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REVIEW

Management of low-dose aspirin and clopidogrel in clinical practice: a gastrointestinal perspective

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Abstract Low-dose aspirin, alone or combined with other antiplatelet agents, is increasingly prescribed for cardiovascular prevention. However, the cardiovascular benefits should be evaluated together with the gastrointestinal risks. Low-dose aspirin is associated with upper and lower gastrointestinal injury, although lower gastrointestinal effects are poorly characterized. This gastrointestinal risk differs among antiplatelets drugs users. The most important risk factors are history of peptic ulcer, older age, and concomitant use of non-steroidal anti-inflammatory drugs or dual antiplatelet therapy. Effective upper gastrointestinal prevention strategies are available and should be used in at-risk patients taking low-dose aspirin or clopidogrel. Proton pump inhibitors seem to be the best gastroprotective agents, whereas the benefits of *Helicobacter pylori* eradication are still unclear. Low-dose aspirin has additional effects in the gastrointestinal tract. A large body of evidence indicates that it can protect against different cancers, in particular colorectal cancer. This effect could modify the future indications for use of low-dose aspirin and the risk–benefit balance.

Keywords Low-dose aspirin · Clopidogrel · Gastrointestinal injury · Proton pump inhibitors

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Introduction

Cardiovascular (CV) disease is the most important cause of morbidity and mortality in the world. In this scenario, low-dose aspirin (LDA) (75–325 mg daily) alone or combined with other antiplatelet drugs, such as clopidogrel, is increasingly prescribed for either primary or secondary CV prevention. The benefits of LDA in primary prevention have been questioned due to the balance between the number of CV events avoided and major bleeds caused by LDA [1]. In secondary prevention, the CV benefits substantially exceed the gastrointestinal (GI) risks [2, 3]. LDA has been shown to be effective in preventing about one-fifth of vascular complications in patients with previous myocardial infarction, stroke, or transient cerebral ischemia. This corresponds to an absolute reduction of vascular mortality, namely a 10 % in total mortality and a yearly absolute decrease of 1 % of major coronary events [4]. In this paper, we review the current evidence on the effects of LDA and clopidogrel in the upper and lower GI tract (harmful and beneficial), the risk factors that can increase GI damage and the most appropriate preventive strategies.

Effects of low-dose aspirin in the gastrointestinal tract

Aspirin taken at a high dose behaves as an anti-inflammatory drug and induces a similar damage in the GI tract to

that observed with non-selective non-steroidal anti-inflammatory drugs (NSAIDs). Today, aspirin is being used widely at a low dose for CV prevention, but even at these very low doses, it is associated with upper and lower GI injury.

Upper GI adverse effects in patients receiving LDA

LDA induces a wide spectrum of adverse GI events in the upper GI tract, ranging from symptoms without lesions to severe complications like peptic ulcer bleeding, and even death. Upper GI symptoms in LDA users are common and include heartburn and dyspepsia (including epigastric discomfort, bloating, and early satiety), which can be present in up to 15–20 % of patients [5, 6]. It has been reported that a prior history of dyspepsia was predictive of the onset LDA-related symptoms [6]. The most important outcome associated with upper GI symptoms onset is the low adherence or even discontinuation of LDA therapy, and a discontinuation rate as high as 50 % has been reported [7]. A systematic review has shown that withdrawal of LDA is associated with a threefold-increased risk of CV events. If we focus on secondary prevention, discontinuation of LDA was associated with a 40 % increase in the relative risk of ischemic stroke and myocardial infarction [8, 9]. On the other hand, and unfortunately, clinical symptoms are not predictive of the presence of mucosal damage.

Endoscopic-controlled studies have shown that approximately 60 % of patients taking LDA have upper GI erosions. The incidence of ulcers seems to be lower [10, 11]. Laine et al. evaluated the risk of peptic ulcers with LDA and the interaction with COX-2 selective inhibitors in a double-blind randomized clinical trial (RCT). The 12-week cumulative incidence of ulcers in patients taking LDA was not significantly higher than that observed in patients taking placebo (5.8 vs. 7.3 %). However, the addition of a COX-2 selective inhibitor increased the study ulcer incidence to figures similar to those seen with traditional NSAIDs alone (16.1 % in the LDA group plus rofecoxib and 17.1 % in a group of ibuprofen alone, $p < 0.005$ vs. placebo) [12]. A study of 187 patients taking LDA without gastro-protectant drugs showed an ulcer prevalence of 11 % (95 % CI 6.3–15.1 %) and an ulcer incidence, in 113 patients followed for 3 months, of 7 % (95 % CI 2.4–11.8 %). If we assumed a linear rate of ulcer development, the annual ulcer incidence could reach a high rate of 28 %. Only 20 % of patients had dyspeptic symptoms, which was not significantly different from patients without ulcer [5]. The antrum and particularly the pre-pyloric area are the most frequent locations. Cryer and Feldman [13] published an interesting study that evaluated the long-term effects of LDA in the gastrointestinal tract and its effects on platelet-derived serum thromboxane levels in healthy subjects. All doses of LDA used (10, 81, and 325 mg) for 3 months, significantly reduced gastric mucosal prostaglandin concentration (approximately 40 %) and significantly induced gastric mucosal injury. However, only aspirin at 81 mg and 325 mg/day dose regimens reduced duodenal prostaglandin levels and only the 325-mg dose induced duodenal injury. These findings could explain aspirin's predominant gastric toxicity [13]. However, the clinical significance of these endoscopic findings is unclear, since the incidence of GI complications is much lower than the incidence of GI asymptomatic mucosal damage and their correlation with symptoms is weak. Most ulcers are asymptomatic and small, and probably heal over a period of weeks to a few months.

It is estimated that LDA use is associated with a 2–4-fold increase in symptomatic or complicated ulcers [5, 14, 15]. The estimated average excess risk is five cases per 1,000 aspirin users per year [16]. A recent meta-analysis of 61 RCTs estimated that the risk of major upper GI bleeding increased with LDA use (OR 1.55, 95 % CI 1.27–1.90). This risk was higher when LDA was combined with clopidogrel or anticoagulants (OR 1.86, 95 % CI 1.49–2.31 and OR 1.93, 95 % CI 1.42–2.61, respectively) [17]. Observational studies have reported even higher risk estimates of upper GI bleeding [11, 18–20]. Perforation is the other major upper GI complication related to LDA. It is less frequent than bleeding. The annual estimated incidence of perforation in patients older than 65 years is 32.7 per 100,000 patient-years. More than a third of them are associated with LDA users [21, 22].

Death is the worst outcome of GI complication, but mortality data related to LDA are scarce. The Spanish Mortality Study collected information on GI complications and deaths attributed to NSAID and/or LDA use (mostly due to secondary CV prevention). In this study, the death rate attributed to NSAID/aspirin use was 15.3 deaths/100,000 users and up to one-third of all deaths could be attributed to LDA use [23].

Lower GI adverse effects in patients receiving LDA

The association of LDA use with upper GI damage is well documented, however data on their effects on the lower GI tract are less clear, although the evidence is growing in the last years. The effect of non-aspirin antiplatelet drugs on the risk of lower GI complications is much less studied.

A systematic review found a small increase of fecal blood loss (0.5–1.5 ml/day) in LDA users. This amount increases up to 10 ml/day in some patients who take high-dose aspirin (>325 mg/day) [24]. One study in healthy volunteers showed that even enteric-coated LDA was associated with asymptomatic damage in 50 % of volunteers, and a few of them developed ulcers in their small

bowel [25]. The mechanisms of damage and the real clinical impact of most findings are not yet clear. However, it might be possible that these small bowel lesions could explain why some LDA users develop bleeding of "unknown" source, iron deficiency anemia, or hypoproteinemia.

On the other hand, several studies have evaluated the relationship between LDA and the development of diverticular bleeding and diverticulitis. A study in Health Professionals concluded that LDA significantly increases the risk of both events. After adjustment for risk factors, patients taking LDA had a HR = 1.25 (95 % CI 1.05–1.47) for diverticulitis and a HR = 1.70 (95 % CI 1.21–2.39) for diverticular bleeding [26]. A recent Japanese prospective study evaluated the effects of various drugs (including LDA and clopidogrel) in diverticular disease. The drugs significantly associated with diverticular bleeding were some NSAIDs, LDA, clopidogrel, and cilostazol. Dual antiplatelet therapy carried a higher risk than monotherapy (single therapy, adjusted OR 2.0, 95 % CI and dual, adjusted OR 4.1, 95 % CI) [27].

Our group has quantified the relative risk of upper and lower GI bleeding associated with the use of NSAIDs, antiplatelets drugs, and anticoagulants. NSAIDs, anticoagulants, LDA, and non-LDA antiplatelet agents were associated with upper and lower GI bleeding. The adjusted relative risks of upper and lower GI bleeding for LDA were 1.7 (95 % CI 1.2–2.6) and 2.7 (95 % IC 1.8–4.1), respectively. For non-LDA antiplatelets agents (clopidogrel in >80 % of cases), RRs were 2.8 (95 % IC 1.4–5.8) and 1.8 (95 % CI 1.0–3.2), respectively [28].

Benefits of LDA in the lower gastrointestinal tract: LDA and colorectal cancer

A large body of clinical and experimental evidence indicates that aspirin can protect against different cancers, in particular colorectal cancer (CRC) [29–45]. This effect may be of interest when benefits and risk are considered, especially in patients with LDA treatment for primary CV prevention. Four RCT, which have included almost 3,000 patients, have evaluated the role of LDA in preventing the recurrence of colorectal adenomas [29–31]. This meta-analysis [32] showed a statistically significant 17 % risk reduction of developing any adenoma. Moreover, the benefit was higher for advanced adenomas, with a relative risk reduction of 28 % for any dose of LDA. This preventive effect of aspirin emerged rather quickly (1 year) after initiation of aspirin use.

Most case–control and cohort studies have found that regular aspirin use was associated with reduced risk of CRC [33]. A systematic review of case–control studies showed a statistically significant reduction of long-term risk of developing CRC (OR 0.62, 95 % CI 0.58–0.67) in regular aspirin users compared with non-users, as well as a significant reduction of the proportion of metastatic cancers at CRC diagnosis (OR 0.69, 95 % CI 0.57–0.83) [34]. Two cohort studies of US health professionals (47,363 men and 82,911 women) showed that regular aspirin users had a 21 and 23 % lower risk of CRC, respectively, over 18 and 20 years of follow-up [35, 36]. An analysis of 662,424 patients enrolled in the Cancer Prevention Study II cohort showed that daily aspirin for at least 5 years was associated with a 32 % reduced risk of CRC [37]. Moreover, in a separate analysis of the Nurses Health Study cohort, regular aspirin use also reduced the risk of death from CRC by 28 % and the risk of death from any cancer by 12 % [38].

Rothwell et al. [39] reported the long-term follow-up on cancer outcomes of four RCT that originally were designed to evaluate the effect of aspirin on CV disease prevention. Median treatment duration was 6 years and median follow-up was 18.3 years. Treatment with aspirin (a dose between 75 and 500 mg/day) reduced the 20-year risk of CCR by 24 % and CRC-associated mortality by 35 %. The benefit was higher with longer durations of treatment and in proximal CRC. An absolute reduction of 1.76 % ($p = 0.001$) in 20-year risk of any fatal CRC after 5 years of daily treatment with aspirin (75–300 mg) was observed. Two large RCT of alternate-day aspirin treatment in healthy subjects [40, 41] showed no effect of aspirin on the incidence of CRC over 10 years of follow-up [41]. Several plausible explanations for the contrast with results concerning data from Rothwell's meta-analyses include; a shorter follow-up, alternate-day dosing regimens, and lower equivalent daily dose of aspirin.

Three RCT have primarily evaluated the efficacy of aspirin in high-risk CRC patients. In 206 patients with familial adenomatous polyposis (FAP), high-dose aspirin (600 mg/day) was compared to placebo in the Colorectal Adenoma/Carcinoma Programme (CAPP)-1 [42]. In this study, the mean size of the largest polyps was significantly reduced. The number of polyps in the rectum and sigmoid colon was also reduced. Another recent Japanese double-blind RCT evaluated the influence of LDA (100 mg/day for 6–10 months) in 34 patients with FAP (17 in the placebo group and 17 in the LDA group). The increase in mean diameter of polyps tended to be greater in the placebo group [43]. In the Colorectal Adenoma/Carcinoma Programme (CAPP)-2, 1,009 patients with a diagnosis of Lynch syndrome were treated with either high-dose aspirin (600 mg/day) or placebo for 29 months [44]. Aspirin did not decrease the risk of new adenomas or CRC (RR 1.03, 95 % CI 0.7–1.4).

Effects of clopidogrel in the GI tract

It is unclear whether clopidogrel injures the GI mucosa, or whether it only induces bleeding in an already damaged

mucosa due to its antiplatelet effects. Fork et al. [46] published an endoscopy study that included 36 healthy volunteers who were randomized to clopidogrel (75 mg/day) or LDA (325 mg/day) for 8 days and found that short-term treatment with clopidogrel did not induce macroscopic damage. The CAPRIE trial found that clopidogrel had a modest significant advantage over LDA for the prevention of stroke, myocardial infarction, and vascular disease in 19,185 patients and was significantly associated with lower incidence of major GI bleeding compared to LDA (0.52 vs. 0.72 %, $p < 0.05$) [47]. Observational studies have reported that clopidogrel was associated with nearly the same relative risk of ulcer bleeding as LDA. A recent observational study compared upper GI lesions in patients taking clopidogrel and LDA. The frequencies of symptomatic peptic ulcer in patients taking clopidogrel were higher than in LDA users (39 vs. 24 %, $p = 0.007$). Most of them were located in the stomach [48]. Also, in our recent study, we have found that clopidogrel use was associated with an increased risk of lower GI bleeding [RR 1.8 (95 % CI 1.0–3.2)] [28].

A prospective double-blind RCT comparing LDA plus esomeprazole against clopidogrel alone among 320 patients with coronary disease or stroke who had prior ulcer bleeding and tested negative for *Helicobacter pylori* demonstrated a significantly higher proportion of recurrent ulcer bleeding in the clopidogrel arm (8.6 vs. 0.7 %, $p < 0.001$) during the 12 months of study [49]. A subsequent RCT with similar design has shown similar results [50]. These data suggest that clopidogrel should not be used alone as an alternative to LDA plus gastroprotective agent in patients with high GI risk. Hence, the ACCF/ACG/AHA 2008 Expert Consensus Document on the prevention of GI risk of antiplatelet therapy does not recommend the substitution of clopidogrel for LDA in high-risk patients to reduce the risk of recurrence ulcer bleeding [51].

On the other hand, we can mention shortly that clopidogrel inhibits platelet aggregation via selective and irreversible inhibition of the adenosine diphosphate P2Y12 receptor and is metabolized to the active metabolite by cytochrome P450 system. Other drugs that are metabolized the same could competitively inhibit the enzyme and impair its metabolism. Observational studies suggested that use of PPI in combination with clopidogrel might be associated with an increased relative risk of CV events. Post hoc analyses have failed to demonstrate a clinically significant interaction [52]. The results of the COGENT study [53] showed no differences in CV events between patients on dual antiplatelet therapy (aspirin and clopidogrel) plus omeprazole and dual antiplatelet therapy plus placebo, but the later had a higher incidence of major GI bleeding. Based on these and other data, the expert consensus [50] recommended PPI treatment in patients receiving dual antiplatelet therapy patients at high risk of GI bleeding.

Risk factors associated with upper GI bleeding in LDA users

The risk of upper GI complications differs among LDA users. Risk factors are less well known than those for NSAIDs users, but in general, it is believed that risk factors for NSAIDs and LDA are similar. Several risk factors for GI bleeding in patients taking LDA have been reported: (1) history of peptic ulcer disease, (2) older age, (3) concomitant use of NSAIDs or other antiplatelet agents, (4) concomitant use of anticoagulants, (5) severe comorbidity, (6) high doses, and (7) *H. pylori* infection. Also, other potential risk factors have been mentioned, such as concurrent use of corticoids, male gender, smoking and alcohol use, and high body mass. The relative risk of GI bleeding increases with the number of adverse risk factors present in any patient (Fig. 1).

History of peptic ulcer disease or history of gastrointestinal bleeding

Current evidence shows that history of complicated or uncomplicated peptic ulcer is an important risk factor in LDA users [54–59]. In a case-control study, a prior history of complicated peptic ulcer (OR 6.5, 95 % CI 2.0–21.2) and a prior history of uncomplicated peptic ulcer (OR 2.1, 95 % CI 2.0–21.2) were identified as risk factor for upper GI bleeding among LDA users [54].

Age

Although age is believed to be an important risk factor, scarce and somehow contradictory evidence was available [19, 55–58]. However, in 2009, a meta-analysis of serious

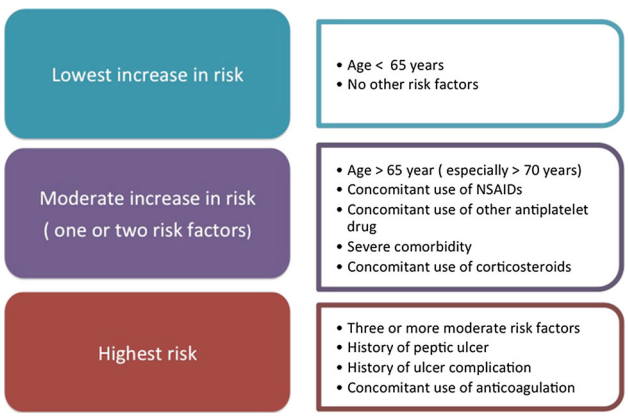

Fig. 1 Risk factor stratification for GI complications in LDA users

vascular events and major bleeds in six primary prevention trials (95,000 individuals) and 16 secondary prevention trials (17,000 individuals) showed that age (per decade) was associated with an increased risk of major extracranial bleed (RR 2.15, CI 95 % 1.93–2.39) [4].

Concomitant use with NSAIDs

Concomitant use of NSAIDs is frequent among LDA users (approximately 20–25 % in clinical trials), mainly in the elderly. This combination increases further 2–3-fold the risk compared to monotherapy with LDA [14, 20, 54, 55, 57, 60, 61]. Current data have shown that selective COX-2 inhibitors produce significantly fewer ulcers [RR 0.26 (95 % CI 0.23–030)] and ulcer complications [RR 0.39 (95 % CI 0.31–0.50)], as well as better GI tolerability compared with non-selective NSAIDs [62]. However, evidence from subgroup analyses of a systematic review of RCT [62] and several RCT (CLASS [63], TARGET [64] and SUCCES-1 [65] studies) shows that the GI benefits of selective COX-2 inhibitors over non-selective NSAIDs might be reduced with the co-administration of LDA. A meta-analysis of all available trials that include users of LDA combined with NSAIDs (selective and non-selectives) showed a lower GI complication risk in patients taking a selective COX-2 inhibitor plus LDA compared with those taking non-selective NSAIDs plus LDA [RR 0.72 (95 % CI 0.62–0.95)] [66]. It must be pointed out that these studies were non-randomized trials and the data were obtained from indirect comparisons.

Concomitant use with other non-aspirin antiplatelet agents

Dual antiplatelet therapy (usually LDA + clopidogrel) is recommended in several scenarios: (1) patients with a recent non-ST segment elevation acute coronary syndrome (at least 1 month, and with a preference of 12 months if the bleeding risk is not high) and (2) patients with coronary stents (treatment for at least 12 months in drug-eluting stent and 4 weeks in a bare metal stent) [51]. Most data show that dual therapy increases the risk of GI bleeding to a higher degree (2–3-fold) than LDA alone. The absolute risk increase was in the range of 0.6–2.0 % [51].

A cohort study of 38,077 patients on LDA treatment showed that patients who received dual antiplatelet therapy for secondary prevention of vascular events had a non-significantly higher risk of upper GI bleeding than patients who received LDA alone (OR 1.6, 95 % CI 0.85–3.05) [55]. The Clopidogrel in Unstable Angina to Prevent Recurrents Events (CURE) trial also corroborated those results. In this trial, 1.3 % of patients taking dual antiplatelet therapy had GI bleeding versus 0.7 % of LDA users [67]. In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial, the combination therapy (clopidogrel and LDA) was compared also with LDA alone. The risk of moderate-to-severe bleeding was higher during the first year and significantly higher in the dual antiplatelet group [68]. One of the important limitations of these studies was that most of them did not specify the GI bleeding location.

Concomitant use of anticoagulants

Anticoagulants do not directly affect the GI mucosa, but have a high anti-hemostatic effect. Most data suggest that concomitant use of anticoagulant and LDA increases the risk of GI bleeding to a higher degree than LDA alone. In the Thrombosis Prevention trial, patients were randomized to warfarin plus LDA or LDA alone; 0.55 % of patients on combined therapy compared to 0.39 % of patients on LDA alone therapy developed a major upper GI bleeding. The differences were non-significant [69]. In another study, six out of 1,206 patients treated with LDA alone and 21 out 1,208 patients treated with LDA plus warfarin had GI bleeding [70]. Masclee et al. [71] recently published a case series analysis of data from 114,835 patients with upper GI bleeding. They showed that monotherapy with LDA increased the risk of diagnosis of upper GI bleeding (incidence rate ratio 3.1); the excess risk from concomitant use of LDA with anticoagulants was 1.9. There are also other studies that were not able to show an interaction between both therapies [57, 58].

Severe co-morbidities

The presence of severe comorbidity as a risk factor for upper GI complications in LDA users has been poorly defined and studied. In 2002, a study by Lanas et al. [56] found that patients with an upper GI bleeding had a more frequent history of chronic pulmonary obstructive diseases. In a prospective Chinese cohort study of 991 patients, hypertension was a risk factor for upper GI bleeding in a multivariate analysis [57]. However, in a cohort study of 903 patients, hypertension, diabetes mellitus, atrial fibrillation, and rheumatic disease were not associated with an increased risk of upper GI bleeding among LDA users [59].

H. pylori infection

Evidence about the interaction between *H. pylori* infection and LDA is scarce and controversial. A recent systematic review evaluated the influence of *H. pylori* on upper GI bleeding risk in LDA users. The authors concluded that current data do not allow performing meta-analyses and

that no firm conclusion could be drawn on these issues [72]. We reported the first study that found *H. pylori* infection as an independent risk factor for upper GI bleeding in LDA users (OR 4.7, 95 % CI 2.0–10.9) [56]. In the MAGIC study, published recently, *H. pylori* was associated with an increased risk of ulcer in LDA users (OR 1.83, CI 95 % 1.18–2.88, $p = 0.0082$) [73]. In contrast, a cohort study showed that *H. pylori* infection may be a protective factor against LDA-induced gastric erosions [74]. At baseline, 48.5 % of *H. pylori*-positive patients had gastric erosions vs. 66.4 % in *H. pylori*-negative patients ($p = 0.17$); after 3 months of follow-up, the reported rates were 40 vs. 64 % ($p = 0.029$). Gastric erosions may be a precursor to peptic ulcers, but they are an endpoint clinically less relevant than ulcer bleeding.

Iijima and colleagues evaluated the possible biphasic effects of *H. pylori* infection on LDA-induced gastropathy depending on the gastric acid secretion level. They concluded that in the presence of sufficient amounts of gastric acid, *H. pylori* and aspirin could synergistically damage the gastric mucosa, while in the absence of sufficient gastric acid, the infection could even suppress the aspirin-induced gastropathy. This biphasic effect could explain the existing controversy in the literature on the role of *H. pylori* infection in GI risk in LDA users [75, 76].

Aspirin-related risk factors

Aspirin as an antiplatelet agent that can induce or increase GI bleeding via its antiplatelet effects, without affecting the integrity of the mucosal barrier. The PERFORM trial included 18,000 patients with a recent ischemic stroke. The rates of GI bleeding were not significantly different in patients treated with LDA (100 mg daily) compared to those treated with terutroban. Terutroban is an antiplatelet agent that antagonizes the TXA2 receptor without effect on COX-1 [77].

- *Aspirin dose* Aspirin-induced GI complications seem to be dose related in the range of 30–1,300 mg daily. This is based on indirect comparison of different trials and on a limited number of direct comparisons of different LDA doses [55, 59–61, 78–81]. This dose–response relationship reflects at least two COX-1-dependent components; (1) dose-dependent inhibition of COX-1 in the GI mucosa and (2) dose-independent inhibition of COX-1 in platelets. Because of this, the antithrombotic effect of aspirin can be dissociated, at least in part, from its GI effect. If we focus on the different doses of LDA, the results of several observational studies were inconsistent in demonstrating a lower GI risk with "low" LDA [55, 59–61]. A meta-analysis of RCT by McQuaid et al. [81] that compared "low" LDA (<162.5 mg/day) with "high" LDA (162.5–325 mg/day) did not show a lower risk of upper GI complications with the lowest doses. Despite this, current recommendation is to use the lowest possible aspirin dose (≤100 mg/day) for the prevention of a CV event, since within this dose range (75–100 mg/day) the aspirin effect on CV event prevention is not affected, whereas the GI risk could be diminished.
- *Aspirin duration* The risk of GI complications with aspirin seems to be higher in the first month of treatment. With longer durations, the risk decreases, but then remains constant over time [4, 14, 20, 54, 60]. This phenomenon has been explained as the consequence of gastric adaptation to LDA [60, 82] or as consequence of a fall in the proportion of susceptible individuals due to treatment withdrawal following GI intolerance, GI complication, or other adverse effects [4].
- *Aspirin preparation* The use of enteric–coated or buffered preparations do not reduce the risk of GI complications [60]. The reason for this is explained on the understanding that the main effect of aspirin on the gastric mucosa depends on the systemic effects rather than in the local "topical" effects of these compounds [19].

Prevention of gastrointestinal damage induced by antiplatelet agents

In order to minimize the upper GI damage induced by antiplatelets, there are several strategies that are used, which include: (1) reducing modifiable risk factors (including eradication of *H. pylori* infection), (2) using the most appropriate aspirin dose, and (3) using gastroprotective agents (Fig. 2).

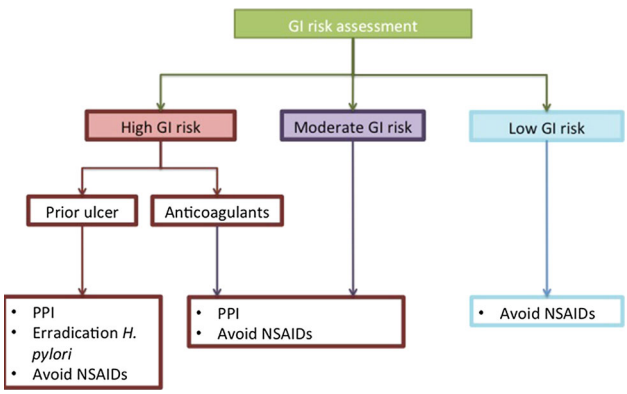

Fig. 2 A proposed treatment algorithm for LDA users

Reducing modifiable risk factors

Avoiding the concomitant use of LDA and NSAIDs

Guidelines strongly suggest avoiding the combination of LDA and NSAIDs if at all possible. In addition, concomitant use of LDA with ibuprofen and naproxen should be avoided because these NSAIDs interfere with the antiplatelet effect of LDA [83, 84]. This is due to competition between both drugs for a common docking site within the COX-1 channel. If these combinations are used, LDA should be taken first and with time enough before dosing with ibuprofen or naproxen, although still the interaction is possible [85, 86]. Due to the long period of drug release with enteric-coated compounds, the chance of interaction between drug doses is very high.

Eradication of H. pylori infection

In LDA users without a history of peptic ulcer, the role of *H. pylori* eradication is controversial. Data are very scant. A small RCT, which included 32 patients, evaluated the role of eradication previous to beginning long-term LDA treatment. Eradication seemed to have a protective effect at 4 months of follow-up [85]. The ongoing Helicobacter Eradication Aspirin Trial (HEAT) study, whose objective is to evaluate the relationship between *H. pylori* eradication and the incidence of upper GI bleeding, can provide quality evidence on the role of eradication in primary prevention in LDA users [86].

Several studies have evaluated the role of eradication in preventing recurrence of peptic ulcer (secondary prevention) in LDA users. Chan and colleagues performed a RCT that compared long-term PPI treatment with *H. pylori* eradication as prevention strategies in patients who had a history of upper GI bleeding. The rebleeding rate was similar in both groups at 6 months of follow-up, although the small sample size of the study left the question open [87]. The largest long-term prospective cohort study has been published recently and evaluated the *H. pylori* eradication as a secondary prevention strategy [88]; 904 patients were included and were followed for 10 years or until death. All patients were LDA users and were divided into three cohorts: (1) *H. pylori*-positive patients with bleeding peptic ulcers in whom *H. pylori* was eradicated, (2) *H. pylori*-negative patients with bleeding ulcers, (3) new users of LDA without prior peptic ulcer. None of them received regular PPI treatment. The incidence (per 100 patient-years) of upper GI bleeding was not significantly different between the *H. pylori*-eradicated cohort (1.09; 95 % CI 0.61–1.98) and the cohort of patients without any history of peptic ulcer (0.67; 95 % CI 0.42–1.06). Although *H. pylori* eradication seemed beneficial in LDA users, subanalysis of the *H. pylori*-related peptic ulcer bleeding cohort showed that despite *H. pylori* eradication, in the presence of other risk factors, these patients had a higher risk of ulcer bleeding than the non-peptic ulcer history cohort. Moreover, *H. pylori*-negative patients with bleeding ulcers had a high risk of recurrent ulcer bleeding. The impact of these findings is also limited because of the lack of direct comparisons and the clinical differences between the cohorts.

In summary, eradication may reduce the risk of ulcer bleeding in patients taking LDA, but more evidence is necessary. Not to use maintenance PPI treatment in patients taking LDA with history of ulcer bleeding may be yet too risky.

Gastroprotective agents

Strategies to decrease the risk of GI complications from LDA use are less well studied compared to the available information for NSAID, but have been evaluated in observational studies and RCTs. Three types of drugs have been used: misoprostol, proton pump inhibitors (PPI), and H2 receptor antagonists.

Misoprostol

Aspirin predominantly inhibits the COX-1 in the GI mucosa producing prostaglandin depletion and consequently ulcer development. An endoscopic study showed that misoprostol, synthetic prostaglandin-E1, significantly lowered the incidence of erosions in healthy volunteers taking LDA [89]. Moreover, misoprostol seems to be superior to placebo for preventing recurrence of gastric ulcers among patients with prior peptic ulcer who are taking LDA and other NSAIDs [90]. Adverse effects with misoprostol use when compared to other effective drugs have probably prevented the widespread use of this approach.

PPIs

PPIs are potent inhibitors of gastric acid secretion. Several studies have explored the impact of PPIs on reducing endoscopic damage and the risk of GI complications in users of LDA.

Two interesting endoscopic studies showed that both omeprazole and lansoprazole significantly reduce GI lesions in healthy volunteers taking LDA [10, 91]. The ASTERIX trial evaluated the efficacy of esomeprazole (20 mg/day) in the prevention of endoscopic peptic ulcers in patients taking LDA [92]. The proportion of patients with gastric or duodenal ulcer during 26 weeks of treatment was significantly lower for esomeprazole than for

placebo (1.3 vs. 5.4 %, respectively, $p = 0.0007$). Patients treated with esomeprazole also had a significantly lower proportion of erosive esophagitis and dyspeptic symptoms. The OBERON trial [93] explored two different doses of esomeprazole in a similar setting. Esomeprazole significantly reduced the development of peptic ulcer with both doses, ($p < 0.0001$) compared with the placebo (1.5 % of patients treated with esomeprazole 40 mg, 1.1 % of patients treated with esomeprazole 20 mg, and 7.4 % of patients treated with placebo developed peptic ulcers).

In order to evaluate the efficacy of PPI in the prevention of recurrence of ulcer complications, Lai et al. [94] performed a RCT that compared lansoprazole (30 mg/day) with placebo in LDA users with history of peptic ulcer and who had already received *H. pylori*-eradication therapy. Patients were treated with lansoprazole or placebo for 1 year. Patients on lansoprazole had significantly less recurrence of ulcer complications than those treated with placebo (1.6 vs. 14.8 %). This study suggested that probably *H. pylori* eradication is not sufficient to prevent ulcer bleeding recurrence in high-risk LDA users. Combined treatment (*H. pylori* eradication plus PPI) seems the most adequate therapy for these patients. Sugano et al. [95] published the LAVANDER study this year. This was a double-bind, randomized, placebo-controlled, and prospective trial that evaluated the efficacy of esomeprazole (20 mg once daily) for 72 weeks in the prevention of recurrent peptic ulcer in LDA users. The authors concluded that esomeprazole 20 mg over 48 weeks prevented the recurrence of peptic ulcers. Ulcer-free rates were consistently lower in the placebo group through week 48. Interestingly, 45 % of patients were *H. pylori* positive, which suggests that esomeprazole protected against ulcer recurrence irrespective of *H. pylori* status. The recent published PLANETARIUM study evaluated the efficacy, dose–response relationship (10 and 5 mg and active control) and safety of rabeprazole for peptic ulcer recurrence over 24 weeks in Japanese patients on LDA treatment. The cumulative recurrence rates of peptic ulcers were 1.4 and 2.8 % in rabeprazole groups (5 and 10 mg, respectively), significantly lower than those in the active control group (21.7 %). In rabeprazole groups, there were no bleeding ulcers. Therefore, rabeprazole prevented the recurrence of peptic ulcers without any evidence of a major dose–response effect in patients on LDA therapy [96].

The COGENT study [53] evaluated in 3,873 patients both the occurrence of CV and GI events in patients taking dual antiplatelet therapy; 51 patients had a GI event (bleeding, symptomatic ulcers or erosions, obstruction or perforation). In the omeprazole group, the event rate was 1.1 % compared with 2.9 % in the placebo group (HR 0.34, 95 % CI 0.18–0.63, $p < 0.001$). The rate of upper GI bleeding was also significantly lower in the PPI group (HR 0.13, 95 % CI 0.03–0.56). No differences in CV events were present at the end of the study between the two arms, which rejected the hypothesis that omeprazole and clopidogrel interaction could have a clinical impact on the occurrence of CV events in patients taking dual therapy plus a PPI [53].

H2 receptor antagonist

These drugs can suppress gastric acid production by up to 70 % over 24 h. There are scarce data on their use as gastroprotective agents in LDA users. A RCT developed in Scotland compared high-dose famotidine (20 mg/12 h) for 12 weeks vs. placebo in LDA users without ulcers at baseline [97]. Patients treated with famotidine had a significantly lower incidence of ulcers than in the placebo group (3.8 vs. 23.5 %, respectively). There are several relevant concerns to consider; (1) the rate of *H. pylori* infection was higher in the placebo group and (2) some patients of famotidine group did not have final endoscopy evaluation.

Two prospective case–control studies developed by our group showed conflicting data on the efficacy of H2 receptor antagonists. In the first study, published in 2001, the risk of upper GI bleeding in patients taking LDA was not significantly reduced by H2 receptor antagonist use (OR 0.5, 95 % CI 0.2–1.2) [54]. In the second study, published in 2007, H2 receptor antagonists significantly reduced the risk of upper GI bleeding in LDA users (RR 0.40, 95 % CI 0.19–0.73) [98]. Today, considerable evidence supports that PPI are more effective than H2 receptor antagonists as gastroprotective agents in antiplatelet users. Ng et al. [99] compared directly PPI (pantoprazole 20 mg) with high-dose famotidine (40 mg twice) in the prevention of recurrence of uncomplicated or complicated peptic ulcers in LDA users. Recurrent GI bleeding and uncomplicated ulcer rates were significantly more common in the famotidine group than in the pantoprazole group (7.7 vs. 0 %, $p < 0.05$ and 12.3 vs. 0 %, $p < 0.05$, respectively). A recent nested case–control study investigated the impact of different prevention strategies against GI complications in LDA or NSAIDs users; 2,049 cases and 20,000 controls were included [100]. The relative risk of upper GI bleeding associated with PPI use was 0.58 % among LDA users, 0.18 % among clopidogrel users, and 0.17 % among dual antiplatelet therapy users. The corresponding estimates for H2 receptor antagonists tended to be smaller.

Interruption of antiplatelet agents in the case of acute bleeding

The discontinuation of platelet inhibition in patients who develop acute GI bleeding may have fatal consequences. There are two different scenarios: patients treated with

LDA for CV prevention who develop upper GI bleeding and hospitalized patients who have just undergone a stent placement and develop a acute GI bleeding. In the first clinical scenario, one RCT showed that patients who received early reintroduction of LDA had lower all-cause 8-week mortality rates (1.3 vs. 12.9 %). This difference was mainly due to lower mortality attributable to CV, cerebrovascular, or GI complications (1.3 vs. 10.3 %). The recurrent ulcer bleeding at 30 days was higher in the early LDA group (10.3 vs. 5.4 %), but this difference was not considered statistically significant [101]. A recent retrospective cohort study that included 118 patients who received LDA and were treated for bleeding ulcer showed that patients with cardiovascular comorbidities who discontinued LDA therapy had an almost sevenfold increase in risk for death and CV events (HR 6.9, 95 % CI 1.4–34.8). The median follow-up period was 2 years after hospital discharge [102]. In patients who have undergone a stent placement, the risk of thrombosis depends on the time interval between stent implantation and discontinuation of antiplatelet therapy. Dual antiplatelet therapy is recommended for at least 12 months after drug-eluting stents and at least 4 weeks after placement of a bare metal stent.

Basing on the current evidence, and in agreement with an expert consensus report [51], we believe that patients with active ulcer bleeding should be treated endoscopically followed by high-dose PPI therapy. If endoscopy shows peptic ulcer with low-risk stigmata, LDA should not be withdrawn. If endoscopy shows high-risk stigmata, LDA could be discontinued and reintroduced early, preferably within 3 days after the last dose. If LDA was indicated for the primary prevention, a re-evaluation of the actual indication of LDA treatment should be performed and if considered appropriate reintroduced after ulcer healing or earlier. If the GI bleeding event occurs soon after the placement of coronary stent, the risk of thrombosis is very high. In this setting, early endoscopy followed by a high dose of PPI is the best option. A close collaboration with the cardiologist is necessary in order to balance the risks and benefits of maintaining one or the two antiplatelet agents.

Conclusions

LDA and clopidogrel have proven to be effective in preventing vascular events, mainly in secondary prevention, but their use is associated with an increased upper and lower GI risk. Upper GI bleeding can occur in pre-existing and/or "de novo" aspirin-induced gastroduodenal lesions. Not all patients taking antiplatelets have the same risk. Gastrointestinal risk factors need to be better defined, especially for the development of complications in the lower GI tract. Effective upper GI prevention strategies are available and should be prescribed in at-risk patients taking LDA, clopidogrel, or both. PPI co-therapy seems to be the best option for upper GI prevention.

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