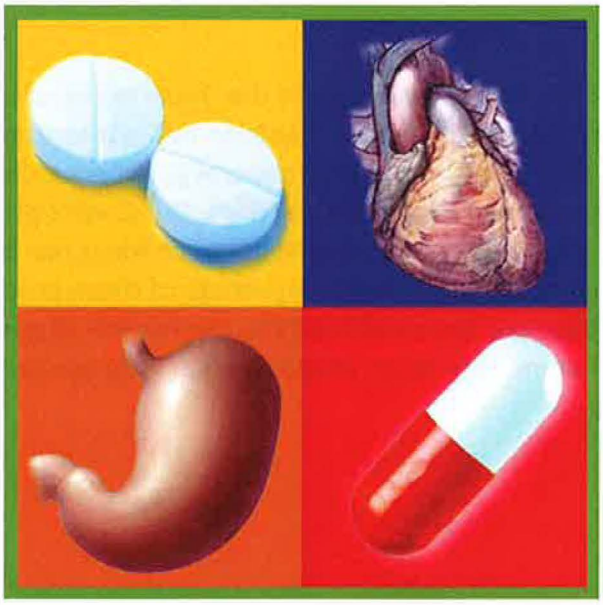
Balancing Gastrointestinal Risks and Cardiovascular Benefits of Anti-Platelet Therapies



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This is to acknowledge that Dr. Byron Cryer has disclosed financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Byron Cryer will not be discussing off-label uses in his presentation.

In treating cardiovascular disease, clinicians commonly are caught between competing considerations of cardiovascular benefit and gastrointestinal (GI) risks. Because platelets have an important role in the pathophysiology of coronary artery and coronary stent thrombosis, drugs which prevent platelet thrombosis have acquired a critical role in the prevention of atherothrombotic complications of vascular disease. In recent years the use of anti-platelet therapies has been markedly increasing, primarily for the prevention of coronary artery and coronary stent occlusion (1-4). Additionally, in the prevention of cerebrovascular occlusion, anti-platelet therapies are among the principal treatments (5). As evidence accumulates regarding the benefits of anti-platelet therapies in the treatment of cardiovascular and cerebrovascular diseases, the use of these agents in clinical practice continues to increase even more.

Currently, two categories of oral antiplatelet therapies, aspirin and the thienopyridines (clopidogrel and prasugrel), are available or are under clinical development for the prevention of atherothrombotic complications in patients with the acute coronary syndrome or who are or are undergoing percutaneous coronary intervention (PCI) (6). Although the evidence is clear from several well-designed trials that the anti-platelet therapies have clinical benefit, the increasing use of these agents in clinical practice is associated with increasing gastrointestinal (GI) complications such as ulceration and GI bleeding. Because of the increasing rates of ulcer and GI complications being encountered with these drugs, this chapter will focus on management strategies which may reduce the gastrointestinal risks of patients who take anti-platelet therapy, especially those patients at highest risk for development of a GI event while using these anti-platelet agents.

Mechanisms of GI Injury with Anti-Platelet Therapies

Aspirin reduces platelet activity by inhibiting the cyclooxygenase (COX) enzymes. While aspirin can inhibit COX-1 and COX-2 isoenzymes, the platelet is primarily comprised of COX-1. Aspirin permanently inhibits platelet COX-1 at relatively low dosages, resulting in inhibition of platelet activity (7). COX-2 mediated effects of aspirin, primarily the analgesic and anti-inflammatory consequences, are inhibited at higher aspirin dosages. Aspirin irreversibly inhibits the metabolism of arachidonic acid to thromboxane A_2 (TXA_2), which is highly sensitive to aspirin's effects, causing complete suppression of platelet TXA_2 production within a few doses of aspirin (7). This inhibition of TXA_2 decreases platelet aggregation, causes vasodilation, reduces the proliferation of vascular smooth muscle cells, and decreases atherogenicity.

In the gastrointestinal mucosa, the principal metabolic products of COX enzymes are the prostaglandins, substances which protect against gastrointestinal mucosal injury. In the presence of a COX inhibitor, such as aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs), gastrointestinal COX is inhibited which results in increased degrees of gastrointestinal mucosal injury. At daily aspirin dosages which are much lower than desirable for optimal cardiovascular efficacy, such as with 10 mg aspirin per day, gastric COX

is markedly inhibited, mucosal prostaglandins are reduced to 60% of baseline and gastrointestinal ulceration occurs (8). Therefore, there is likely not a dose of daily administered aspirin which is therapeutically efficacious without conferring gastric mucosal injury.

Clopidogrel is an effective anti-thrombotic because it blocks platelet activation of adenosine diphosphate (ADP) by irreversibly binding to platelets' ADP receptor, thereby preventing the ADP-dependent activation of the GpIIb-IIIa complex, the primary platelet receptor for fibrinogen. **(Figure 1)**

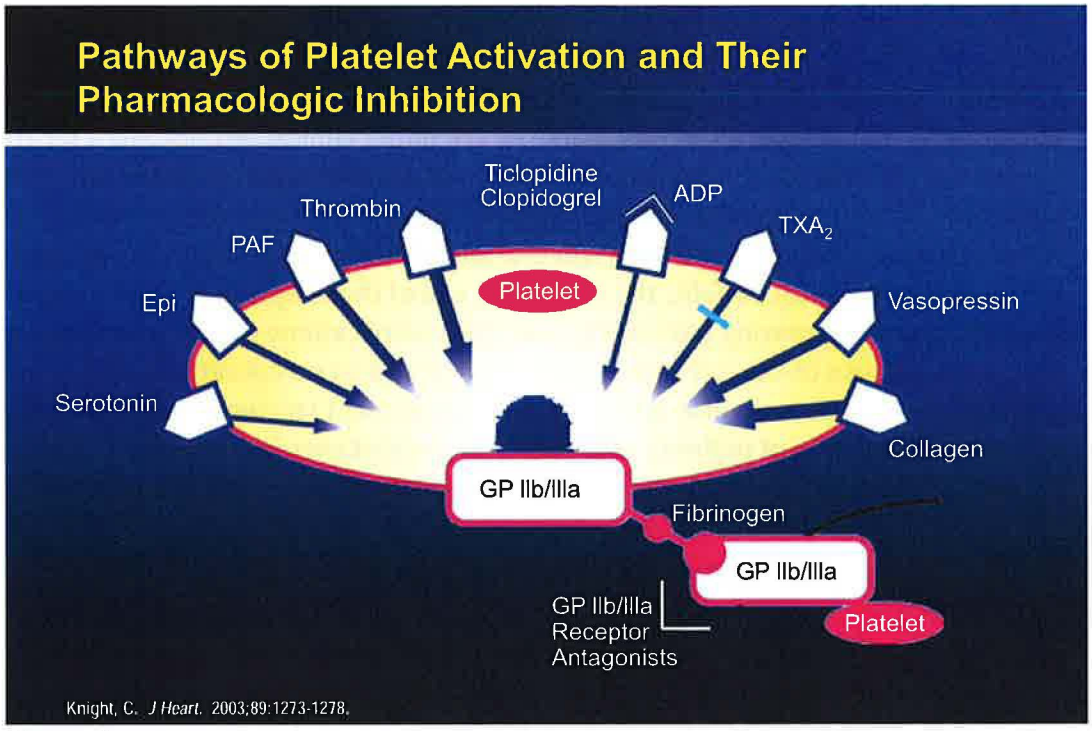

Figure 1

In the CAPRIE trial, a randomized, prospective study of the efficacy of clopidogrel 75 mg and aspirin 325 mg daily for secondary prevention of thrombotic vascular events, clopidogrel was marginally more effective than aspirin and resulted in modestly lower GI bleeding than aspirin (0.5% vs. 0.7%) (9). In short-term endoscopic evaluations of healthy volunteers, clopidogrel causes less gastroduodenal damage than aspirin 325 mg daily (10) and, in observational trials of populations taking anti-platelet therapies, clopidogrel has a non-significant, slightly lower rate of GI bleeding than aspirin (11). Despite this reduction, thienopyridines' GI risks are not zero. In fact, use of prasugrel in patients with acute coronary syndromes with scheduled PCI is associated with significantly reduced rates of cardiovascular ischemic events when compared to clopidogrel (12). However, prasugrel's increased cardiovascular efficacy is somewhat offset by an increased risk of major GI bleeding, including fatal bleeding (12). Furthermore, use of thienopyridines in high GI risk patients can result in high rates of GI bleeding. In patients with a prior history of GI

bleeding, recurrent GI bleeding after only one year of clopidogrel can be observed in as high of 9% of patients taking this agent (13). These observations indicate that, while it may have previously been assumed that the thienopyridines were the GI safe alternatives to aspirin, these agents in fact are associated with considerable GI risks as well.

The mechanism which underlies thienopyridine's GI injury is currently unclear. However, it has been hypothesized that agents such as clopidogrel and prasugrel may cause their GI injury through an impairment of ulcer healing (14). Platelet aggregation plays a critical role in ulcer healing through the release of various platelet derived growth factors that promote angiogenesis, which is essential for ulcer healing. For example, thrombocytopenic animals have reduced ulcer angiogenesis and impaired gastric ulcer healing (15). ADP receptor antagonists impair gastric ulcer healing by inhibiting platelet release of proangiogenic growth factors such as vascular endothelial growth factor (VEGF) (15), that promotes endothelial proliferation and accelerates ulcer healing. Interestingly, new chemotherapeutic agents comprised of monoclonal antibodies directed to circulating VGEF have GI bleeding as a major clinical toxicity (16). Impairment of platelet activity has also been suggested in endoscopic studies to contribute to the mechanism of clinical GI bleeding associated with clopidogrel. (17) While clopidogrel and other agents which impair angiogenesis might not be primarily responsible for GI ulcer induction, their anti-angiogenic effects may impair healing of background ulcers which, when combined with their propensity to increase bleeding, may convert small, silent ulcers into large ulcers that bleed profoundly.

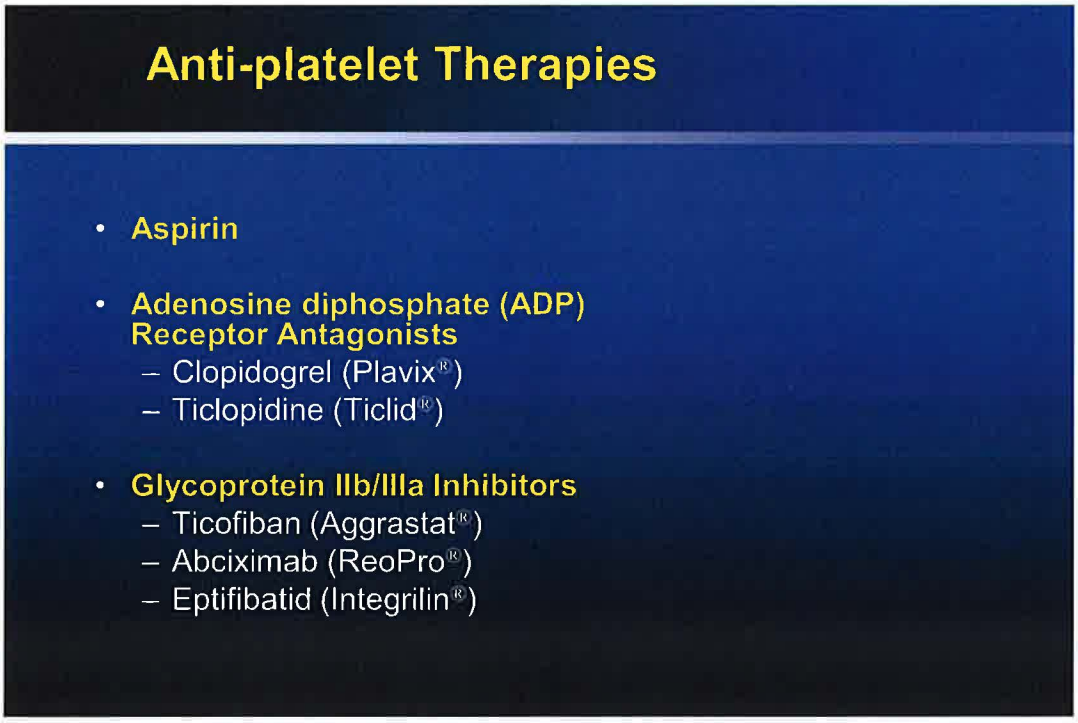

Table 1

Magnitude of Gastrointestinal Ulceration Complications with Anti-Platelet Therapies

Aspirin

Estimates of the incidence of gastrointestinal complications with cardioprotective doses of aspirin come from several prospectively conducted studies of patients taking low-dose aspirin for primary of secondary prevention of cardiovascular events. Although the point estimate of the incidence of GI events with aspirin varies across the prospective trials, meta-analyses of these studies indicate that the relative risk of a GI event in a patient taking low-dose aspirin increases by 1.5 to 3.2 fold when compared to non-aspirin taking individuals (18,19). **(Figure 2)**

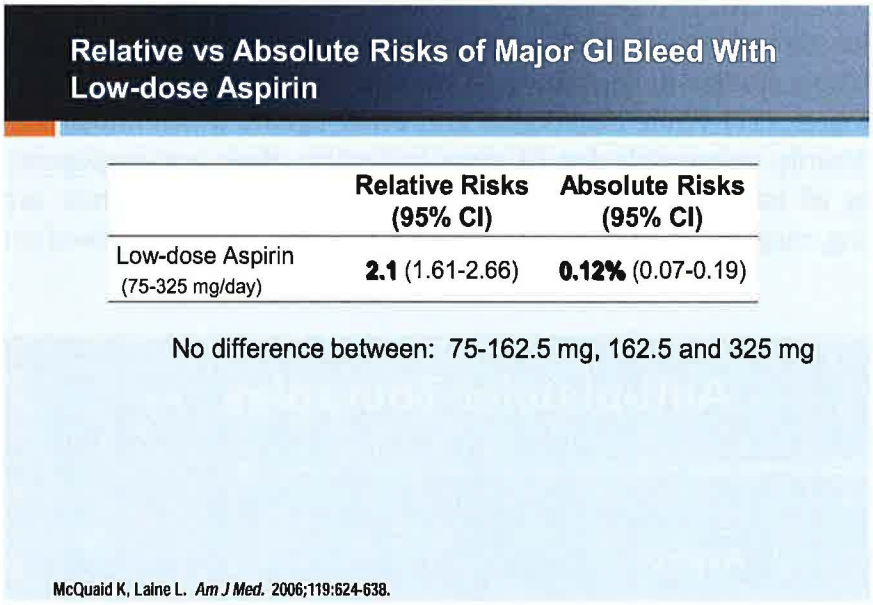

Figure 2

However, the absolute risk of aspirin's clinical risks on an individual basis are small and are estimated to range from 1 to 5 out of 1000 exposed patients (21,22). On the other hand, when these data are viewed from a population perspective, the population impact of the GI adverse effects of low-dose aspirin is likely substantial when considering that is has been estimated that 50% of adults aged 20-80 in the United States are candidates for low-dose aspirin. (22) Furthermore, the excess risk attributable to aspirin will vary in parallel to the underlying gastrointestinal risk of a patient. In the patient with a combination of risk factors, such as age over 70 and past history of ulcer complication, the attributable risk is increased to above 10 extra cases per 1,000 person-years (20).

Clopidogrel

In the CAPRIE trial, a randomized trial comparing clopidogrel and aspirin for the prevention of ischemic events, clopidogrel had modestly lower rates of GI bleeding compared to aspirin (0.5% versus 0.7%, respectively), (9). Extrapolating from that trial, substituting clopidogrel for aspirin in 1000 patients would result in a reduction of two patients with GI bleeding. In patients at high risk for GI bleeding, rates of GI bleeding on clopidogrel will be considerably higher (13). In clinical practice, however, clopidogrel is rarely given as a stand alone anti-platelet therapy and the dual-anti platelet strategy of clopidogrel plus aspirin is a much more commonly encountered combination. Thus, rates of GI events with dual anti-platelet therapy better reflect clopidogrel's actual GI effects in clinical practice.

Dual Anti-Platelet Therapy

In patients who are at high-risk for development of coronary occlusion, such as those with drug eluting coronary stents, at least 1 year of dual anti-platelet therapy is currently recommended (23). In clinical trials comparing the dual anti-platelet strategy of clopidogrel plus aspirin to aspirin therapy alone, the dual anti-platelet strategy is associated with an approximate 2-fold greater incidence of GI complications when compared to either agent alone (2, 24, 25) Observational studies indicate a 7-fold increase in upper GI bleeding with the combination therapy when compared to aspirin (26), with GI risk increasing in patients who are at higher risk. Clearly, in certain patients dual anti-platelet therapy can be a strategy associated with considerable risks of GI bleeding. Therefore, identification of high risk patients and, in such patients, incorporation of strategies to reduce their GI risk would be clinically prudent.

Patients at Risk for Ulcers and GI Complications while on Anti-Platelet Therapies

Across all therapeutic categories, strategies aimed at reducing GI risks should ideally target patients most at risk for the development of complications. With the anti-platelet therapies, there has not been as much work done in the identification of patients at greatest risk of developing GI complications as with other categories of medications such as the NSAIDs. However, because of several large scale clinical trials which have been conducted in the evaluation of efficacy of aspirin and the thienopyridines, there are sufficient emerging data to suggest which groups constitute highest GI risk patients among those taking anti-platelet therapies (1-4,9,13,19-21). **(Table 2).**

Table 2. Demonstrated Risk Factors for Ulcers on Anti-Platelet Therapies*

Aspirin	Clopidogrel
Prior ulcer complication	Prior ulcer complication
Prior ulcer disease	Combination of clopidogrel with NSAID
Advanced age	Combination of clopidogrel with aspirin
Helicobacter pylori	Combination of clopidogrel with anticoagulant
Dose of cardioprotective aspirin	
Combination of aspirin with NSAID	
Combination of aspirin with anticoagulant	

* Risk factors were compiled from data presented in several studies (references 1-4, 9, 13, 19-21)

Aspirin

Among aspirin-taking patients, analyses of large patient care databases in the United Kingdom and Spain indicate that patients taking aspirin with advancing age, a past history of uncomplicated ulcer and a past history of complicated ulcer, all are at increased risk for development of an ulcer (**Figure 3**) (20,27).

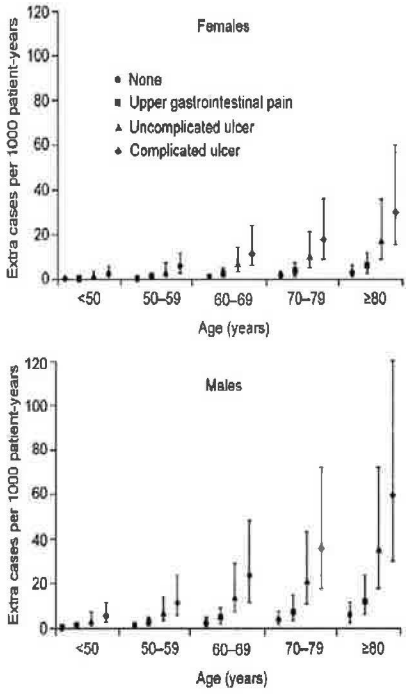

Figure 3. Risk Factors for Development of Gastroduonenal Ulcers and Ulcer Complications in Patients Taking Cardioprotective Doses of Low Dose Aspirin. This meta-analysis which used data derived from prospective trials of low-dose aspirin for primary and secondary prevention of cardiovascular events assess risk factors associated with development of ulcer and ulcer complications. (20).

The most significant risk factor for an aspirin-induced complication is a history of prior complicated ulcer disease, as 15% of patients with a prior history of bleeding ulcer who are taking aspirin at a dose of 100 mg/day will have a recurrent bleeding ulcer at one year (28). Advancing age is also a risk factor. Although there does not appear to be a threshold age at which risk dramatically increases, the risk increases linearly at rate of approximately 1% per decade of advancing age (27).

Helicobacter pylori (*H. pylori*) infection is also a risk factor for development of ulcers and of ulcer complications in patients taking low-dose aspirin. In endoscopic studies of aspirin users, Helicobacter pylori-infected patients aged 60 years or greater who received low-dose aspirin were more likely to develop duodenal ulcers than aspirin taking patients without the infection (29,30). In a case-control study of low-dose aspirin users, *H. pylori* increased the risk of upper GI bleeding 5-fold when compared to non-infected patients with upper GI bleeding (Lanas). It is clear that *H. pylori* increases risk of ulcers related to low-dose aspirin. However, the data have not been as straightforward as to whether eradication of *H. pylori* prior to starting aspirin will reduce future ulcer risk in patients with a history of ulcer. In a 6-month randomized trial of *H. pylori* eradication compared maintenance therapy with omeprazole in aspirin users with *H. pylori* infection and a bleeding ulcer history, rates of recurrent ulcer bleeding were comparable among the two treatment groups suggesting that *H. pylori* eradication alone may reduce ulcer risk with low dose aspirin to the level obtained with proton pump inhibitor (PPI) co-therapy (32). In another prospective randomized study, all low-dose aspirin users with *H. pylori* infection and a history of ulcer bleeding were treated for *H. pylori* prior to being randomized to a PPI or placebo. One year later, rates of recurrent bleeding were significantly 9-times higher in those who had received eradication therapy alone, suggesting that treatment for *H. pylori* alone in high-risk users of low-dose aspirin may be insufficient to reduce their subsequent bleeding risks. (28). However, in this study two-thirds of the patients with recurrent ulcer bleeding who had received *H. pylori* treatment had persistent *H. pylori* infection after treatment or were concomitantly taking NSAIDs. Thus, recurrent bleeding in patients in this study reflected failure to eliminate the H. pylori infection rather than failure of effective eradication to reduce subsequent aspirin-related GI bleeding. In a more recent and larger prospective trial, patients with a prior history of bleeding ulcer who were infected with *H.* pylori, but who also had confirmation of successful *H. pylori* eradication prior to starting low dose aspirin, had very low (~1%) rates of recurrent bleeding ulcers in up to 4 years of follow-up without concomitant PPI therapy (21). Therefore, a reasonable conclusion from these studies regarding the contribution by *H. pylori* to the risk of aspirin-related GI bleeding is that confirmed eradication of *H. pylori* results in considerable reductions in risk of recurrent bleeding in high GI risk patients who take aspirin.

Dose of aspirin also appears to be related to GI ulcer risk, as a higher range of low-dose aspirin, between 100 and 325 mg/day, contributes to an increased risk of gastric or duodenal ulcer. (18,19). Although meta-analyses of risk of aspirin dose and GI bleeding certainly suggest a trend in favor of lower doses of aspirin being associated with reduced GI risk, no study has been able to prove that 81 mg of aspirin daily is associated with statically

fewer GI complications than 325 mg of aspirin per day. It has also been suggested that modifications to the formulation of aspirin might be associated with a lower GI bleeding risk. However, when enteric-coated and buffered aspirin formulations have been compared to plain aspirin for their risks of major GI bleeding, GI risks were not lowered by the modified formulations of aspirin. (33,34).

Concurrent use of low-dose aspirin with an NSAID is also a risk factor for GI ulcer complications. Observational studies have noted that, compared to the risk of low-dose aspirin taken alone, when low-dose aspirin is combined with an NSAID the relative risk upper GI complications increases by 2 to 4 fold. (35,36). In certain clinical scenarios, patients achieve cardiovascular benefit from the addition of anticoagulants such as heparin or coumadin to low-dose aspirin. However, addition of heparin or coumadin to low-dose aspirin may increase risks of major bleeding by 50% to 2-fold, respectively (37, 38).

Clopidogrel

Similar to observations with low-dose aspirin, in patients taking clopidogrel as the sole anti-platelet therapy, a prior history of bleeding has been observed in several studies to be a risk factor which places these patients at substantial risk for GI complications on clopidogrel. In a retrospective cohort analysis of patients taking clopidogrel, 22% of patients with a prior history of GI bleeding had recurrent GI bleeding while taking clopidogrel while no patients without a prior history of GI bleeding had bleeding while on this anti-platelet agent (39). Prospectively conducted trials of patients with prior histories of ulcers have demonstrated rates of recurrent GI bleeding ranging from 9 to 13% of patients by one year (13, 40).

Concomitant use of clopidogrel with an NSAID had also been suggested by observational studies to increase clopidogrel's GI risks. In one observational study, concurrent use of clopidogrel with an NSAID increased the relative risk of upper GI bleeding by 15.2 (95% CI, 4.1 – 56.5), (36). A substantial increase in GI bleeding risk is also conferred by the combined used of clopidogrel, anticoagulants and aspirin (41). Studies of clopidogrel have not yet reported the effects of advancing age or *H. plyori* on clopidogrel's GI risks. However, since all other risk factors studied with clopridogrel have shown consistent similarity to GI risk factors with aspirin, for the present time it would be prudent to assume that these other as of yet unstudied GI risk factors with clopidogrel are similar to those seen with aspirin. Furthermore, any risk factor demonstrated in association with either of the individual anti-platelet therapies, should be similarly be assumed to be associated with GI risk with combination anti-platelet therapy.

Strategies to Reduce Gastrointestinal Risk of Anti-platelet Therapies

Therapy for management of GI risk with anti-platelets agents needs to be tailored depending on whether one is attempting to treat an already established ulcer or GI bleed associated with anti-platelet therapies or attempting to prevent an ulcer or GI bleeding from developing in patients taking these medications.

Prevention Ulcers and GI bleeding in Patients Taking Anti-Platelet Agents

As discussed in previous sections, while relative risk of a GI bleed is increased 1.5 to 3.2 fold that patients taking anti-platelet therapies (18,19), the absolute risk to any individual patient is relatively small. Thus, it is not likely cost-efficient to treat all patients taking anti-platelet agents with strategies which will reduce their subsequent risks of a gastrointestinal event. A more tailored approach which identifies those patients at greatest risk of developing GI bleeding on anti-platelet therapy is a more efficient approach to manage gastrointestinal risk. (**Table 1**). Recent guidelines have been published which suggest an approach for reducing GI risks in patients taking anti-platelet agents (**Figure 4)** (42).

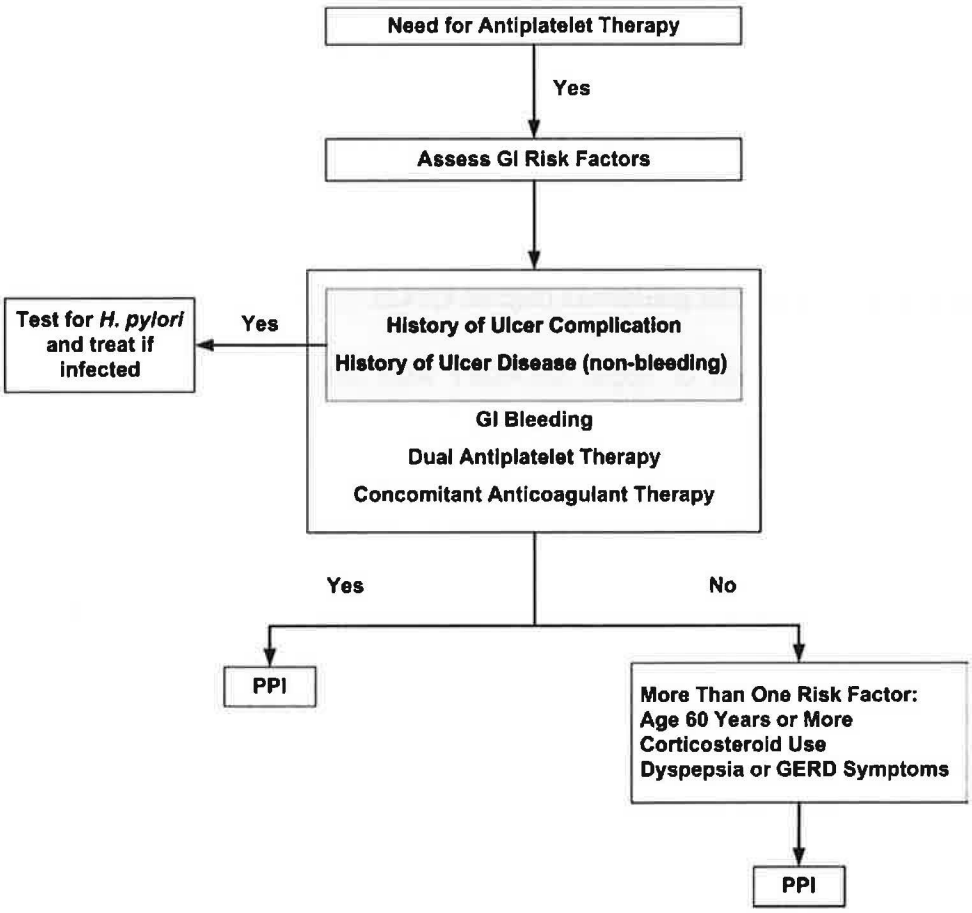

Figure 4. Approach to Reducing GI Risks in Patients Taking Anti-Platelet Therapies. Expert consensus guideline recommended by American College of Cardiology Foundation, American College of Gastroenterology and the American Heart Association. (42).

The initial step in reducing gastrointestinal risk of anti-platelet therapies is to assess whether the patient has a continued requirement for anti-platelet therapy. Depending on the indication for aspirin and/or clopidogrel and the length of time on therapy, some

patients may be able to have anti-platelet therapy withdrawn. For example, clopidogrel in combination with aspirin is recommended for specifically defined time periods for patients presenting with acute coronary syndrome and following PCI or coronary artery bypass grafting (4). In patients who require continued treatment with anti-platelet therapies, the next step is to assess the presence of factors which may place the patient at greater GI risk. Because the majority of patients who chronically take anti-platelet agents will never develop clinically significant ulceration, the ideal candidates for cotherapy are those considered as high risk for NSAID-induced ulcers **(Table 2; Figure 4)**. Patients with multiple GI risk factors will certainly be the most compelling candidates for strategies to reduce their risk. In all patients with a prior history of peptic ulcer or a history of ulcer complications should be tested for the presence of *H. pylori* infection should be assessed in all patients and those with the infection should be given therapies for the eradication of *H. pylori* prior to starting anti-platelet therapy (42, 43).

After assessment and treatment of *H. pylori* in patients with prior ulcer or GI bleeding histories, further reduction in GI risk in other high-risk patients who require anti-platelet agents is primarily accomplished by prescribing drugs that when co-administered with anti-platelet agents protect against mucosal ulceration. While various co-therapies that have been considered are discussed in the following sections, PPIs are the risk reduction strategy most commonly recommended by guidelines (**Figure 4**) (42).

Prostaglandins. Prevention of upper GI injury with low-dose aspirin is dependent on the presence of GI mucosal prostaglandins (8). In short-term studies of healthy volunteers, misoprostol, the synthetic PGE_1 analogue, reduces gastric mucosal injury (44). Studies using capsule endoscopy demonstrate that low-dose enteric-coated aspirin frequently damages the small intestine, and misoprostol significantly reduces small intestinal injury related to aspirin (45). In patients taking low-dose aspirin plus an NSAID, misoprostol can effectively reduce the incidence of endoscopic ulcers (46). The disadvantages to misoprostol are that it may cause dose-related diarrhea and is not effective in treating dyspepsia associated with aspirin.

Nitrates. Since a component of gastrointestinal injury is felt to be related to a reduction in mucosal blood flow, compounds which maintain gastrointestinal blood flow are conceptual targets as agents which might reduce GI injury due to anti-platelet therapies. As nitrates are vasodilators, their efficacy in prevention of GI injury with anti-platelet agents has been evaluated in products in clinical development. Endoscopic trials indicate that a fixed dose combination tablet of aspirin and nitric oxide, NO-aspirin, causes fewer endoscopic lesions in the upper GI tract than aspirin (47). Also, an epidemiological study reported that the use of nitrates is associated with risk reduction of ulcer bleeding in patients who take low-dose aspirin (48).

However, a subsequent case-control study by the same group revealed that nitrates did not effectively reduce the relative risk of hospitalizations for upper GI bleeding in patients taking low-aspirin (100-300 mg per day) or clopidogrel. **(Figure 5)** (49)

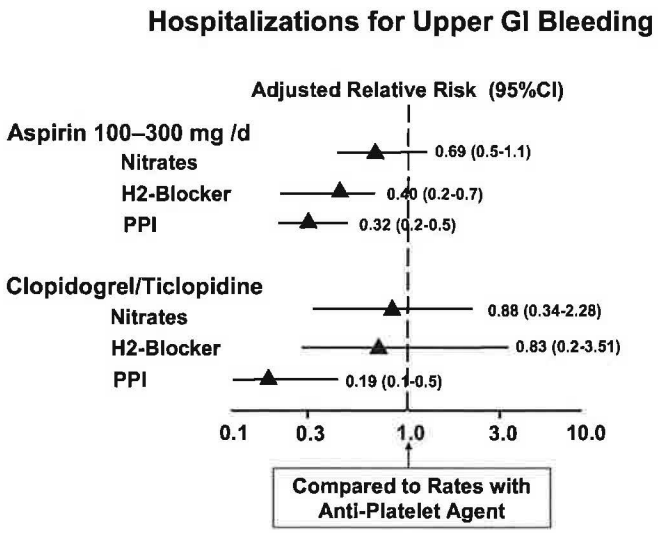

Figure 5. Comparison of Strategies for Prevention of Upper GI Bleeding. The adjusted relative risks (and 95% CI) of a hospitalizations for upper GI bleeding in Spain are presented in this case-control study of 2777 cases of patients with upper GI bleeding and 5532 controls without bleeding. The relative risks of upper GI bleeding with nitrates, H_2-receptor antagonist and proton pump inhibitors (PPI) are shown as compared to the bleeding rates associated with aspirin or clopidogrel/ticlopidine without co-therapy. Figure constructed using data presented in reference (49).

Therefore, nitrates cannot be recommended with confidence as effective strategies to reduce the GI risks of anti-platelet therapies.

H_2-Receptor Antagonists. Very few studies have evaluated the efficacy of H_2-receptor antagonists (H_2RAs) in the prevention of GI injury with anti-platelet agents. A small retrospective cohort analysis demonstrated that after 1 year of clopidogrel, 22% of patients taking concomitant H_2RAs had recurrent upper GI bleeding while no patient taking clopidogrel plus a PPI had recurrent bleeding (39). A recent case-control study revealed that, compared to patients taking anti-platelet therapy without protective co-therapy, H_2RAs can significantly reduce the risk of patients admitted to hospital with upper GI bleeding while taking low-dose aspirin (RR 0.32, 95% CI 0.2-0.5) but not in those taking clopidogrel (RR 0.83, 95% CI 0.2-3.5)(49) **(Figure 3)**. While this study did not assess the efficacy of H_2RAs of prevention of upper GI bleeding in patients taking dual anti-platelet therapies, it can be assumed that H_2RAs would not be effective in prevention of GI bleeding with clopidogrel plus aspirin since this strategy was ineffective in preventing GI bleeding with clopidogrel alone.

Proton Pump Inhibitors. Use of PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole) as prophylaxis for GI injury due to anti-platelet therapies has become an attractive strategy for many clinicians. Support for this practice comes from several

randomized control trials and observational studies. In a randomized control trial of low-dose aspirin users with prior histories of bleeding ulcers, after eradication of *H. pylori*, use of a PPI was associated with a statistically significant 89% reduction in recurrent ulcer bleeding at one year (28). In a 6-month randomized trial of *H. pylori* eradication compared to maintenance therapy with omeprazole in aspirin users with *H. pylori* infection and a recent history of ulcer bleeding, rates of recurrent ulcer bleeding were comparable between the two treatment groups (0.9% and 1.9%, respectively) (32). In a more recent prospective study of *H. pylori*-negative patients with histories of aspirin-induced upper GI bleeding, PPI administered along with low-dose aspirin was much more effective than clopidogrel alone in reducing rates of recurrent upper GI bleeding (0.7% and 8.6%, respectively p=0.001) (13). Finally, observational studies suggest that PPIs very effectively reduce upper GI bleeding risks associated with monotherapy with low-dose aspirin (RR 0.32, 95% CI 0.2-3.5) and with monotherapy with clopidogrel (RR 0.19, 95% CI 0.1-0.5) (49).

The sum of the above evidence from trials of differing design indicated that PPIs are very effective therapies in the prevention of GI injury with either aspirin or clopidogrel monotherapy. However, for the more commonly used dual-anti-platelet therapies there are fewer data evaluating the effectiveness of PPIs. A recent prospectively placebo-controlled, endoscopic trial of the efficacy of various dosages of omeprazole as a strategy to reduce gastroduodenal erosions and ulcers indicated that omeprazole at doses of 20 and 40 mg significantly reduced short-term erosive GI injury by as much as 80% in patients taking clopidogrel and low-dose aspirin (50) (**Figure 6**).

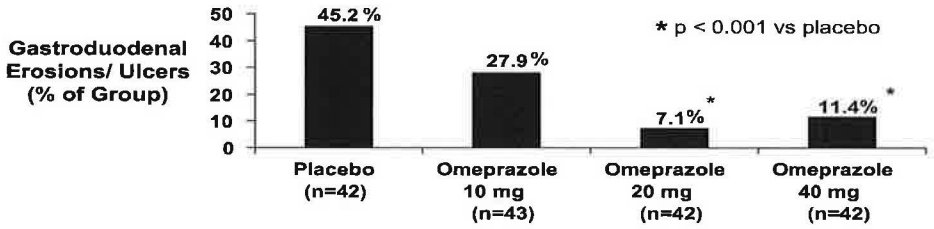

Figure 6. Omeprazole for the Prevention of Endoscopic Gastroduodenal Mucosal Injury with Clopidogrel plus Aspirin. H. pylori negative healthy volunteers (n-174) taking clopidogrel 75 mg daily plus aspirin 325 mg daily for 14 days were randomized to placebo or omeprazole 10 mg, 20mg or 40 mg. Compared to placebo endoscopically-assessed mucosal injury was significantly reduced with omeprazole at doses of 20mg and 40 mg daily ($p < 0.001$) with the 20 mg dose associated with the greatest reduction of injury (~80%). Figure taken from data presented in reference (50).

The COGENT-1 (Clopidogrel and the Optimization of Gastrointestinal Events; NCT00557921) study was designed to evaluate GI events in patients with coronary artery disease taking low-dose aspirin randomized to a fixed-dose, single combination tablet of clopidogrel plus

omeprazole 20 mg or to clopidogrel alone. This study which had the recruitment goal of 8000 patients was powered to evaluate clinically significant GI outcomes with the PPI/clopidogrel combination. Unfortunately, the study was prematurely terminated in January 2009 after enrolling only 2000 patients. Therefore the only currently available data supporting PPIs as effective therapies to prevent GI injury from dual anti-platelet therapies are from a short-term endoscopic trial (50).

Treatment of Ulcers and GI bleeding in Patients Taking Anti-Platelet Agents

Healing of bleeding ulcers formed as a consequence of anti-platelet therapy can be effectively accomplished, assuming that these agents can be discontinued. A clinical challenge which clinicians frequently encounter is when a patient who requires chronic anti-platelet therapy presents with GI bleeding, for example a patient with recent percutaneous revascularization. In a clinical trial of patients chronically taking low-dose aspirin for cardiovascular indications who presented with bleeding gastric or duodenal ulcers, after initial withholding of aspirin, successful endoscopic treatment of bleeding ulcers and treatment with PPIs, patients were randomized to low-dose aspirin or to placebo (51). Rates of recurrent upper GI bleeding one month after endoscopic treatment were similar in the aspirin and placebo groups (19% and 11%, respectively; p=0.25). However, 30 day mortality was much higher in patients in whom aspirin had been withheld (placebo users) when compared to patients in whom aspirin was restarted (15% vs. 2%, p=0.01), with the majority of the deaths in the placebo group attributable to cardiovascular reasons. This study's results suggest that it may be more dangerous to withhold aspirin for 1 month in patients with cardiovascular disease than to restart it immediately after successful endoscopic treatment of their bleeding ulcers followed by continuous intravenous infusion of PPI (51).

With regard to management of acute GI bleeding in patients on dual anti-platelet therapy, clinicians need to balance the increased cardiovascular risks which prompted the indication for dual anti-platelet therapy against the risks of recurrent GI bleeding. Recent guidelines recommend that endoscopic therapy may be performed in high-risk cardiovascular patients on dual anti-platelet therapy and that collaboration between the cardiologist and gastroenterologist should balance the risks for bleeding against the risk of cardiovascular thrombosis on an individual basis (42, 52). In patients in whom individualized cardiac and GI risk stratification suggest that anti-platelet therapies could be withheld for control of acute GI bleeding, the optimum period before re-introduction of anti-platelet therapy has not been established in clinical trials (42, 52).

Potential PPI Interaction with Clopidogrel

Given the growing evidence that a PPI might decrease risk for GI bleeding in patients taking clopidogrel, this risk reduction strategy is seeming a reasonable recommendation for high GI risks patients taking clopidogrel either alone, or in combination with low-dose aspirin.

However, recent evidence suggests that clopidogrel may be less effective when taken with a proton pump inhibitor. **(Figure 7)**

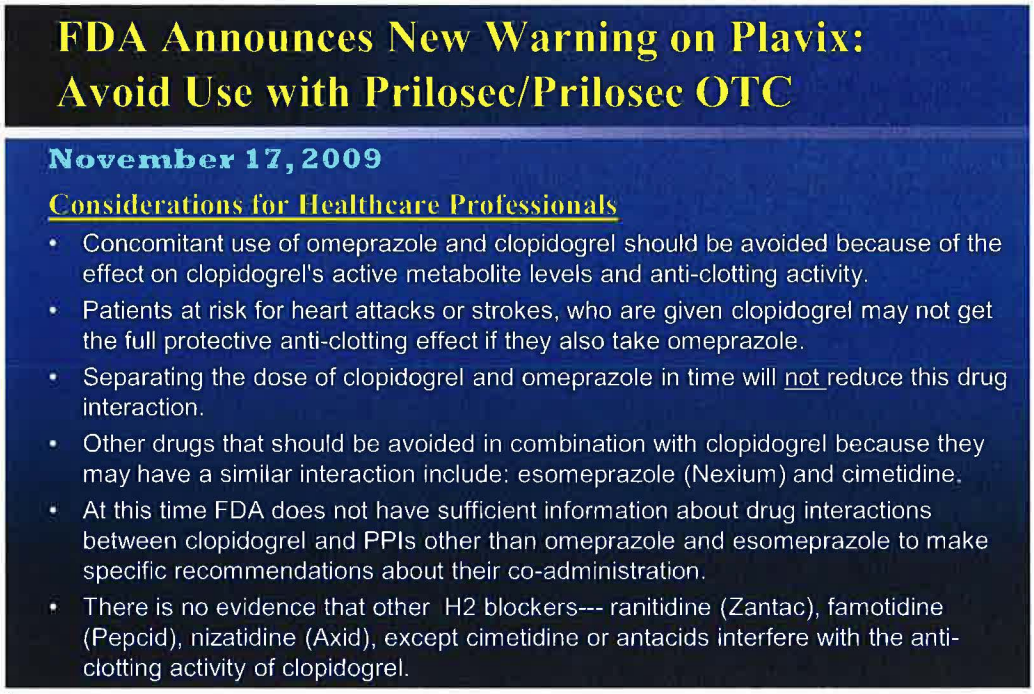

Figure 7

Clopidogrel is a pro-drug which must be activated by the CYP2C19 enzyme in the liver to its biologically active metabolite which inhibits platelet activity. The pro-drug has no intrinsic anti-platelet activity without activation. Evidence that activation of CYP2C19 pathway is clinically relevant to clopidogrel's therapeutic effect comes from several lines of evidence. First, patients with genetic polymorphisms of the CYP219 enzymes who, by virtue of this polymorphism, have less effective hepatic metabolism of clopidogrel, show a marked decrease in their platelet responsiveness to clopidogrel. (53) Furthermore, patients receiving clopidogrel with a history of coronary artery disease without a functioning CYP2C19 gene have higher rates of coronary stent thrombosis and myocardial infarction than patients without the genetic mutations (54, 55).

Omeprazole is a potent inhibitor of CYP2C19, but all PPIs may inhibit CYP219 to some extent (56). Studies assessing the short-term effects of omeprazole on the intermediate end-point of clopidogrel's inhibition of platelet activation in blood samples from patients demonstrate that after 7 days of use, omeprazole decreases clopidogrel's anti-platelet efficacy (57). Other studies of other PPIs, lansoprazole, pantoprazole and esomeprazole, do not demonstrate this effect on the intermediate end-point of platelet responsiveness (58,59). Consistent with the hypothesis, observational studies indicate a higher cardiovascular event rate in patients taking PPIs along with clopidogrel and aspirin compared to patients taking dual anti-platelet therapy without PPIs (60, 61). However, in these observational studies PPIs were used in a greater number of patients with cardiovascular risk factors.

Thus it is not yet clear whether the perceived increased rate of cardiovascular events in those taking PPIs is the result of channeling of higher cardiovascular risk patients to receive PPI treatment. **(Figure 8)**

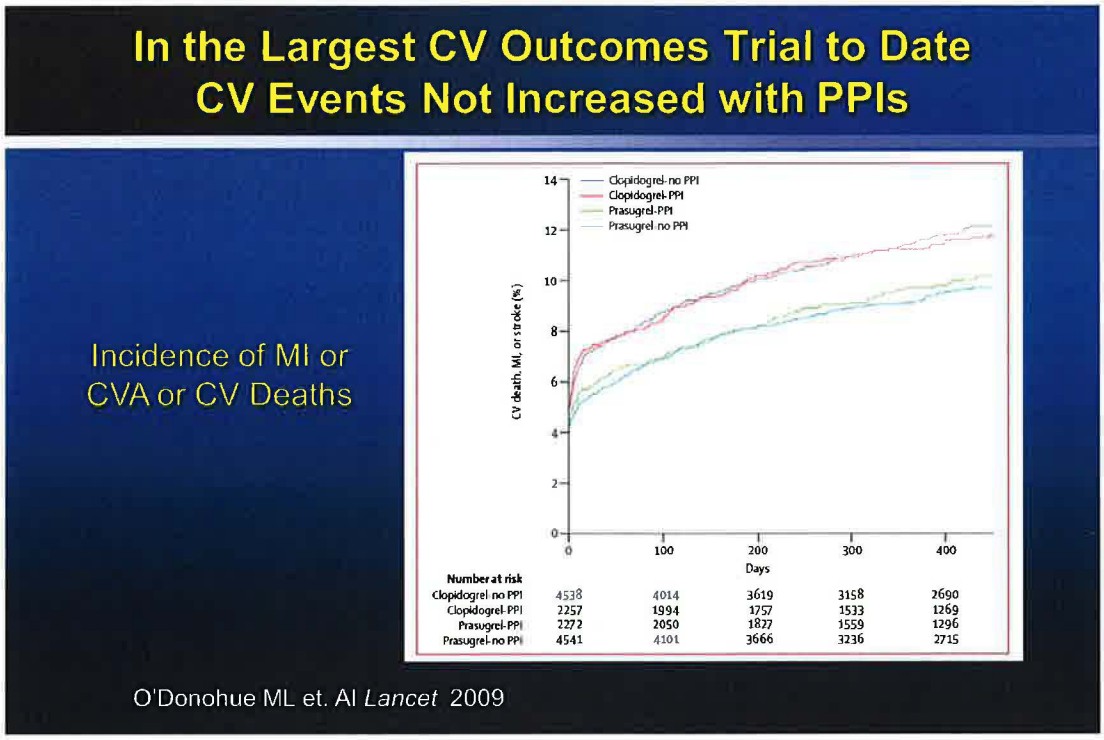

Figure 8

The question of whether PPI treatment diminishes the anti-platelet efficacy of clopidogrel would ideally be best evaluated by a randomized, placebo-controlled trial. Currently, there is no evidence that other acid inhibitory agents such as the H_2-receptor antagonists or antacids interfere with the anti-platelet activity of clopidogrel. Whether concurrent use of a PPI with clopidogrel represents a safety concern or not is currently being evaluated by the U.S. Food and Drug Administration (62). Until more specific regulatory guidance is available, current recommendations are that patients taking both PPIs and clopidogrel concurrently should be considered on a case by case basis to continue their PPI (or not) depending on the balance of the gastrointestinal and cardiovascular considerations for that particular patient until more definitive data become available (63).

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