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Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases

P. SERRANO*, A. LANAS†, M. T. ARROYO† & I. J. FERREIRA*
*Service of Cardiology and †Service of Digestive Diseases, Hospital Clínico Universitario 'Lozano Blesa', Zaragoza, Spain

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SUMMARY

Background: Most patients with vascular-occlusive diseases benefit from low-dose aspirin (75–325 mg/day). However, they have an increased risk of upper gastrointestinal bleeding (UGIB).

Aims: To analyse the incidence and factors influencing the occurrence of UGIB in patients taking low-dose aspirin for the prevention of cardiovascular diseases outside clinical trials.

Methods: We studied 903 consecutive patients discharged on low-dose aspirin from the Cardiology Department of a general hospital. Data were collected from medical charts and structured telephone interviews.

Results: Forty-one patients (4.5%) presented with UGIB requiring hospitalization during follow-up (45 ± 22 months). The incidence of UGIB was uniform during follow-up (1.2 UGIB per 100 patient years). Multivariate analysis showed that a history of peptic ulcer or UGIB [risk ratio: 3.1, 95% CI: (1.5–6.5)] and aspirin dose (per 100 mg/day) [1.8 (1.5–2.9)] was associated with higher risk of UGIB. On the other hand, antisecretory [0.22 (0.07–0.75)] and nitrovasodilator drugs [0.73 (0.55–0.96)] were associated with a decreased risk.

Conclusions: Cardiovascular patients on long-term low-dose aspirin have a stable risk of major UGIB, which is higher than published controlled clinical trials. Antisecretory and nitrovasodilator drugs protect from UGIB, whereas previous peptic ulcer or UGIB and higher doses of aspirin increase the risk.

INTRODUCTION

In Western countries, more than 40% of deaths are due to cardiovascular diseases. It has been shown that antiplatelet therapy with low-dose acetyl-salicylic acid (ASA) (75–325 mg/day) reduces the risk of vascular death and the risk of nonfatal myocardial infarction and stroke in patients with previous myocardial infarction, unstable angina, nonhaemorrhagic stroke or a transient ischaemic attack.[1–3] Low-dose ASA is also beneficial in a much wider range of patients, including those with peripheral vascular disease, those undergoing coronary angioplasty or coronary bypass grafting[4] and also high-risk populations for the primary prevention of cardiovascular events. Recent epidemiological data suggest that aspirin may also be effective in the prevention of different forms of gastrointestinal (GI) cancer.[5, 6] This wide range of indications results in a progressive increase of the prevalence of low-dose ASA users with age.

It has also been reported, however, that low-dose ASA use is associated with a small but significant increase in the risk of upper and lower GI bleeding.[7–9] Weil *et al.*[8] found that any dose of aspirin was associated with an increased risk of GI bleeding and that the risk of GI bleeding due to low-dose aspirin was dose-related (Odd's ratio 2.3 for 75 mg/day; 3.2 for 150 mg/day; 3.9 for 300 mg/day). Despite different attempts to avoid the contact of aspirin with the stomach or duodenum, similar Odd's ratios have been reported for plain, enteric-coated or buffered aspirin.[10] In a prospective

Correspondence to: Dr Angel Lanas, Service of Digestive Diseases, Hospital Clínico Universitario 'Lozano Blesa', 50009 Zaragoza, Spain.
Tel.: 34 976 761238; fax: 34 976 761 236;
E-mail: alanas@posta.unizar.es

case-control study,[11] it has also been confirmed that, after adjusting for confounding factors, low-dose ASA use increased the risk of major upper GI bleeding events by a factor of 2.4, which was three times lower than that found for common NSAID use.

Unlike NSAIDs, however, both the absolute frequency of major upper GI bleeding events requiring hospitalization, and the risk factors associated with complications in patients treated with low-dose aspirin are not well-defined. Data on the prevention of low-dose aspirin-induced GI damage are also scarce and weak. Based on indirect evidence from nonaspirin NSAIDs studies, misoprostol and omeprazole would provide protection against upper GI damage.[12–14] The effect of nitric oxide releasing drugs administered either orally or parenterally on the risk of major gastrointestinal damage induced by either aspirin or NSAIDs is still under investigation.[15, 16]

Although two case-control studies have suggested a protective effect of nitrates on the risk of upper gastrointestinal bleeding,[11, 17] we think it should also be demonstrated in a cohort study limited to patients with cardiovascular disease outside clinical trials, to avoid possible selection biases.

Cardiovascular or cerebrovascular diseases are very common and their frequency increases with age. Most of these patients are treated with low-dose aspirin, thus increasing their risk of GI bleeding. The objective of this study was to assess the risk/incidence of upper GI bleeding in a representative cohort of patients who are prone to taking low-dose aspirin on a chronic basis (patients with cardiovascular diseases) and to determine the predictors (risk factors and prophylaxis factors) for upper GI bleeding in this population. This was considered of great importance in order to design appropriate therapeutic guidelines for patients on long-term use of low-dose aspirin.

MATERIALS AND METHODS

The Hospital Clínico Universitario 'Lozano Blesa' of Zaragoza is a General Hospital attending an area of 259 000 inhabitants, with 99% of the population within the National Health System. We studied all consecutive patients diagnosed with cardiovascular diseases who were discharged on low-dose aspirin regimens (75–325 mg/day) from the Service of Cardiology between November 1992 and June 1996. The planned follow-up period of observation was 5 years following hospital discharge. The study population represents the standard patient on low-dose aspirin regimens discharged from hospital with heart disease.

Data were collected between November 1997 and July 1999 by structured telephone interview using a standardized questionnaire carried out by the same cardiologist, contrasting all the information with the medical charts from hospital and out-patients clinics at the same time as the telephone call. In this way, data on reason for aspirin, other medical history besides upper GI bleeding, and other medications were confirmed by chart review in all cases. Because patients were telephoned at home, they were able to collect all their medical records and present medications, ask for help from their relatives, or be telephoned again for more accurate information. In all patients who reported a possible bleeding complication, the event was also confirmed by additional data from the medical records, in order to investigate the characteristics of the bleeding.

It is important to note that all cardiologists and gastroenterologists of the area are members of the Hospital Services of Cardiology and Gastroenterology. The main outcome of the study was the occurrence of a major upper GI bleeding event, defined as the presence of melena and/or haematemesis confirmed by hospital staff and requiring hospital admission. Interviews consisted of questions regarding: affiliation data, past medical history, cause for anti-aggregation with aspirin, diseases appearing during follow-up (directly questioning on gastrointestinal bleeding), medications during follow-up, and likely causes for changes in medication.

After completion of the follow-up, information regarding *Helicobacter pylori* infection in patients was collected. Some patients had undergone tests for *H. pylori* infection (^{13}C-urea breath test, urease test or histology test) before or during follow-up. In other patients, *H. pylori* status was obtained by serology test[17, 18] carried out in blood samples, if they were available and stored from previous clinical visits and there was previous oral patient informed consent.

The study was approved by the ethics committees of our hospital, and all the patients gave oral informed consent before the telephone interview.

Sample size estimation

For patients on low-dose aspirin therapy, we considered a theoretical incidence of the primary end-point (upper

gastrointestinal bleeding) of 1–3% per patient-years.[7–9] Thus, during a follow-up of 4.5 years we expected an event rate between 4 and 12% for average patients. Based on our previous data,[11] we assumed a proportion of patients taking antisecretory drugs of 15% and a proportion of patients taking nitric oxide donor drugs of 30–50%, given that a higher use of nitric oxide donor drugs should be expected in patients discharged from the cardiology service on low-dose aspirin, most of them with ischaemic heart disease. With a two-sided $\alpha = 0.05$ the study was expected to have 80% power to detect an overall relative-risk reduction of 50% for those on antisecretory drug therapy or any other protective factors.[11] We planned to follow 900 patients for 4.5 years, to have a potential follow-up of 4050 patient-years at risk.

Statistical analysis

All statistical analyses were performed with SPSS 10.0. Statistical significance was considered when $P < 0.05$, and all contrasts were bilateral. Results are expressed as mean ± standard deviation. We performed survival analysis to detect variables influencing or modifying the risk of hospitalization due to an upper gastrointestinal haemorrhage during follow-up.

Survival statistical analyses were performed as follows. The observation periods started in the month of hospital discharge from the Cardiology Department in all cases. Follow-up finished either the month of gastrointestinal bleeding, the month of stopping aspirin, the month of stopping nitric oxide donor drugs, or the month of the telephone interview (if no gastrointestinal bleeding, aspirin or nitrovasodilator withdrawal had previously occurred).

With every possibly influencing variable, we performed a bivariate analysis, describing the survival function (Kaplan–Meier curves) without taking into account other variables in each analysis, using the Mantel–Haenszel (log-rank) or Breslow statistic when appropriate. In a second step, log minus log plot was used to check the proportionality assumption. The plot exhibited constant differences between strata. Afterwards, a multivariate analysis was performed by the Cox proportional hazard model (Cox regression) to estimate a model that adjusted the effect of all influencing variables together on the risk of upper gastrointestinal haemorrhage. RR is the relative risk of suffering an upper GI haemorrhage in people with and without the risk factor from the Cox proportional hazards model. All variables were codified as dummy variables, except aspirin dose and nitrovasodilators. Aspirin dose was codified as 100 mg/day = 1, 200 mg/day = 2, 75 mg/day = 0.75, and so on. The standard dose of nitrovasodilator drugs was considered 50 mg/day of transdermal nitroglycerine or 50 mg/day of oral isosorbide mononitrate. The standard dose of nitrovasodilator was codified as 1, half the standard dose = 0.5, double the standard dose = 2, and so on.

RESULTS

Description of the study population

From the initial population of 1224 consecutive patients discharged from the Cardiology Service on low-dose aspirin, a total of 321 were excluded from the analysis: 86 patients had missing or unreliable information, 153 had died by the time of the telephone call (none of them due to upper GI bleeding), 77 were impossible to contact after three telephone calls and five refused to attend the telephone interview. The remaining 903 patients with complete and reliable data were analysed.

Table 1 describes the baseline characteristics and past medical history of the study population. All the study population was discharged on low-dose aspirin

Table 1. Baseline characteristics, tobacco use, alcohol intake and past medical history of the population studied

$n = 903$ (100%)	n (%)
Male sex	667 (73.9)
Age (years ± s.d.)	65 ± 12
Active smoking	82 (9.1)
Past-smoking history	405 (44.9)
Daily alcohol use	273 (30.2)
Hypertension	358 (39.6)
Hypercholesterolemia	302 (33.4)
Diabetes	169 (18.7)
Prior angina	473 (52.4)
Prior Q myocardial infarction	419 (46.4)
Prior non-Q myocardial infarction	50 (5.5)
Prior angioplasty	138 (15.3)
Prior stent	58 (6.4)
Prior coronary bypass grafting	53 (5.9)
Stroke	57 (6.3)
Peripheral vascular disease	55 (6.1)
Atrial fibrillation	141 (15.6)
Prior peptic ulcer disease	128 (14.2)
Prior upper GI bleeding (peptic lesions)	46 (5.1)
Rheumatic disease	109 (12.1)

treatment, and the most likely indication for anti-aggregation was secondary prevention of ischaemic coronary disease (83.6%, 755/903). Table 2 summarizes all indications for anti-aggregation at discharge and Table 3 describes the prevalence of use of cardiovascular or gastrointestinal drugs. Of all patients on low-dose aspirin, three (0.3%) were on 75 mg/day, 27 (3%) were on 100 mg/day, 341 (37.8%) were on 125 mg/day, 89 (9.9%) were on 150 mg/day, 416 (46.1%) were on 200 mg/day, eight (0.9%) were on 250 mg/day, and 19 (2.1%) were on 300 mg/day. Eighty-five per cent (225/265) of transdermal nitroglycerin users were on 10 mg/day, and the most common doses of oral nitrates were 40 mg/day (24.3%, 57/235) and 60 mg/day (47.7%, 112/235). Of patients taking H_2-receptor antagonists (86.5%, 109/126 ranitidine and 13.5%, 17/126 famotidine), 63.5% (80/126) were at standard recommended dose (300 mg/day for ranitidine and 40 mg/day for famotidine) and 36.5% (46/126) at maintenance dose (half the standard dose). However, 95.8% (68/71) of patients on proton pump inhibitors (92.9%, 66/71 omeprazole and 7.0%, 5/71 lansoprazole) used the standard dose (20 and 30 mg/day, respectively) and only a minority took half the standard dose (4.2%, 3/71).

Table 2. Indications for anti-aggregation at discharge

n = 903 (100%)	n (%)
Secondary prevention of ischaemic coronary disease	755 (83.6)
Primary prevention of ischaemic coronary disease	47 (5.2)
Chest pain under study	23 (2.5)
Atrial fibrillation	63 (7)
Other (dilated cardiomyopathy, atrial flutter, syncope…)	15 (1.7)

Table 3. Prevalence of use of gastrointestinal and cardiovascular drugs in the study population

Drugs	n (%)
NSAIDs	19 (2.1)
Antisecretory therapy	197 (21.8)
Anti-H_2 drugs	126 (13.8)
Proton pump inhibitors	71 (7.9)
Nitric oxide donor drugs	500 (55.4)
Oral nitrates	235 (26)
Transdermal nitroglycerin	265 (29.4)
Calcium channel blockers	405 (44.9)
Beta-blockers	201 (22.3)
ACE inhibitors	250 (27.7)
Diuretics	149 (16.5)
Statins	213 (23.6)
Amiodarone	73 (8.1)
Digoxin	58 (6.4)

Nine hundred and three patients were followed up for a mean of 45 ± 22 months. Forty-one of them (4.5%) were hospitalized because of an upper gastrointestinal bleeding episode; an incidence of 1.2 upper GI bleedings per 100 patient-years, which was uniformly distributed during the follow-up period. There were eight additional patients who suffered a mild gastrointestinal haemorrhage that did not require hospitalization. Among those who had an upper GI haemorrhage, 12/41 (29%) had a bleeding gastric ulcer, 10/41 (24%) had a bleeding duodenal ulcer, and 19/41 (46%) had acute gastroduodenal mucosal lesions. Figure 1 shows the risk of upper GI bleeding requiring hospitalization in the total population of the study showing a constant risk in the cohort.

Risk factors affecting upper GI bleeding in the study population

Of all clinical factors considered (Table 1), the presence of a history of peptic ulcer or upper GI bleeding due to peptic lesions was the only factor significantly associated with the development of an upper GI bleeding episode ($P = 0.049$) (Figure 2). On the other hand, antisecretory drugs ($P = 0.047$) and nitrovasodilator drugs ($P = 0.046$) were found to be associated with a decreased risk of serious upper GI bleeding (Figures 3 and 4). Sex and age (higher vs. lower than 65 years of

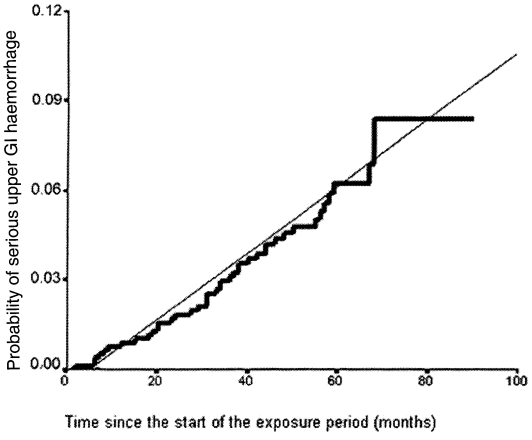

Figure 1. Probability of upper GI bleeding requiring hospitalization in the total cohort of patients.

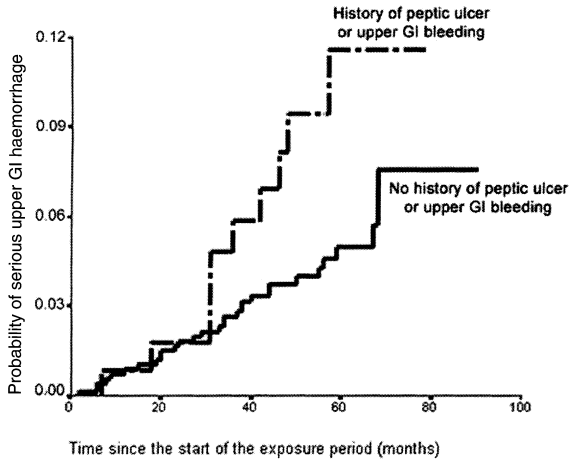

Figure 2. Probability of upper GI bleeding requiring hospitalization in patients with and without a history of peptic ulcer or upper GI bleeding ($P = 0.049$).

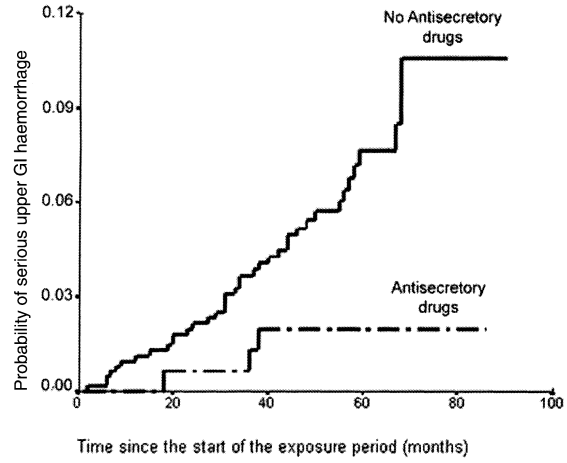

Figure 3. Probability of upper GI bleeding requiring hospitalization in antisecretory drug users and nonusers ($P = 0.047$).

age) were not associated with upper GI bleeding in this population of low-dose aspirin users. Nineteen patients were regular users of nonaspirin NSAID. Four of them suffered from upper gastrointestinal bleeding during follow-up ($P = 0.0005$). Over a third of the population drank alcohol daily (44.6% of men and 4.4% of women). Daily alcohol use was not associated with an increased risk of bleeding.

A multivariate analysis by Cox regression (Table 4) showed that aspirin dose and prior peptic ulcer or upper GI bleeding were the most important factors that increase the risk of upper GI bleeding. On the other hand, antisecretory therapy and nitric oxide donor therapy were associated with a lower risk of upper GI

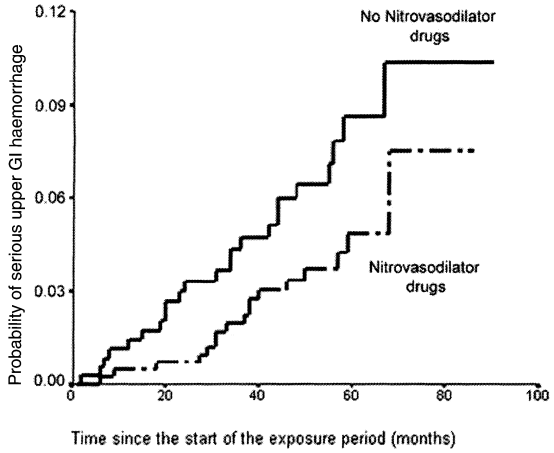

Figure 4. Probability of upper GI bleeding requiring hospitalization in nitrovasodilator drug users and nonusers ($P = 0.046$).

Table 4. Multivariate relative risk of upper GI bleeding requiring hospitalization in 903 aspirin users

$n = 903$ (100%)	RR (95% CI)	P
History of peptic ulcer or upper GI bleeding	3.1 (1.5–6.5)	0.003
Aspirin dose (per 100 mg/day)	1.8 (1.5–2.9)	0.016
Antisecretory therapy	0.22 (0.07–0.75)	0.015
Nitric oxide donor therapy	0.73 (0.55–0.96)	0.026

haemorrhage in this population on low-dose aspirin. NSAID use was found to be associated with upper GI bleeding in this cohort of patients in the univariate analysis, but it was not in the multivariate analysis.

H. pylori *infection and antisecretory therapy*

The status of *H. pylori* infection was determined in 341 patients of the entire population of the study and was positive in 240 patients (70.4%). Of the 174 patients who had either a history of peptic ulcer or a history of ulcer bleeding at the time of hospital discharge from the Cardiology Service, only 20 had undergone a previous test for the diagnosis of *H. pylori* infection and all were positive. Of these 20 patients, 11 had received successful *H. pylori* eradication prior to hospital discharge and none of these patients developed a bleeding episode. The status of *H. pylori* infection was further determined during or after follow-up in another 40 patients, but none of these received eradication therapy during the period of observation. In all, of 60 patients with a history of peptic ulcer, 55 were positive for the infection (91.6%).

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