantly reduced cardiovascular mortality in patients undergoing percutaneous coronary revascularization and stenting, however, with the cost of increasing the risk of bleeding. The management of patients with prior coronary stenting who are on DAPT and present recurrent chest pain mimicking angina can be challenging in many clinical settings. In these cases, angina triggered by stent thrombosis or restenosis should be differentiated from angina-like symptoms caused by a gastrointestinal disease, and anemia resulting from occult or manifest gastrointestinal bleeding should be promptly diagnosed as it can represent the precipitating factor for triggering or aggravating angina.

CONFLICT OF INTEREST

Nothing to declare.

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