Review

Gastrointestinal malignancies and cardiovascular diseases—Non-negligible comorbidity in an era of multi-antithrombotic drug use

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Summary Nowadays, antiplatelet and anticoagulant drug medications are indicated in patients with a variety of cardiovascular disorders, such as atrial fibrillation, coronary artery disease, and peripheral artery disease. Among cardiology patients, regardless of gastrointestinal (GI) protection, we do not infrequently encounter those patients who have signs and symptoms that are suggestive of GI tract problems. We should bear in mind that such GI signs and symptoms may be attributed to GI cancers, as well as to benign or clinically insignificant lesions. Several clinical studies have shown, albeit controversially that the predictive value of positive fecal occult blood for colorectal malignant neoplasm may not be lower in patients taking antithrombotic medication. In addition, it has been shown that in patients taking antithrombotic drug(s), diagnosed colorectal malignancies are in a relatively earlier phase, suggesting that antithrombotic drugs may facilitate the detection of otherwise unrecognized cancers. The possibility also exists that certain cardiovascular disease may be associated with a higher risk of GI malignant neoplasms. There has been no established evidence concerning whether more aggressive GI tract screening will reduce the probability of cancer death in cardiology patients; nevertheless, GI tract lesions should not be overlooked among cardiology patients, especially when unexplained anemia, gastrointestinal symptoms, or positive fecal occult blood test is present, and GI tract screening should be performed with appropriate timing.

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Introduction

Evidence is accumulating over the benefits of both primary and secondary treatment strategies for cardiovascular disease [1,2] and stroke [3,4], and the use of antiplatelet and anticoagulant drugs continues to increase. On the other hand, as a trade-off, the need for gastrointestinal (GI) tract protection, mainly against bleeding [5] is increasing, because GI bleeding is one of the most common causes of adverse drug reaction-related admissions [6]. In fact, Ko et al. recently reported that 2.5% of patients were hospitalized for bleeding within a year of percutaneous coronary intervention, and more than half of these admissions were due to GI bleeding [7]. Therefore, minimization of the duration of antithrombotic drug use should be considered, especially when dual or triple therapy is used. Although acid suppressants may effectively reduce antithrombotic drug-induced GI bleeding [8], malignant neoplasm in such patients might be overlooked under the simple presumption that progressive anemia and/or a positive fecal blood test (FOBT), which has high sensitivity for colorectal neoplasm [9], may be caused by bleeding from benign or non-significant lesions propagated by the antithrombotic drugs, leading to lack of further examination, for example, by GI endoscopy. It should be questioned, however, whether antithrombotic use will increase or decrease the positive predictive value of cancer screening, because bleeding from malignant neoplasm, as well as from non-malignant lesions, might be facilitated by antiplatelet and anticoagulant drugs.

The emergence of a new class of antithrombotic drugs [10,11] and gastroprotective agents [12], coupled with an increase in the use of dual and triple therapies, makes it difficult and rather complex to answer this question; in addition, environmental changes might alter the risk of GI bleeding from non-malignant and malignant lesions [13]. It has been suggested that the prevalence and/or discovery of malignant neoplasm may show an increasing trend in Japan, considering that modalities for GI tract screening, such as endoscopies [14] and computed tomography colonography [15], are increasingly available and feasible, and that GI tract malignancies may become more prevalent according to the rapid aging of the population [16]; therefore, cardiologists may have to take the most cautious approach of checking for concomitant GI tract malignancies in cardiology patients. Here, we briefly review the prediction of cancer by endoscopic examination in subjects taking antithrombotic drugs, and the incidence of GI tract malignancies in patients with cardiovascular disease.

Upper gastrointestinal bleeding by antithrombotic drugs

Antithrombotic drug medication increases the incidence of upper GI bleeding, although the frequency of this bleeding may differ according to the population studied and to the types of ulcer protective medication administered [17]. Although antiplatelet drug medication has been shown to be effective in preventing myocardial infarction [18], GI bleeding is still one of the limiting factors for antiplatelet use [19]. In a positive cohort study including 32,989 men, for example, Huang et al. showed that long-term regular aspirin use increased the risk of GI bleeding, especially from the upper GI [20]. Furthermore, in a case–control study comparing patients who had a history of gastric or duodenal bleeding with 7193 matched controls, clopidogrel increased the risk of upper GI bleeding with an odds ratio of 2.3 [95% confidence interval (CI) 0.9–6.0] [21]. Clopidogrel may not induce gastric damage in healthy subjects [22]; however, it may increase the incidence of recurrent peptic ulcer in patients with atherosclerosis and a history of peptic ulcers [23]. Oral anticoagulants may also significantly increase the risk of upper GI bleeding with a relative risk of 1.77 [24].

The risk of upper GI bleeding by antiplatelet agents has been shown to be enhanced when dual antiplatelet drugs are used or when anticoagulant drug is concomitantly used. Yusuf et al. showed that addition of clopidogrel to aspirin, which acts favorably in patients with acute coronary syndrome, increased the risk of major bleeding, with an increase in the frequency of GI bleeding from 0.7% to 1.3% [25]. By analyzing the Health Improvement Network UK primary care database, Garcia Rodriguez et al. found that use of low-dose aspirin increased 2-fold the risk of upper GI bleeding as compared with nonuse, and that the risk of upper GI bleeding was further increased when clopidogrel and oral anticoagulants were used concomitantly, with a relative risk of 2.08 and 2.00, respectively [24]. In patients with upper GI hemorrhage that was confirmed endoscopically, Lanas et al. reported that the use of non-aspirin antiplatelet agents increased upper GI bleeding with a relative risk of 3.2 (95% CI 2.2–4.4) [26]. In that study, the prescription of a proton pump inhibitor for a thienopyridine (clopidogrel or ticlopidine) user profoundly reduced the risk of upper GI bleeding with a relative risk of 0.19 (95% CI 0.07–0.49) [26]. A recent consensus statement from the American College of Cardiology Foundation task force recommended the use
of proton pump inhibitors for the therapy and prophylaxis of aspirin-associated GI injury to prevent adverse GI events with antiplatelet therapy [27].

The incidence of upper GI bleeding from a peptic ulcer is increased by antithrombotic drugs; however, whether such drugs also increase the risk of upper GI bleeding from malignant neoplasm seems to have been less extensively studied. By analyzing the data of patients who were referred for evaluation of a positive FOBT and who underwent colonoscopy and same-day upper GI tract endoscopy, Bini et al. found that there was no difference in the frequency of upper GI lesions between those who were taking warfarin and those who were not, although colonic lesions were significantly more common in the warfarin group [28]. Furthermore, in a double-blind, prospective study, Greenberg et al. reported that aspirin did not cause significant gastric or duodenal mucosal endoscopic lesions [29], although healthy volunteers were enrolled in the study.

Colorectal bleeding, positive fecal occult blood test, and antithrombotic drugs

A randomized trial has shown that screening for colorectal cancer by FOBT and, if positive, by subsequent diagnostic evaluation using colonoscopy, for example, reduces mortality from colon cancer [30]. The American Cancer Society, the American Gastroenterological Association, and the United States Preventive Task Force recommend an annual FOBT to detect cancer, and flexible sigmoidoscopy, colonoscopy, double-contrast barium enema, or computed tomographic colonography to detect adenomatous polyps and cancer in subjects aged 50 years and older with the goal of cancer prevention [31].

It may therefore be questioned whether antithrombotic medication will increase the need for colonoscopic examination by increasing FOBT positivity. If antithrombotic drugs increase the frequency of a positive FOBT by facilitating hemorrhage from cancer and/or adenomatous polyps, these drugs may beneficially increase the chance of detecting these life-threatening neoplasms. On the other hand, if antithrombotic drugs increase the likelihood of hemorrhage from non-malignant colorectal lesions, then antithrombotic drug use may unfavorably reduce the cost-effectiveness of the FOBT; if positive predictive value decreases, the cessation of antithrombotic drugs during stool collection may have to be considered.

Several clinical studies, although not large-scale, have been designed to answer this question. In a double-blind, prospective study, Greenberg et al. reported that, in the absence of frank ulceration, low-dose aspirin did not result in a positive FOBT [29]. In that study, however, healthy volunteers underwent only 30 days of treatment with daily aspirin or placebo. In a prospective, cross-over study, in which 100 participants over 40 years of age were enrolled, the same group reported that aspirin, but not warfarin, caused a small but clinically insignificant increase in occult fecal blood; therefore, patients taking either low-dose aspirin or warfarin can be managed in the same fashion as patients not taking these medications [32]. Again it should be noted that, essentially healthy subjects who were not on antithrombotic drugs on a regular basis were enrolled in that study. The target population property is an important parameter affecting the results of such studies, because the risk of anticoagulation-related bleeding may increase in older subjects and in those who are concomitantly using other antithrombotic drugs [33].

Kahi and Imperiale conducted a prospective cohort study, in which 193 patients with a mean age of 66 years were referred for colonoscopy to evaluate a positive FOBT result. Patients on warfarin treatment were excluded from this study. Among 135 patients on regular aspirin or non-steroidal anti-inflammatory drug (NSAID) treatment, 29 (21%) had findings to explain the positive test results, as compared with 11 (19%) among 58 non-users, indicating that aspirin and NSAID use may not increase the frequency false-positive FOBT results [34]. This study’s results seem to have more clinical relevance than Greenberg’s study, because it involved individuals who took aspirin for primary or secondary prophylaxis of cardiovascular or cerebrovascular disease. Nevertheless, Kahi et al.’s study was limited in that right-sided colitis, and vascular lesions were also considered to be lesions that would explain the positive test results, although the tests were primarily developed for the detection of advanced neoplasia (cancer, large polyps, or polyps ≥10 mm, or polyps with villous histology).

In a prospective study, Bini et al. investigated patients referred for the evaluation of a positive FOBT [28]. Among 210 patients on warfarin, and 210 patients not on warfarin, adenoma was found in 39 (18.6%) and 29 (13.8%), and carcinoma in 18 (8.6%) and 22 (10.5%), respectively, indicating that warfarin treatment may not increase the risk of detecting non-neoplastic lesions in FOBT-positive subjects. The frequency of GI lesions was greater in those with a higher international normalized ratio, although the difference was not statistically significant. It is of note that, as compared with patients who were not taking oral anticoagulants, those taking warfarin showed an increased frequency of the detection of ‘early-stage’ colorectal cancers. Bini et al. suggested that the earlier detection of colorectal cancer in patients taking warfarin may be explained by the unmasking — by anticoagulation therapy — of bleeding from early stage lesions that otherwise would not have been diagnosed [35,36], although this notion requires further evaluation.

In contrast, Sawnhey et al. found that use of anticoagulant and antiplatelet medications lowered the positive predictive value of FOBT for advanced colonic neoplasia by analyzing the data of patients who were referred for colonoscopy for a positive FOBT [37]. They found that the positive predictive value of FOBT for advanced colonic neoplasia and colorectal cancer, respectively, was 30.5% and 4.2% among antithrombotic drug non-users, and 20.5% and 3.4% among aspirin users (Fig. 1). In addition, clopidogrel appeared to have a more negative effect on the positive predictive value of FOBT, as compared with aspirin and warfarin.

Clarke et al. studied the data of 846 participants with a positive FOBT who underwent colonoscopy, of which 301 patients were taking regular antithrombotic medication (aspirin, n = 183; warfarin, n = 26; others, n = 127) [38]. In this study, 47.5% of anticoagulant users were found to have colorectal neoplasia, whereas a significantly higher
percentage (56.5%) of anticoagulant non-users were found to have neoplasia.

Notwithstanding these observations [37,38], however, and considering that the main purpose of colorectal screening is to detect neoplastic disease, we cannot neglect the possibility of colorectal cancers in patients with a positive FOBT, even in those taking antithrombotic drugs, because the extent of reduction in the positive predictive value was, although statistically significant, small. If previously unrecognized colorectal malignancies can indeed be more easily discovered by anticoagulant [39] or antiplatelet [40] therapy, we cannot neglect a positive FOBT in patients who are taking antithrombotic drugs.

Coronary heart disease and gastrointestinal cancers

Several previous studies have suggested that GI tract malignancies are more prevalent in subjects with coronary artery disease (CAD). This information is important because antithrombotic drugs are more frequently given to patients with coronary heart disease. Sawhney reported that, among those patients who underwent colonoscopy, CAD was an independent predictor for advanced colonic neoplasia [37]. Chan et al. reported that among subjects who underwent colonoscopy, colorectal cancer was found in 19.0% patients with CAD as compared with 7.7% without. This study included only data from patients who had signs and symptoms associated with the GI tract; namely, abdominal pain, altered bowel habit, iron deficiency anemia, constipation, diarrhea, inflammatory bowel disease, melena, positive fecal occult blood, and per-rectal bleeding [41]. More recently, Chan et al. conducted a clinical study in which patients were recruited for screening colonoscopy after undergoing coronary angiography for the first time for suspected CAD. In this study, advanced colorectal lesions, defined as the presence of cancer or adenomas with a villous component, high-grade dysplasia, or a size of 1 cm or larger were found in 18.4%, 8.7%, and 5.8%, while prevalence of cancer was found in 4.4%, 0.5%, and 1.4%, of the CAD-positive, CAD-negative, and general population groups, respectively [42]. The prevalence of colorectal neoplasm was higher in CAD-positive patients than in CAD-negative patients. It is possible that the greater prevalence of colorectal neoplasm in CAD-positive patients may be attributed to the fact that many risk factors are shared between CAD and colorectal neoplasm, such as advanced age, male sex, smoking, obesity, and diabetes [43]. The unexpectedly high prevalence of colorectal cancer (4.4%) and advanced neoplasia (18.4%) in CAD-positive patients which Chan et al. found in this study, however, needs to be confirmed in other studies [44].

In an analysis of cross-sectional data from Korean men who presented for a health check-up, Yang et al. recently reported that subjects with significant coronary disease, as shown by computed tomography coronary angiography, had a greater prevalence of advanced adenoma [45] (Fig. 2). Although coronary artery lesion was not validated by coronary angiography in this study, it is of value that the study subjects underwent colonoscopy irrespective of the presence or absence of fecal occult blood. Notably, about 20% of the subjects who had significant CAD had advanced adenoma, indicating the intense association between coronary atherosclerosis and colorectal adenoma in Korean men.

Atrial fibrillation and gastrointestinal cancers

Several previous studies have suggested that there is a higher prevalence of GI cancers in patients with atrial fibrillation. In a case—control study with 5—10 years of observation, Muller et al. reported that atrial fibrillation and flutter were associated with colon cancer with higher probability than those without [46]. Guzzetti et al. reported in a case—control study that prevalence of atrial fibrillation was greater in patients admitted for surgical treatment of colorectal cancer than in those admitted for non-neoplastic diseases with an odds ratio of 3.5 (95% CI 1.6—7.2) [47]. Warfarin therapy can be problematic in cancer-harboring patients because of a higher risk of bleeding [48,49]. Although the causal and resultant relationships remain clear, impairment of autonomic function [50], and
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Abnormalities in hormonal and immune systems [51] are suspected to be involved in the underlying mechanism linking atrial fibrillation and cancer. We should be aware of this association between atrial fibrillation and colorectal cancer by checking for fecal occult bleeding in these patients.

Heart failure and gastrointestinal cancers

Antithrombotic drugs may be prescribed for patients with heart failure because of the presence of atrial fibrillation, CAD, and reduced ejection fraction, although the role of antithrombotic therapy in patients with chronic heart failure has long been debated, and remains controversial [52]. In parallel with an improvement in the prognosis of heart failure patients, noncardiac causes are increasingly accounting for a substantial proportion of deaths, especially among elderly heart failure patients. Pons et al. reported that, in a study with a median of follow-up of 36 months, among 960 patients with New York Heart Association functional class II or III, there were 351 deaths, of which 94 (27%) were due to noncardiovascular causes; in addition, 39% of the noncardiac deaths were attributed to malignancies [53] (Fig. 3). We may have to become more aware of the possibility of the presence of undiagnosed malignancies to further improve the prognosis of patients with heart failure.

Certain comorbidities, including cancer, were found to be associated with increased long-term mortality and hospitalizations in the heart failure patient [54], and this association may be attributed to the fact that heart failure and cancers share several risk factors in common; these include cigarette smoking, diabetes, and obesity [55,56]; however, the complex interactions between comorbidities and outcome in heart failure patients have not been fully established [57].

Figure 3 Cause of death in heart failure patients (A) and non-cardiovascular causes of death in heart failure patients (B). (For interpretation of the references to color in this artwork, the reader is referred to the web version of this article.) Adapted from Pons et al. [53].

Figure 4 Kaplan–Meier curves for death due to cancer among controls (Control Group) and in patients with peripheral arterial disease (PAD Group). *Log rank test p < = 0.05. Adapted from Fiotti et al. [63].
Peripheral artery disease, abdominal aneurysm, and gastrointestinal cancers

It has been recognized that colorectal neoplasm may occasionally coexist with abdominal aortic aneurysm (AAA), which causes a dilemma for the surgeon because it is often difficult to decide whether to treat the carcinoma or the aneurysm first [58,59]. Yamamoto et al. reported that, among 408 patients admitted for elective surgery of AAA (248 patients) or peripheral atherosclerotic disease (PAD; 244 patients) who underwent FOBT, 104 (25.5%) had a positive FOBT and thus underwent further colorectal investigation by barium enema, and if lesions were found to be present, by subsequent colonoscopy. Six (1.5%) colorectal carcinomas and 16 (3.9%) advanced adenomas were found and about one-third of positive FOBT patients appeared to have advanced neoplasm [60], the incidences of which seem to be several-fold higher than that among the general population. The observed prevalence of advanced neoplasia was higher than that reported in the general population [61,62].

By following-up patients with PAD together with sex- and age-matched controls from 1974 to 1998, Fiotti et al. found that PAD patients had a significantly higher mortality rate than controls, and the commonest cause of death was cancer, mostly of the lung, stomach, and colon [63]. In Fiotti et al.’s study, a higher incidence of cancer of the GI tract was observed in PAD patients as compared with control subjects (0.40 vs. 0.19, 100 patient-yr, p < 0.05) (Fig. 4). Furthermore, Komori et al. reported that among 222 patients with AAA admitted between 1985 and 1992, 7 patients (3.2%) were found to have concomitant gastric cancer [64]. Although the percentages may vary according to the population studied, several studies have reported a lower incidence of concomitant AAA and GI tract malignancy. For example, Nora et al. found that, among a series of 3500 AAA.s repaired at the Mayo Clinic over a 12-year period, only 17 (0.7%) were associated with a colorectal malignancy [65]. Furthermore, Robinson et al. reported that, among 1337 aneurysms treated over a 10-year period, 19 (1.4%) were associated with a concomitant colorectal malignancy [66]. It should be noted, however, that routine FOBT screening and subsequent colonoscopy may not have been performed in all of this study. These findings support the notion that GI tract malignancies may be occasionally encountered with abdominal aneurysm, which may make the surgical decision more complex than if they were absent [64].

Should we discontinue antithrombotic drugs before endoscopic examination to prevent a negative predictive value?

Because usage of antithrombotic drugs may increase the negative-prediction for colorectal cancers in FOBT-positive subjects [37,38], some studies recommend the temporary cessation of such medication, when it does not pose a risk to the patient-from the viewpoint of cost-effectiveness. However, this situation may differ according to the country and health insurance system. Needless to say, whether antithrombotic drugs should be stopped or converted into heparin for the purpose of biopsy is another important issue to be considered.

Conclusions

Along with the improvement of the prognosis of cardiovascular disorders, it is logically thought that number of the cardiology patients who will eventually experience malignant disease will increase, considering cancer is one of the aging-associated diseases. In addition, several previous reports suggested the higher incidence of GI malignancies in patients with cardiovascular diseases [41,67]. There is no firm evidence to support the notion that GI tract cancer is underdiagnosed in cardiology patients, and that more aggressive GI tract screening would reduce the probability of cancer-associated death in cardiology patients. On the other hand, however, several previous reports showed that the risk of GI tract cancers and/or advanced neoplasm might be increased in patients with coronary heart disease, atrial fibrillation, aortic aneurysm, and PAD [42,47,60]. In addition, a possibility has been suggested that antiplatelet and anticoagulant drug use might lead to earlier discovery of GI tract cancer by unmasking bleeding from advanced neoplasms that may be in an early stage [35,36,40]. GI tract lesions should not be overlooked among cardiology patients, especially when unexplained anemia, gastrointestinal symptoms, or positive FOBT is present, and GI tract screening should be performed with an appropriate timing. Along with the improvement of prognosis of cardiovascular disease, we may have to pay more attention to the treatment and/or management of comorbidities that may have a substantial impact on the prognosis and health-related quality of life, such as chronic kidney disease [68], psychological status [69], and GI malignancies.

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